The Australian Short Course on Intensive Care Medicine

2003 Handbook
The Australian
Short Course on
Intensive Care Medicine

2003 Handbook

Editor
L.I.G. Worthley
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FMC = Flinders Medical Centre   RAH = Royal Adelaide Hospital

Dinner at:
19:00 hr, Wednesday 2nd April 2003
‘House of Chow’
82 Hutt St, Adelaide
### REGISTRANTS

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<th>Name</th>
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### FACULTY

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<tr>
<th>FMC</th>
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<tr>
<td>Dr. L. Worthley (L.W)</td>
<td>Dr. R. Young (R.Y)</td>
<td>Dr. J. Cooper (J.C)</td>
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<td>Dr. A. Bersten (A.B)</td>
<td>Dr. M. Finnis (M.F)</td>
<td>Dr. P. Morley (P.M)</td>
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<td>Dr. P. Thomas (P.T)</td>
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<td>Dr. M. Chapman (M.C)</td>
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<td>Dr. A. Slater (A.S)</td>
<td>Dr. N. Edwards (N.E)</td>
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<td>Dr. T. Brownridge (D.C)</td>
<td>Dr. S. Peake (S.P)</td>
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* = registrants for Interactive sessions at the FMC
† = registrants for Exam oriented sessions at the RAH
PREFACE

A working knowledge of the basic sciences of anatomy, physiology and pharmacology is the basis for the understanding and management of the critically ill patient. This year the Australian Short Course on Intensive Care Medicine handbook has included a review of the basic sciences of the endocrine system with chapters on neuroendocrine, renal and thyroid function. I have also included chapters on disorders of adrenal and thyroid function as well as a chapter on diabetes mellitus. As with the previous editions, the course registrants presentations (or those that have been submitted on time) have also been included.

This handbook still remains the working document of the Australian Short Course on Intensive Care Medicine and is designed to supplement the course. During the sessions, you may find it useful to mark and note the text to facilitate your recall and review of the course at a later date. Along with the previous editions I trust that you will also find this edition useful.

Dr. L.I.G. Worthley
Adelaide, March 2003
NEUROENDOCRINE REGULATION

The anterior pituitary produces growth hormone (GH, somatotropin), prolactin (PRL), luteinising hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and adrenocorticotropic hormone (ACTH). The posterior pituitary stores vasopressin (ADH) and oxytocin, which are produced by neurones of the hypothalamus. A feedback relationship exists between the anterior pituitary and the gonads, thyroid and adrenal glands. When the gonads are removed LH and FSH rise; ACTH increases when the adrenal glands are removed and TSH increases when the thyroid is removed. When the pituitary gland is removed, secondary hypogonadism, hypoadrenalism and hypothyroidism occur; whereas antidiuretic hormone and oxytocin secretion may not be affected, providing their hypothalamic neuronal site of origin remains intact.

The pituitary is under the control of the hypothalamus, which produces thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH), luteinising hormone releasing hormone (LHRH), growth hormone releasing hormone (GHRH), growth hormone-release inhibiting hormone (i.e. somatostatin), prolactin release inhibiting factor (PIF) and prolactin releasing factor (PRF). These mediators enter the pituitary portal vascular system and are carried through the pituitary stalk to the anterior lobe of the pituitary. Somatostatin inhibits TRH-stimulated TSH release and TRH stimulates prolactin release. The major prolactin release inhibiting factor is dopamine, thus dopaminergic blocking agents such as phenothiazines increase prolactin levels whereas dopaminergic agents (e.g. bromocriptine, dopamine) decrease prolactin levels.

ENDOCRINE CHANGES IN THE CRITICALLY ILL

In response to acute ‘stress’ (e.g. trauma, sepsis, pyrogens, burns, surgery, hypotension, pain, hypoglycaemia, severe exercise and emotional trauma) the sympathetic system and the adrenal medulla release catecholamines, and the renin-angiotensin-aldosterone system increases plasma renin activity (PRA), angiotensin II (AII) and aldosterone levels. A subset of critically ill patients have been described who have inappropriately low aldosterone levels despite elevated PRA, plasma AII and ACTH levels, and normal potassium and atrial natriuretic peptide levels. This effect may be caused by tumor necrosis factor or adrenal ischaemia inhibition of aldosteronogenesis, or a shift in steroidogenesis from mineralocorticoid to glucocorticoid due to prolonged ACTH stimulation. Generally, the hypothalamo-pituitary response to acute ‘stress’ involves only the release of prolactin, vasopressin, growth hormone, ACTH (which in turn stimulates cortisol, aldosterone and small amounts of sex steroid, biosynthesis and release) and ACTH related peptides, although plasma levels may range widely due to the pulsatile nature of their secretion. During ‘stress’, the plasma gonadal steroid and thyroid hormone levels decrease, whereas the production and plasma levels of TSH, FSH, LH and oxytocin may increase, decrease or remain unaffected.
Plasma PTH levels have also been reported to increase in response to severe stress (e.g. cardiac arrest). The hormone liberation provoked by ‘stress’ is outlined in Table 1.1.

### Table 1.1  Hormonal liberation due to stress

<table>
<thead>
<tr>
<th>Sympathetic nerves</th>
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<tr>
<td>Noradrenaline</td>
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<td>Adrenal medulla</td>
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<td>Adrenaline, and noradrenaline</td>
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<tr>
<td>Renin-angiotensin</td>
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<td>Angiotensin II</td>
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<td>Pituitary</td>
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<td>Neurohypophysis</td>
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<td>Vasopressin</td>
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<td>Adenohypophysis</td>
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<td>Adrenocorticotropic hormone</td>
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<tr>
<td>Beta-lipotropin</td>
</tr>
<tr>
<td>Prolactin</td>
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<tr>
<td>Growth hormone</td>
</tr>
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**Growth hormone (somatotropin)**

Growth hormone is secreted in a pulsatile fashion (greatest at night) from the anterior pituitary under the control of the hypothalamic hormones, growth hormone releasing hormone (GHRH) and growth hormone-release inhibiting hormone (i.e. somatostatin). It has a plasma half life of 6 - 20 minutes and the daily output in an adult is estimated to be 0.2 - 1.0 mg. The effects of growth hormone are mediated directly through a cell membrane receptor (causing sodium retention, insulin resistance, lipolysis, protein synthesis, epiphyseal growth) and indirectly through stimulation of hepatic secretion of insulin-like growth factor-I (IGF-I; somatomedin-C).

While growth hormone has been used for many diseases associated with waisting (e.g. AIDS, COPD, burns, postoperatively, congestive cardiomyopathy, liver transplantation, renal failure), no consistent benefit has been demonstrated with its use. Recently, two large prospective randomised, placebo-controlled trials in critically ill patients, revealed that growth hormone was associated with an increased mortality, (although it was given in large doses at a stage when many of the patients may have been GH sensitive rather than GH resistant). High doses of GH is harmful and is not recommended for the treatment of acute catabolism in critically ill patients.

**Insulin like growth factor**

The insulin-like growth factor family consists of insulin (synthesised in the beta cells of the pancreas), IGF-I and IGF-II (which are synthesised primarily in the liver). IGF-I has insulin like activity (approximately 6% that of insulin on a molar basis, although it circulates at a 1000 fold higher concentration than insulin, with less than 1% circulating free), antilipolytic activity, increases protein synthesis and epiphyseal growth and supresses hypothalamic GHRH secretion and pituitary GH secretion. Greater than 99% of the IGF’s are bound to a family of 6 high affinity binding proteins (which allow them to have a prolonged circulating half-life while preventing them binding to the IGF receptors with subsequent activation). They suppress
Endocrine Regulation in the Critically Ill

circulating insulin and glucagon levels, inhibit hepatic glucose output, increase glucose uptake, and decrease circulating free fatty acids and amino acids. IGF-II is essential for embryonic development (as is IGF-I) although in adult life its physiological role is unknown. Recently, the IGF’s have been shown to be potent antiapoptotic agents. Insulin, IGF-I and IGF-II bind to two membrane associated receptors that are tyrosine kinases (i.e. the insulin receptor and the IGF-I receptor) with insulin stimulating the insulin receptor predominantly and IGF-I stimulating the IGF-I receptor predominantly. The predominant regulator of IGF-I is growth hormone, although insulin also stimulates hepatic secretion of IGF-I (and IGF-I in turn supresses insulin secretion). However, in critically ill patients plasma GH levels are normal or elevated and plasma IGF-I levels are usually very low.

THE ADRENAL CORTEX

Normal adrenocortical function

The zona faciculata and zona reticularis (i.e. the middle and inner adrenal cortical zones) secrete glucocorticoids and small amounts of androgens and oestrogens. The zona glomerulosa (i.e. the outer adrenal cortical zone) secretes aldosterone.

Corticotropin releasing hormone

Corticotropin releasing hormone (CRH) is synthesised in the hypothalamus and carried to the anterior pituitary in portal blood to stimulate the anterior pituitary to secrete ACTH, which in turn causes the adrenal cortex to secrete cortisol. Corticotropin releasing hormone is the major (but not the only) regulator of ACTH release. Vasopressin, oxytocin, angiotensin II and beta-adrenergic agents also stimulate ACTH release. Somatostatin, beta-endorphin and enkephalin decrease ACTH release. Cortisol has a negative feedback on the hypothalamus and pituitary, inhibiting hypothalamic CRH release induced by stress, and pituitary ACTH release induced by CRH. Corticotropin-releasing hormone is released in response to a normal hypothalamic circadian regulation and various forms of ‘stress’.

Adrenocorticotropic hormone (ACTH) or corticotropin

Adrenocorticotropic hormone and the ACTH related peptides are formed from the pituitary precursor molecule pro-opiomelanocortin, which forms gamma melanocyte stimulating hormone, ACTH and beta-lipotropin. Beta-lipotropin forms alpha-, beta- and gamma-endorphins.

ACTH is the only physiologic agent known that stimulates cortisol biosynthesis and release. It also stimulates aldosterone (and small amounts of sex steroid) biosynthesis and release, although normal modulation of aldosterone secretion is by angiotensin II. ACTH has a half-life of 10 - 15 min. Both ACTH and cortisol are secreted cyclically throughout a 24 hr period. A decrease in circulating glucocorticoids is not a potent stimulus to ACTH secretion as the rate of ACTH secretion is determined largely by two opposing forces of neural and other influences. The magnitude of circulating glucocorticoids, however, inhibits ACTH secretion.

Cortisol

The normal daily output of cortisol is 40 - 80 µmol/day (i.e. 15 - 30 mg/day), producing a maximum plasma cortisol level of 110 - 520 ηmol/L (4 - 19 µg/dL) at 8 - 9 am, and a minimal cortisol level of < 140 ηmol/L (< 5 µg/dL) after midnight. The aldosterone output in a normal individual on a sodium intake of 100 - 150 mmol/day is 200 - 500 ηmol/day (i.e., 70 - 180 µg/day).
Endocrine Regulation in the Critically Ill

g/day). In a normal subjects with severe sodium restriction or patients with severe heart failure
the aldosterone secretion may increase to 1100 - 1400 ηmol/day (400 - 500 µg/day).19

Cortisol promotes muscle protein catabolism and stimulates gluconeogenesis to produce
glucose from the amino acids provided by the protein catabolism, it also promotes the lipolytic
effect of catecholamines. Cortisol enhances vascular smooth muscle and myocardium
responsiveness to noradrenaline or adrenaline and renal water excretion, all of which are
impaired in the absence of glucocorticoids. The half-life of cortisol is 60 - 90 min.

Cortisol exists in plasma in a bound form bound to both an alpha-globulin called transcortin
or corticosteroid-binding globulin (CBG) and albumin, and also exists in a free form. The free
hormone is the active form. At normal levels of total plasma cortisol (e.g. 375 ηmol/L or 13.5 µ
g/dL) less than 5% exists as free cortisol in the plasma. Cortisol binding by CBG in normal
subjects can bind approximately 700 ηmol/L (i.e., 25 µg/dL). At levels greater than this the
increase in plasma cortisol is largely in the unbound fraction. When CBG levels rise (e.g.
pregnancy) the total cortisol level rises, a reciprocal change occurs with depressed transcortin
levels (e.g. with cirrhosis, burns and nephrotic syndrome).

In pharmacological doses, glucocorticoids have anti-inflammatory and immunosuppressive
effects causing a reduction in the peripheral lymphocyte, eosinophil and monocyte count, and
an increase in neutrophil count.20 The relative potencies of the commonly used glucocorticoids
are listed in Table 1.2.

Table 1.2 Characteristics of the commonly used glucocorticoids

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose (mg)</th>
<th>Mineralocorticoid potency</th>
<th>Glucocorticoid potency</th>
<th>duration of action (hr)</th>
<th>Plasma half life (min)</th>
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<tr>
<td>Cortisone</td>
<td>25</td>
<td>1</td>
<td>0.8</td>
<td>8</td>
<td>90</td>
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<td>Hydrocortisone</td>
<td>20</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>90</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
<td>0.8</td>
<td>4</td>
<td>24</td>
<td>200</td>
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<tr>
<td>Methylprednisolone</td>
<td>4</td>
<td>0.5</td>
<td>5</td>
<td>24</td>
<td>200</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
<td>0</td>
<td>25</td>
<td>36</td>
<td>300</td>
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</table>

Hydrocortisone is the synthetic equivalent of cortisol and is assigned the glucocorticoid and
mineralocorticoid equivalent of 1 (one). Prednisone and prednisolone are equivalent, as are
triamcinolone and methylprednisolone, and betamethasone and dexamethasone.21

Adrenocortical response to ‘stress’

The hypothalamus responds to the stress of surgery, trauma, hypoglycaemia and sepsis by
increasing ACTH secretion. Plasma cortisol levels in critically ill patients are usually elevated
above 555 ηmol/L (i.e., 20 µg/dL) with a loss in the diurnal rhythm. However, the range is
wide.22 The maximum stress-induced output of cortisol is thought to be up to 555 µmol/day
(i.e., 200 mg/day), with corresponding plasma levels of approximately 1650 ηmol/L (i.e., 60 µ
g/dL).23

Reports of occult hypoadrenalism with cardiovascular decompensation in acutely ill
patients,24 adrenal hyporesponsiveness in some patients with severe inflammation25 or septic
shock,26 and agents such as etomidate which suppress cortisol synthesis, being associated with
increased mortality,27,28 indicate that cortisol secretion is important in the critically ill
patient.29,30 However, the cortisol concentration appropriate for an acute illness is unknown,
and there is no correlation between severity of illness and cortisol levels,31 indicating that the
relationship between cortisol secretion and mortality, is far from clear. This uncertainty is even greater in patients who are already taking corticosteroid medication.

With bilateral adrenal haemorrhage the serum cortisol levels are usually less than 50 ηmol/L, and the diagnosis of hypoadrenalism is not in doubt. In critically ill patients (particularly those in whom the baseline cortisol level is less than 350 ηmol/L), glucocorticoid replacement (e.g., 50 - 300 mg of hydrocortisone/day as a continuous infusion) should be used if a short synacthen test does not double the baseline level or elicit a rise in serum cortisol of at least 250 ηmol/L. In critically ill patients, a plasma cortisol level of more than 700 ηmol/L (i.e., 25 µg/dL) probably rules out adrenal insufficiency. One study found 25% of critically ill patients with an eosinophilia (>3%) had an abnormal low-dose short synacthen test and may be a useful sign in critically ill patients who have adrenal insufficiency.

In a recent multicentre, placebo controlled, randomised, double blind study of mechanically ventilated, critically ill patients with septic shock unresponsive to intravenous fluids and catecholamine infusions, 7 days of intravenous hydrocortisone (50 mg 6-hourly) and nasogastric tube instillation of 9-α-fludrocortisone (50 µg in 10 - 40 mL water) significantly reduced the 28 day mortality (NNT 7 patients to save one additional life) in patients with relative adrenal insufficiency (i.e. those who had a cortisol rise of < 9 µg/dL or 250 µmol/L at 30 or 60 minute following 0.25 mg of synacthen intravenously). In this study approximately 2/3 of patients were found to have relative renal insufficiency, and there was a slight increase in mortality in patients who were adrenal ‘responsive’ who received cortisol and 9-α-fludrocortisone compared with the placebo group.

REFERENCES
Chapter 2

DISORDERS OF ADRENAL FUNCTION

ADRENOCORTICAL DEFICIENCY

Aetiology

Primary adrenocortical insufficiency (Addison’s disease)

Primary adrenocorticoïd insufficiency is caused by a primary autoimmune disease in 70% of cases, 50% of whom have antiadrenal antibodies and some of whom have other autoimmune diseases (e.g. pernicious anaemia, type I diabetes mellitus, thyroiditis and myasthenia gravis). Other causes include sudden withdrawal of corticosteroids, granulomatous diseases (e.g. tuberculosis, cryptococcus, histoplasmosis), cytomegalovirus (particularly in AIDS patients), bilateral adrenal haemorrhage [e.g. retroperitoneal haemorrhage following trauma, ruptured aortic aneurysm, anticoagulants or disseminated intravascular coagulation in patients who have fulminant meningococcal (i.e. Waterhouse-Friderichsen syndrome), pneumococcal or Haemophilus septicaemia], bilateral adrenal thrombosis and infarction (e.g. antiphospholipid syndrome\textsuperscript{1,2,3}), tumour metastases, sarcoidosis, fluconazole\textsuperscript{4} and ketoconazole (although the testosterone secretion is usually reduced more than cortisol secretion, and plasma cortisol levels are often normalised by a compensatory rise in ACTH secretion),\textsuperscript{5} and etomidate.\textsuperscript{6,7} Rifampicin induces the cytochrome P\textsubscript{450} enzymes, and accelerates the metabolism of cortisol, which may precipitate an adrenal crisis early in the course of antituberculous chemotherapy.\textsuperscript{8} The adrenal disease must involve destruction to greater than 90% of the gland before signs and symptoms of hypoadrenalism appear.

Secondary adrenocortical insufficiency

1. Long-term corticosteroid therapy

Suppression of secretion of ACTH and atrophy of the adrenal cortex become progressively greater as the doses of glucocorticoids exceed physiological levels (e.g. a daily dose greater than 37.5 mg of hydrocortisone, 7.5 mg of prednisolone, or 2 mg of dexamethasone) and the longer the treatment is continued,\textsuperscript{9} although some patients may show adrenal suppression after only 5 days of corticosteroid therapy.\textsuperscript{10}

The suppression is less if the steroid is given as a single dose in the morning (matching the circadian pattern) than when the dose is divided throughout the day, and almost normal adrenal responsiveness to ACTH may be maintained when up to 80 mg of prednisolone is given on alternate days.\textsuperscript{11,12} When a patient has been on glucocorticoids for prolonged periods, inhibition of hypothalamic-pituitary-adrenocorticol function may persist for 12 months after treatment is withdrawn,\textsuperscript{13} which may lead to an adrenal crisis if the patient is subjected to ‘stress’ during this period.\textsuperscript{14}

2. Pituitary dysfunction

Post partum necrosis (i.e. Sheehan’s syndrome) or pituitary apoplexy may cause secondary adrenocortical insufficiency.
Sheehan’s syndrome is caused by a sudden hypotensive post partum episode, causing a susceptible hypertrophied pituitary gland to develop ischaemic infarction. This disorder usually presents with pituitary insufficiency over a prolonged period and often requires hormonal replacement therapy.

Pituitary apoplexy is an acute haemorrhagic infarction of a pituitary adenoma, which may present with sudden onset of a severe headache, visual loss, cranial nerve palsy, nausea, vomiting and depression of consciousness. The onset may be over minutes, causing death, or over 24 - 48 hr. Treatment may require neurosurgical decompression and hormonal replacement therapy.

**Clinical features**

The clinical features of hypoadrenalism caused by gradual adrenal destruction are usually insidious in onset. The symptoms include, salt craving, asthenia, malaise, weakness, fatigue, alteration in personality, depression, confusion, delirium, psychosis, anorexia, nausea, vomiting, diarrhoea, abdominal pain (which may be severe), arthralgias, fever (or pyrexia of unknown origin) and weight loss. The signs include, postural and supine hypotension, vitiligo and flexural contractures. There is also an increased sensitivity to central nervous system depressant drugs including opioids.

The patient who presents with an adrenal crisis may appear to be in ‘septic’ shock (with high cardiac output and decreased systemic vascular resistance, or low cardiac output with normal systemic vascular resistance) or hypovolaemic shock (with decreased preload, myocardial contractility and increased systemic vascular resistance), although the features of eosinophilia and hypoglycaemia are uncharacteristic of a ‘septic’ or ‘hypovolaemic’ event. The cardiovascular effects are probably secondary to a reduction in intravascular volume (due to vomiting and chronic salt wasting) and reduction in myocardial contractility and peripheral resistance due to a reduction in adrenoreceptor sensitivity to catecholamines.

In primary adrenal insufficiency the ACTH levels rise causing hyperpigmentation due to the melanocyte-stimulating properties of ACTH. The areas of pigmentation occur at the elbows, belt-line, scars and hand creases. Longitudinal pigmentation of nails and bluish black patches of pigment on the buccal mucosa may also occur. Patients with primary ACTH deficiency are not hyperpigmented or hyperkalaemic because the melanocyte stimulating effect of excess ACTH is absent and aldosterone production and stimulation occurs via angiotensin II.

**Investigations**

These include:

1. **Plasma biochemical tests.** Hyponatraemia, hyperkalaemia (with a Na⁺:K⁺ ratio of < 25:1), hypoglycaemia, hypercalcaemia and renal tubular acidosis (type IV) are characteristic findings of primary adrenocortical insufficiency.

2. **Complete blood picture.** Eosinophilia, lymphocytosis and a normocytic anaemia (which may be masked by the decrease in plasma volume) may be present.

3. **ECG.** While hyperkalaemia may be severe (e.g. > 7 mmol/L) and associated with ECG changes, cardiac arrest from hyperkalaemia due to Addison’s disease has not been reported, probably due to the slow rise in plasma potassium and presence of hypercalcaemia.

4. **Urine electrolytes.** With primary adrenocortical insufficiency the urine sodium loss is greater than 40 mmol/L and potassium loss is usually less than 20 mmol/L.

5. **Chest X-ray.** Characteristically, the chest X-ray reveals a small heart.

6. **Short synacthen test.** This requires plasma cortisol levels to be measured before (i.e. baseline level), and at 30 and 60 min after 0.25 mg of synacthen is given intravenously or intramuscularly. The plasma cortisol level should increase to two or three times the basal
Adrenal Disorders

level and be more than 500 \( \mu \text{mol/L} \) with stimulation, if the adrenal cortex is responsive. In the critically ill patient the cortisol rise should be at least 250 \( \mu \text{mol/L} \).

Typically the basal plasma cortisol levels are more than 200 \( \mu \text{mol/L} \) rising to 500 \( \mu \text{mol/L} \) after administering the synacthen. In Addison’s disease the baseline cortisol levels are often < 100 \( \mu \text{mol/L} \) (if ACTH levels are also measured then they are usually > 200 \( \mu \text{g/L} \)), and with stimulation the plasma cortisol does not rise. If secondary (i.e., pituitary) adrenocorticoid insufficiency is suspected (e.g. ACTH level < 10 \( \mu \text{g/L} \)), then 1 mg of synacthen is administered intramuscularly daily for three days, and 48 hr after the last dose a short synacthen test is performed. If hydrocortisone has been administered, the short synacthen test may be performed 24 hr after the last dose.

In the critically ill patient impaired adrenocortical function may be determined better by the low-dose short synacthen test, where a plasma cortisol level < 500 nmol/L, 30 minutes after 1 \( \mu \)g of synacthen indicates impaired adrenal reserve. A modification of this test, known as the low-dose corticotropin test (baseline plasma cortisol levels are taken before 1 \( \mu \)g synacthen is administered i.v., then plasma cortisol is taken 30 minutes later, with a normal response being defined as a stimulated plasma cortisol level > 550 nmol/L), has been used to detect partial adrenocortical insufficiency.

7. Thyroid function studies. While treatment of myxoedema should include hydrocortisone to guard against the development of an adrenal crisis, patients with Addison’s disease may have an elevated TSH with low or normal thyroxine levels which are completely reversible with hydrocortisone therapy alone.

8. Acute phase reactants. C-reactive protein and the non specific serum marker procalcitonin have been used to differentiate septic shock from Addisonian shock (i.e. both are elevated in the former and are within normal limits in the latter).

9. CT scan. CT scanning of the adrenal glands may reveal adrenal haemorrhage or carcinomatous infiltration.

Treatment

The management of the patient depends on whether the patient has a non-‘crisis’ hypoadrenalism or an adrenal ‘crisis’.

1. Non-‘crisis’ hypoadrenalism. The treatment of an acute episode of hypoadrenalism in the absence of hypotension is oral cortisone varying from 12.5 to 50 mg daily, with the average dose usually being 37.5 mg daily (e.g. 25 mg in the morning and 12.5 mg in the evening, with meals, although 12.5 mg with all three meals, may reduce the mid-afternoon trough, and improve the sense of well-being). Fludrocortisone 0.05 - 0.1 mg is often administered as well. During an intercurrent illness the cortisone dose is increased to 75 - 150 mg daily. The patient is monitored and assessed clinically (e.g. sense of well-being, arthropathy, temperature) and by the plasma potassium, blood pressure and clinical signs of oedema.

2. Adrenal ‘crisis’. An acute adrenal insufficiency or adrenal ‘crisis’ is a life-threatening episode following an acute ‘stress’ event (e.g. trauma, infection, burns, surgery), in a patient who has insufficient glucocorticoid and mineralocorticoid reserve. The ‘crisis’ follows the acute event by presenting with vomiting, hypotension, pyrexia (even rigors), hyperkalaemia, hypoglycaemia and shock resistant to fluid and sympathomimetic amines.

Treatment involves resuscitation with intravenous 0.9% saline, 1 - 2 L over 2 - 4 hr (which may require right heart catheter and arterial monitoring), thereafter the fluid regimen is governed by cardiovascular status. Hydrocortisone 100 mg is usually administered intravenously as a loading dose, followed by 300 mg/day (e.g. 50 mg intravenously 4-hourly). The hydrocortisone may be reduced to 50 - 100 mg over the next 1 - 3 days. If hypoglycaemia
exists then 50 mL of 50% dextrose solution is infused over 3 min. The hyperkalaemia usually does not require specific therapy. Because the concentration of cortisol in the blood during maximum stress is less than 2750 \( \text{nmol/L} \) (i.e., 100 \( \mu\text{g/dL} \)) and the daily production of cortisol is 200 mg and as cortisol distributes in the ECF, has a half-life of 90 min and a clearance rate of 200 L/day, theoretically a loading dose of 10 mg followed by an infusion of 8 - 10 mg/hr (i.e. 200 mg in 24 hr) is all that is required for hormone replacement during acute stress.

3. Steroid replacement in patients undergoing major surgery. In patients who have been on long term corticosteroid therapy, large and complex regimens are usually recommended for intraoperative and postoperative steroid replacement. However, with excess replacement there is an increased susceptibility to infection, impaired wound healing and decrease in glucose tolerance. The normal adrenocortical response due to major surgery is a cortisol secretion of 75 - 150 mg/24 hr. For major surgery the hydrocortisone required to prevent adrenal insufficiency is 25 mg as an intravenous bolus, at the induction of anaesthesia, followed by 100 mg as an intravenous infusion during the next 24 hr, which is then followed by the patients normal maintenance dose.

4. Withdrawal of corticosteroid treatment. If the patient has been treated with a morning dose of prednisolone for 7 - 10 days, withdrawal of treatment may be rapid. If corticosteroids have been used for many years as an anti-inflammatory agent, then the disease activity may be monitored by using C-reactive protein or ESR as the prednisolone is withdrawn by 2.5 mg every 1 - 3 weeks. Once the dose of prednisolone is 10 mg or less, the dose reduction may be by increments of 1 mg amounts. The function of the adrenal cortex may also be assessed by the short synacthen test.

CUSHING’S SYNDROME

Cushing’s syndrome is caused by pituitary ACTH overproduction in 70% (i.e. Cushing’s disease which usually caused by a pituitary microadenoma), ectopic ACTH overproduction in 15% (often associated with a small cell carcinoma of the lung), adrenal tumours in 15% and ectopic CRH overproduction in < 1% of cases. Excessive exogenous glucocorticoid administration can also cause Cushingoid features. Pseudo-Cushing’s syndrome (i.e. patients who have clinical features similar to glucocorticoid excess) may occur in chronic alcoholism, COPD, obesity and chronic depression.

Clinical features

Glucocorticoid excess is characterised by muscle weakness (i.e. proximal myopathy), central distribution of adipose tissue (e.g. ‘moon’ facies, ‘buffalo’ hump, and ‘lemon on toothpicks’ obesity), hypertension, purple striae, hirsutism, oedema, glucose intolerance, amenorrhoea, osteoporosis, fatigue, bruising, cataracts and psychiatric problems. Glucocorticoid excess from ectopic ACTH production due to a rapidly growing tumour (e.g. small cell carcinoma of the lung) usually presents with rapid onset of hypertension, pigmentation, hypokalaemia, weight loss and muscle weakness. Whereas ectopic ACTH production from a slowly growing tumour (e.g. thymic, pancreatic, or ovary carcinoma, medullary carcinoma of the thyroid or bronchial adenoma) usually presents with a classical Cushing’s syndrome.

Investigations

These include:

1. Urinary ‘free’ cortisol. A 24 hr urinary ‘free’ cortisol measures the amount of cortisol that is unbound (and hence active and filtered by the kidney) over a 24 hr period. This test reflects hypercortisolism, although it may also be positive in patients with ‘stress’ and
depression, and may be falsely negative in up to 15% of patients with hypercortisolism\textsuperscript{35} and in patients with renal failure.\textsuperscript{36} It is a useful screening test and a level greater than 275 $\text{nol}/\text{day}$ (i.e., 100 $\mu$g/day) is an indication for a dexamethasone suppression test.

2. **Dexamethasone suppression test.** This test is performed by measuring the plasma cortisol at 08.00 hr after the oral administration of 1 mg of dexamethasone at 24.00 hr the night before. Normally the plasma cortisol will be suppressed below 100 $nol/L$ (i.e. 3.6 $\mu$g/dL). Borderline values are between 100 and 150 $\text{nol}/\text{L}$ (i.e. 3.6-5.4 $\mu$g/dL) and abnormal values are greater than 150 $\text{nol}/\text{L}$ (5.4 $\mu$g/dL). While, depression, alcohol abuse, stress, oral contraceptives or anticonvulsants, and 20 - 35% of obese patients, may register a nonsuppressed result (i.e. the test has a low specificity), the test has a 95% sensitivity.\textsuperscript{37} A high-dose dexamethasone suppression test may be performed (i.e. 2 mg 6-hourly for 2 days) to maximally suppress the hypothalamic-pituitary-adrenocorticoid function. In the critically ill patient, suppressability of the adrenal cortex is unachievable,\textsuperscript{38} and thus the dexamethasone suppression test cannot be used to diagnose hypercortisolism in these patients. The diagnosis of Cushing’s syndrome in a critically ill patient has to await for the acute illness to be corrected. Dexamethasone will supress cortisol production in the rare ectopic ACTH syndrome.\textsuperscript{33}

3. **ACTH.** After confirming Cushing’s syndrome, the next step is to detect whether corticotropin is detectable in plasma (e.g. adrenal adenoma or carcinoma supresses ACTH secretion whereas ACTH is readily detectable in Cushing’s disease and the ectopic ACTH syndrome).

4. **CRH test.** Plasma ACTH increases by 50% in most patients with Cushing’s disease (c/f a lower response with patients with the ectopic ACTH syndrome).

5. **CT scan.** CT scanning of the adrenal glands may confirm adrenal hyperplasia or an adenoma.\textsuperscript{36}

6. **MRI scan.** High resolution MRI scanning may be required to detect a pituitary ACTH secreting microadenoma.

7. **Bilateral inferior petrosal sinus ACTH levels.** This is a highly specialised (and sensitive test) to determine whether or not the source of ACTH is the pituitary, and is useful when imaging is negative. A central to peripheral plasma ACTH gradient is found in Cushing’s disease (both before and after CRH) but not in the ectopic ACTH syndrome.\textsuperscript{39}

**Treatment**

Microadenomas are resected by trans-sphenoidal microsurgery. Adrenal adenomas and adrenal hyperplasia may be corrected by surgical excision.

**REFERENCES**

Adrenal Disorders

Adrenal Disorders

NORMAL THYROID FUNCTION

The thyroid hormones 3,5,3-triiodo-L-thyronine (T₃) and L-thyroxine (T₄) increase oxygen consumption (by stimulating Na/K-ATPase and activating mitochondrial metabolic pathways), regulate lipid and carbohydrate metabolism, and are necessary for normal growth and maturation of tissues.¹ ² Thyroid function is controlled by thyroid-stimulating hormone (TSH) which in turn is controlled by thyrotropin releasing hormone (TRH).

**Thyrotropin releasing hormone**

The major function of TRH is to release TSH from the adenohypophysis. However, TRH is also found in the neurohypophysis, brain, brainstem, medulla, spinal cord, pancreas, gastrointestinal tract, adrenal and placenta, and can act as a partial opioid antagonist and inhibit pancreatic secretion. It has also been used to improve motor function in spinocerebellar degeneration and motor neurone disease, and to reduce mortality in experimental shock and limit the neurological deficit in spinal trauma.³ ⁴

**Thyroid stimulating hormone**

TSH is released from the adenohypophysis in response to TRH and the negative feedback effects of T₃ and T₄. Somatostatin (and octreotide), glucocorticoids and dopamine also inhibit TSH release. By binding to specific thyroid follicular cell surface receptors and activating adenylate cyclase, TSH stimulates synthesis and release of T₃ and T₄.

**Thyroid hormones**

The principle thyroid hormones are T₃ and T₄, which are synthesised in the colloid of the thyroid gland and bound to thyroglobulin until they are excreted into the circulation as free T₃ (FT₃) and free T₄ (FT₄). The normal daily thyroid secretion consists of approximately 100 ηmol (78 µg) of T₄ [35 ηmol (27 µg) of which is converted to T₃ and 45 ηmol (35 µg) of which is converted to rT₃], 5 ηmol (4 µg) of T₃ and 2.5 ηmol (2 µg) of rT₃. As T₃ has approximately 3 times the potency of T₄, and as 87% of the circulating T₁ is formed from peripheral tissue conversion of T₄, virtually all of the action of T₄ is due to the T₃ it gives rise to,⁵ indicating that T₄ functions largely as a circulating thyroid hormone store. Approximately 45% of T₄ is converted to reverse T₃ (rT₃) which has little if any metabolic potency. With systemic illness, malnutrition and with propylthiouracil, propranolol, glucocorticoids and amiodarone therapy, the peripheral conversion of T₄ to T₃ is decreased and plasma rT₃ is increased (both of which are caused by an inhibition of the peripheral 5-monodeiodination). The biological half lives of T₄ and T₃ are 7 days and 24 hr, respectively.

Thyroid hormones circulate either free or bound to thyroxine-binding globulin (TBG), thyroxine binding prealbumin and albumin. Approximately 99.98% of the circulating T₄ is bound (70% to TBG, 20% to thyroxine binding prealbumin and 10% to albumin) and 99.8% of...
the circulating T₃ is bound (50% to TBG, 50% to albumin, and minimal amounts to thyroxine-binding prealbumin). Only 0.02% of the circulating T₄ is free and 0.2% of T₃ is free. The free thyroid hormone is the active form. Measurement of total plasma T₄ or T₃ may be altered due to alteration of the amount of bound thyroid hormone without altering the FT₃ or FT₄ levels.

THYROID FUNCTION TESTS

Plasma TSH
Using two specific monoclonal antibodies, the ultrasensitive TSH assay has improved the sensitivity of the TSH assay to the extent that both hypo- and hyperthyroid states may be discriminated from the euthyroid state. However, an undetectable TSH concentration is compatible with and not diagnostic of hyperthyroidism because it may occur in hypopituitarism, euthyroid patients in the first trimester of pregnancy, early phase of treatment of hyperthyroidism (the TSH may remain suppressed for up to 6 months despite low circulating thyroxine levels) and in patients being treated with dopamine, dobutamine or corticosteroids.⁶,⁷ Plasma values may be taken during any time of the day.

The normal, upper borderline, lower borderline, and levels diagnostic of primary thyrotoxicosis and hypothyroidism, are listed in Table 3.1. In pituitary (i.e. secondary) hypothyroidism, the circulating TSH levels are low relative to the circulating FT₄ levels. The TSH levels are suppressed by adequate T₄ replacement in patients with primary hypothyroidism, but 8 weeks should be allowed after changing the dosage of T₄ to allow adequate equilibration of thyroxine with tissues before measuring TSH levels.

TRH stimulation test
This test is usually performed to confirm the presence of thyrotoxicosis. Following the intravenous infusion of TRH, the TSH increases and reaches a peak within 20 - 45 min then rapidly declines. In hyperthyroidism (or pituitary hypothyroidism) the response is blunted. While the response may be augmented in primary hypothyroidism the response is not consistent.⁸

Total T₄
The total T₄ measurement includes the protein bound as well as the FT₄ fraction, and is subject to false interpretation of thyroid status when there are abnormalities of thyroid binding proteins. For example, an increase in TBG occurs during pregnancy, oral contraceptive treatment, hepatitis and biliary cirrhosis, and a decrease in TBG occurs with androgen treatment, corticosteroid treatment, chronic liver disease and severe systemic illness, all of which may alter the total T₄ levels in the absence of thyroid disease.

Free thyroxine
The FT₄ assay is a radioimmunoassay that uses a T₄ tracer to measure the plasma non-protein bound T₄. The free hormone concentrations correlate better with the metabolic state, and should always be used to assess thyroid status. It is often performed as a second-line test, to investigate an abnormal plasma TSH level. The normal, upper borderline, lower borderline, and levels diagnostic of thyrotoxicosis and hypothyroidism are listed in Table 3.1. In early primary hypothyroidism, the TSH is a more sensitive test than the plasma FT₄, which may be within the normal range. Patients who are on adequate thyroxine replacement therapy have plasma T₄ levels which are slightly higher than normal (i.e. 16 - 32 pmol/L).
### Table 3.1  Free thyroid hormone plasma levels

<table>
<thead>
<tr>
<th></th>
<th>Primary hypothyroid</th>
<th>Lower borderline</th>
<th>Normal</th>
<th>Upper borderline</th>
<th>Primary hyperthyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mU/L)</td>
<td>&gt; 4.5</td>
<td>0.2 - 0.4</td>
<td>0.5 - 3.5</td>
<td>3.6 - 4.5</td>
<td>&lt; 0.2</td>
</tr>
<tr>
<td>Free T&lt;sub&gt;4&lt;/sub&gt; (pmol/L)</td>
<td>&lt; 8</td>
<td>8 - 12</td>
<td>13 - 23</td>
<td>24 - 26</td>
<td>&gt; 26</td>
</tr>
<tr>
<td>Free T&lt;sub&gt;3&lt;/sub&gt; (pmol/L)</td>
<td>4 - 8</td>
<td>8.1 - 10</td>
<td>&gt; 10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Free triiodothyronine

The FT<sub>3</sub> assay is a radioimmunoassay that uses a T<sub>3</sub> analogue tracer to measure the plasma non-protein bound T<sub>3</sub> fraction. While elevated levels confirm thyrotoxicosis, the FT<sub>3</sub> estimation is not a useful test to detect hypothyroidism because low levels only occur late in the disease.

### Other tests

For thyroid masses, ultrasonography is usually performed first to detect whether the enlargement is cystic, solid or multinodular. If it is solid, a radionuclide scan is performed. If a solitary ‘cold’ lesion is found, the mass is biopsied. The radionuclide scan will also detect ‘hot’ nodules and metastatic deposits. If the lesion is multinodular, serum autoantibodies (e.g. antithyroglobulin, antithyroid microsomal antibodies and thyroid-stimulating antibodies) are measured. A CT is performed if a thoracic inlet syndrome due to thoracic extension of the thyroid is suspected.

### THYROID FUNCTION IN NONTHYROIDAL ILLNESS

#### Euthyroid sick syndrome

In patients who have a severe nonthyroidal illness, the TSH level decreases (the degree of which is related to the severity of the illness<sup>9</sup>) and returns to normal within 24 - 48 hr. There is a decrease in FT<sub>3</sub> and increase in rT<sub>3</sub> which is caused by an inhibition of peripheral 5-monodeiodination (due to an increased cortisol level<sup>10</sup> and starvation<sup>11</sup>) which reduces the peripheral conversion of T<sub>4</sub> to T<sub>3</sub> and decreases the clearance of plasma rT<sub>3</sub>. The FT<sub>4</sub> levels are low or normal and the plasma half-life of T<sub>4</sub> is reduced from 7 days to 1 - 5 days.<sup>28</sup> The euthyroid state is maintained in the presence of a reduction in FT<sub>3</sub> levels due to an increase in synthesis of tissues T<sub>3</sub> receptors.<sup>12</sup> Protein binding for T<sub>4</sub> and T<sub>3</sub> is also reduced in acute nonthyroidal illness, contributing to the reduction in total T<sub>4</sub> and T<sub>3</sub> levels. During the recovery phase of the illness, there is often a transient elevation in the TSH level until the FT<sub>4</sub> and FT<sub>3</sub> levels are returned to normal.<sup>13,14</sup> Generally, abnormal thyroid function studies in an acutely ill patient (or during starvation) without clinical signs of thyroid disease should not be treated (as there are no studies that have shown a reduction in mortality with thyroid hormone treatment),<sup>15</sup> but should be reviewed after the acute illness has resolved.<sup>28</sup>

While plasma rT<sub>3</sub> is usually elevated in ‘euthyroid sick syndrome’ and unmeasurable in hypothyroid sick patients the plasma rT<sub>3</sub> level has not been found to differentiate reliably between the two disorders.<sup>16</sup>

#### Euthyroid hyperthyroxinaemia

This condition is characterised by high levels of total T<sub>4</sub> and FT<sub>4</sub>, and high, normal or low levels of FT<sub>3</sub>, in the absence of clinical signs of hyperthyroidism. It is associated with increased T<sub>4</sub> binding and peripheral thyroid-hormone resistance and is caused by drugs that inhibit T<sub>3</sub> formation (e.g. amiodarone, propranolol, cholecystographic contrast agents), heparin, L-
thyroxine therapy, acute psychiatric illness or stress, hyperemesis gravidarum, lead poisoning and hyponatraemia.17,18,19,20

REFERENCES
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Chapter 4

THYROID DISORDERS

SIMPLE (NONTOXIC) GOITRE

This is any enlargement of the thyroid gland, due to hypertrophy and hyperplasia, which is not the result of a neoplastic or inflammatory process and is not initially associated with myxoedema or thyrotoxicosis. The thyroid hypertrophy may be caused by excessive thyroid stimulation due iodine deficiency, ingestion of a goitrogen or a defect in the hormone biosynthetic pathway, although often the cause is unknown.

Clinical features

The thyroid-hormone profile is usually normal and the clinical manifestations, commonly due to the mechanical effects of the enlarged gland, include compression and displacement of the trachea or oesophagus, superior mediastinal obstruction, superior vena cava syndrome (may be associated with a positive Pemberton’s sign, i.e. raising hands above the head causes, facial suffusion, giddiness and syncope). Hoarseness due to recurrent laryngeal nerve damage is rare and suggests carcinoma.

Investigations

These include:

1. Thyroid function studies. These are performed to identify patients who may have toxic multinodular goitre.
2. CT scan. This is performed to identify the extent of thyroid enlargement (and whether there is intrathoracic extension, tracheal compression).
3. Fine needle aspiration. If a solitary nodule exists, then a fine needle aspiration is the test of choice.

Treatment

Thyroid hyperplasia is treated by reducing thyroid stimulation (i.e. reducing TSH secretion). If iodine deficiency or a specific goitrogen can be identified these abnormalities are corrected. Often no cause can be found and L-thyroxine 100 µg daily is administered, with the dose increasing over 4 - 8 weeks to a maximum of 150 - 200 µg/day. The gland should regress within 3 - 6 months of complete suppression of TSH (i.e. TSH level < 0.1 mU/L by an ultrasensitive assay). However, before thyroxine is administered, an ultrasensitive TSH level should be performed. If the TSH is less than 0.1 mU/L and a TRH stimulation test indicates functional autonomy of the thyroid gland, thyroxine administration will be of no benefit and the disorder is likely to be a toxic multinodular goitre. Treatment for the latter requires avoidance of iodine and either surgery (e.g. subtotal or total thyroidectomy) or high dose $^{131}$I.

HYPOTHYROIDISM

Myxoedema is a term applied to chronic hypothyroidism associated with a thickening of skin about the eyes, dorsum of hands and supraclavicular fossa, caused by an increased amount of hydrophilic polysaccharides, hyaluronic acid and chondroitin sulphate in the ground
Thyroid Disorders

substance of the dermis. Approximately 95% of hypothyroid patients have a primary hypothyroid disorder, the remaining 5% are secondary to pituitary or hypothalamic hypofunction.

Aetiology

Primary hypothyroidism may be caused by a congenital abnormality, autoimmune thyroiditis, postablative defect (e.g. surgical removal, radioiodine ablation) or goitrous defect (e.g. hereditary, iodine deficiency, lithium, amiodarone).

Clinical features

The clinical features include bradycardia, atrial fibrillation, hypotension, (cardiogenic shock responsive to triiodothyronine has even been reported), hypothermia (sometimes missed unless a ‘low reading’ thermometer is used), fatigue, lethargy, constipation, intolerance to cold (with erythema ab igne of legs), stiffness and cramping of muscles, thinning of the scalp hair (also thinning of the axillary and pubital hair), periorbital puffiness, a large tongue, pale cool skin, and the voice becomes deep and hoarse. Cerebellar ataxia, obstructive sleep apnoea and hypoventilation may also occur. The heart may be enlarged due to both dilation and pericardial effusion, the abdomen may protrude due to an adynamic ileus and, rarely, psychiatric symptoms (e.g. myxoedema madness) develop. The relaxation phase of deep tendon reflexes are characteristically prolonged (i.e. ‘hung up’) although this may also occur with hypothermia and myotonia.

Investigations

These include:

1. Plasma biochemistry. Hypercholesterolaemia, hyponatraemia, hypermagnesaemia, hypoglycaemia and increased CPK, LDH and AAT may be found.

2. Complete blood picture. A normocytic anaemia may occur. Approximately 12% of patients have pernicious anaemia.

3. ECG. Bradycardia, atrial fibrillation, low voltage QRS complexes, prolonged QTc, with generalised flattening or inversion of T waves may be found. In the event of severe hypothermia, J (Osborne) waves may also be present.

4. Arterial blood gases. Hypercapnia and hypoxia may be found in patients who have alveolar hypoventilation.

5. Thyroid function tests. The TSH is characteristically elevated (unless pituitary hypothyroidism exists) to levels above 20 mU/L and the FT4 and FT3 levels are low. Elevation of the TSH to levels of 5-10 mU/L with normal circulating levels of FT4 may represent a diminished thyroid reserve or ‘subclinical’ hypothyroidism. These patients are often followed up with 6 to 12-monthly thyroid function tests, with commencement of T4 replacement therapy if the TSH doubles from its previous level.

Treatment
Thyroid Disorders

Management of the hypothyroid patient depends upon whether the patient has non life-threatening hypothyroidism, hypothyroidism with angina or myxoedema coma.

**Non life threatening hypothyroidism.** Oral thyroxine 25 µg is administered daily and increased by 25 µg increments at 3 week intervals. The daily dose is administered as a single dose and usually increased until the symptoms resolve, the TSH and FT₄ return to normal limits, and the FT₄ is at the upper limit of normal (i.e. 16 - 32 pmol/L), which usually occurs at a daily dose of 1.8 µg/kg of thyroxine (i.e. 100 - 200 µg/day). If the TSH is elevated, the dose is often insufficient. If the FT₃ is elevated the dose may be excessive. Patients who are on adequate thyroxine replacement therapy often have plasma FT₄ levels which are slightly higher than normal (i.e. 16 - 32 pmol/L) and TSH values lower than normal (i.e. 0.05 - 0.2 mU/L). However, suppression of TSH for prolonged periods should be avoided because of potential adverse effects on morbidity (bone density, atrial fibrillation, dementia) and mortality.

Currently, it is recommended that the thyroxin dose be adjusted to maintain a normal plasma thyrotropin concentration. Indications for reducing the dose are new atrial fibrillation, accelerated loss of bone density, amenorrhea, tiredness, diarrhoea, palpitations or borderline high T₃ concentrations.

If the patient is unable to take oral thyroxine, then intravenous T₃ is administered, as a loading dose of 10 µg followed by an infusion of 20 µg/day. The total daily dose of T₃ ranges from 30 - 50 µg/day. The patients thyroid status is assessed by measuring the TSH and FT₃, or TSH only in acutely ill patients.

**Hypothyroidism with angina.** Hypothyroid patients with angina should be treated with thyroxine because angina improves in the majority of patients rather than worsens. In the event of worsening angina during treatment, heparin should be administered and coronary artery angiography and angioplasty or coronary artery bypass surgery may be required before the hypothyroid state can be corrected.

**Myxoedema coma.** If myxoedema is poorly controlled or remains undiagnosed, the patient may progress to become somnolent or unconscious, particularly if hypnotics or opioids are administered, or in the event of trauma, cerebral vascular accident, surgical operation, hypothermia, infection or hyponatraemia.

Treatment requires:

1. **Resuscitation.** If the patient is hypotensive, intravenous therapy and inotropic agents may be required, monitored with right heart and arterial pressure measurements. Infection requires appropriate antibiotics, and respiratory failure may require endotracheal intubation and careful mechanical ventilation because excessive ventilation will produce severe alkalosis and exacerbate the hypotension. Hypoglycaemia is treated with intravenous dextrose (50 mL of 50% dextrose) and monitored with 2- to 4-hourly blood glucose measurements. Hypothermia is managed by passive warming techniques. If the core temperature is less than 33°C active warming may be undertaken until the core temperature is 33 - 35°C.

2. **Thyroid hormone replacement.** Because thyroxine has a long biological half-life (i.e. 7 days c.f. 24 hr for T₃), requires peripheral conversion to T₃ (which is inhibited by systemic illness - see ‘euthyroid sick syndrome’) and excessive dosages may precipitate myocardial ischaemia or infarction, even in the presence of normal coronary arteries; T₃ is used for urgent thyroid hormone replacement. Experimentally, T₃ has been shown to reduce postischaemic dysfunction, and while high doses of T₃ (e.g. 0.8 µg/kg i.v.) used in the postoperative cardiothoracic bypass patient have not improved survival it does not increase the risk of ischaemic myocardial damage.
Urgent thyroid hormone replacement is achieved by administering 10 µg of T₃ as a bolus, (which has an onset time of 0.5 - 3 hr) followed by an infusion of 20 µg/day and increasing to 30 - 40 µg /day (using a 5% albumin as the T₃ carrier) and monitored with FT₃, TSH levels, ECG and haemodynamic measurements. The additional administration of 100 mg of T₄ is also recommended by some to saturate the large number of unsaturated binding sites.

3. Hydrocortisone: this is administered as an intravenous infusion (e.g. 200 mg/day), because an acute adrenal crisis may be precipitated by thyroxine treatment in hypothyroid patients.

THYROTOXICOSIS

Aetiology

Hyperthyroidism may be caused by, Grave’s disease, toxic multinodular goitre, toxic uninnodular goitre (i.e. adenoma), thyroiditis, excess thyroxine administration (i.e. factitious), drug induced (e.g. amiodarone, iodine, radiocontrast agents, lithium), pituitary TSH adenoma, ectopic TSH production (e.g. chorioncarcinoma, testicular carcinoma) or thyroid carcinoma.

Graves disease. This has three major manifestations: hyperthyroidism with diffuse goitre, dermopathy and ophthalmopathy. Any one of these may appear separately. It is caused by excess thyroid stimulation due to a circulating IgG immunoglobulin that attaches to the TSH receptor on the thyroid cell membrane. The disease is associated with other autoimmune diseases (e.g. pernicious anaemia, insulin-dependent diabetes, Addison’s disease and myasthenia). The hyperthyroidism of Grave’s disease is characterised by phases of exacerbation and remission, with the disease often leading to progressive thyroid failure and hypothyroidism.

Toxic multinodular goitre. This is often seen in the elderly patient who has a long history of goitre and is the result of an autonomous thyroid nodule. The onset of thyrotoxicosis is often subtle, and may present with resistant atrial fibrillation and myopathy (i.e. as an ‘apathetic’ thyrotoxicosis).

Clinical features

The symptoms include agitation, emotional lability, insomnia, increased appetite, weight loss, loose stools, vomiting, excessive sweating, heat intolerance, hairloss, pruritus, undue fatigue, proximal myopathy (e.g. difficulty in rising from a chair, climbing stairs or keeping a leg extended), dyspnoea, palpitations, gynaecomastia and amenorrhoea.

The signs include palmar erythema, warm moist skin, soft finger pulps (acropachy) clubbing, onycholysis (separation of nail from its bed, particularly the distal portion of the ring finger), pretibial myxoedema (i.e. raised violaceous induration of skin overlying the pretibial area and dorsum of feet in patients with Grave’s disease; it may rarely appear on the dorsum of hands and face as peau d’orange), tachycardia, atrial fibrillation, wide pulse pressure, high output cardiac failure, fine tremor, hyperreflexia, proximal myopathy (with a ‘duck waddle’ walk), periodic paralysis, myasthenia, diffuse goitre, and thyroid bruit. In Grave’s disease there are also characteristic ocular signs of:

- Sympathetic overstimulation (e.g. widened palpebral fissure, stare, lid lag, failure to wrinkle brow with upward gaze, tremor of lightly closed lids)
- Ophthalmplegia (e.g. inability to gaze upward and outward, failure to converge, proptosis)
- Congestive oculopathy (e.g. chemosis, conjunctivitis, periorbital swelling, corneal ulceration)
- Other manifestations (e.g. optic neuritis, optic atrophy, enlarged lacrimal glands).
Apathetic thyrotoxicosis is a rare clinical presentation of thyrotoxicosis; it usually occurs in an elderly patient and cardiac failure, rapid and resistant atrial fibrillation and severe myopathy dominate the clinical picture.

Subclinical hyperthyroidism (e.g. normal plasma thyroid hormone levels and low thyrotropin levels) is associated with an increased incidence of atrial fibrillation and increased all cause mortality.

Investigations

These include:

1. **Plasma biochemistry.** Hypokalaemia, hypercalcaemia, hypomagnesaemia, increased alkaline phosphatase, hyperglycaemia, renal tubular acidosis (type I), and hyperbilirubinaemia often occur.

2. **Complete blood picture.** A mild leucocytosis may be present.

3. **Thyroid function studies.** The plasma TSH is unrecordable and unresponsive to TRH stimulation, and the FT$_3$ and FT$_4$ levels are elevated. Rarely, the FT$_4$ is elevated in isolation, in patients who have a T$_3$ thyrotoxicosis variant. Subclinical hyperthyroidism has been defined as a thyrotropin concentration less than 0.1 mU/L (as measured by second generation or third generation sTSH assays) with plasma thyroid hormone levels within the normal range in the absence of pituitary-hypothalamic dysfunction, an acute non-thyroidal illness or treatment with dopamine, dobutamine or high doses of glucocorticoids.

Treatment of non life-threatening thyrotoxicosis

Management may vary depending on whether the thyrotoxicosis is non life-threatening or life threatening (i.e. thyrotoxic crisis; see later). Therapy consists of measures to reduce T$_3$ and T$_4$ synthesis and release, reduce peripheral conversion of T$_4$ to T$_3$, and inhibit the peripheral effects of T$_3$ and T$_4$.

**Antithyroid drugs.** The antithyroid drugs of carbimazole, methimazole and propylthiouracil are commonly used. Carbimazole is metabolised to methimazole and so these two agents are considered to be interchangeable (methimazole dose is approximately 2/3 that of carbimazole). The antithyroid drugs are ineffective against thyrotoxicosis associated with thyroiditis or toxic adenoma and should not be used in these disorders. As propylthiouracil also blocks peripheral conversion of T$_4$ to T$_3$ and is highly protein bound, it is often preferred to carbimazole in thyrotoxic crisis or during pregnancy or lactation.

1. **Propylthiouracil** may be used in partially suppressing doses of 300 - 600 mg a day (100 - 200 mg 8-hourly, as the half-life is 6 hr), reducing by half after 2 - 6 weeks and keeping the FT$_4$ at midnormal levels and the TSH levels suppressed. Another regimen uses propylthiouracil at 200 - 300 mg 4 to 6-hourly to completely suppress the thyroid gland, which requires additional T$_4$ replacement therapy (e.g. 100 µg/day) as well. As the latter regimen completely suppresses TSH, it will also reduce the size of a goitre. Treatment is continued for 6 - 24 months, thereafter reducing the dose and reviewing the patient for biochemical and clinical signs of a return in thyrotoxicosis.

2. **Carbimazole** has a half-life of 6 - 8 hr (i.e. can be given as a single daily dose), is 10 times as potent and is probably less toxic than propylthiouracil, although it has no effect on the peripheral conversion of T$_4$ to T$_3$. The standard dose is 10 - 40 mg daily, or 40 - 60 mg daily with T$_4$ supplementation.
In approximately 5% of patients who are treated with antithyroid drugs, side-effects occur and usually within the first 2 months of treatment. Leucopenia occurs in 0.5% of patients and is the most serious side effect. As it occurs suddenly, routine monitoring of the neutrophil count is of little value. A neutrophil count is performed before therapy and the patient is asked to stop therapy and to report if a fever, mouth ulcers, pharyngitis or stomatitis occur. If the neutrophil count decreases to 1500/mm$^3$ or less, the drug should be discontinued. The agranulocytosis is self limiting and usually only lasts 5 - 15 days, which may resolve more rapidly with glucocorticoid treatment or granulocyte-colony stimulating factor therapy.

Other side-effects include, aplastic anaemia, thrombocytopenia, hepatitis, cholestatic jaundice, nausea, vomiting, headache, skin rashes, urticaria, vasculitis, pruritus, arthralgia, myalgia and fever.

**Beta adrenergic receptor blockers.** Propranolol reduces the peripheral effects of thyroid hormones as well as reducing the peripheral conversion of T$_4$ to T$_3$. The adrenergic-excess like features (probably caused by an increase in tissue adrenergic receptor density as circulating catecholamine levels are usually low) of tachycardia, fever, tremor and agitation often respond rapidly. Beta-adrenergic receptor blockers should not be used in the presence of cardiac failure.

**Ablative therapy.** Partial thyroidectomy or radioactive iodine are used if the disease recurs following drug therapy, if drug toxicity has occurred, or if a large goitre, toxic multinodular goitre or adenoma, exist. Preoperative preparation for partial thyroidectomy is usually undertaken with propranolol (e.g. 40 - 200 mg orally for 1 - 2 weeks, which is continued for 2 - 8 weeks postoperatively); this allows surgery to be performed safely in patients who have moderate hyperthyroidism.

**Thyrotoxic crisis and its treatment**

Thyrotoxic crisis is often precipitated in a poorly controlled or previously undiagnosed thyrotoxic patient, by infection, trauma, surgery, labour or pre-eclampsia, or it may be caused by a massive overdose of thyroxine. Overdoses of up to 10 mg of thyroxine are usually well tolerated. However, with massive overdoses (e.g., 70 - 1200 mg over 2 - 12 days), signs of thyrotoxicosis develop within 3 days and thyrotoxic crisis and coma usually develop after 7 - 10 days.

**Clinical features.** Thyrotoxic crisis is characterised by hyperpyrexia, irritability, delirium, coma, muscle weakness, rhabdomyolysis, sinus tachycardia, atrial or ventricular tachyarrhythmias, hypotension, vomiting, abdominal pain and diarrhoea. Rarely, (particularly in elderly patients) it may present as an apathetic crisis with severe myopathy, tachycardia, hypotension and coma. The differential diagnosis are delirium tremens, opiate withdrawal, phaeochromocytoma, panic attack, mania and amphetamine overdosage.

**Treatment.** This includes:

1. **Resuscitation.** Supportive care with fluids, dextrose and B group vitamins. Ideally oxygen consumption studies and close haemodynamic monitoring should be performed. Digoxin, beta-blockers, verapamil, and amiodarone (which also inhibits peripheral conversion of T$_4$ to T$_3$; its metabolism also yields 3 mg (24 µmol) of free iodine per 100 mg) have all been used to control atrial arrhythmias.

2. **Antithyroid drugs**
   a. **Propylthiouracil** 1000 mg orally (or via the nasogastric tube) as a loading dose followed by 100 mg 2-hourly, is the treatment of choice because it also inhibits peripheral conversion of T$_4$ to T$_3$. 

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b. Carbimazole 60 - 100 mg as a loading dose, followed by 100 - 120 mg/day may be administered if propylthiouracil is contraindicated.

3. Iodine. Large doses of iodine immediately inhibit the uptake of iodine and release of thyroid hormone from a hyperfunctioning gland (Wolff-Chaikoff effect). However, the effect is transient (i.e. lasts 1 - 4 weeks), and iodine should be administered at least 1 hr after antithyroid drugs have been given. Sodium ipodate (1 g/day orally), a radiocontrast agent, also inhibits peripheral conversion of T₄ to T₃, and is often used; otherwise 500 - 1000 mg of sodium iodide is infused intravenously every 8 hr. Lithium (500 - 1000 mg) has been used as an alternative to iodine in patients sensitive to iodine; however, a steady state is achieved only after 5 - 6 days and it only weakly inhibits thyroid hormone release and synthesis. While frequent lithium levels are required to ensure nontoxic levels (i.e. < 1.5 mmol/L).

4. Beta blockers. Propranolol 40 - 200 mg orally usually alleviates the adrenergic-excess like effects. For rapid effect, 1 - 2 mg of propranolol may be administered intravenously over 5 min up to a total of 20 mg, or until the desired effect is achieved. The fever, tachycardia, diaphoresis, agitation, tremor and myopathic features usually respond rapidly. While selective beta-1 blockers do not inhibit peripheral conversion of T₄ to T₃ as effectively as propranolol, these agents may be used in patients with reactive airways (e.g. asthma, COPD). If heart failure exists then beta blockers may cause a marked deterioration in cardiac function leading to severe cardiac failure or cardiogenic shock. Cardiac failure and atrial fibrillation in these circumstances should be treated with digoxin (which may require a higher than normal dose).

5. Dexamethasone. 4 mg 6-hourly, dexamethasone reduces the conversion of T₄ to T₃ and therefore is administered to severely thyrotoxic patients.

6. Other therapy
   a. Oral activated charcoal is used in patients with severe thyroxine overdosage.
   b. Plasmapheresis will increase T₄ clearance in severe thyroxine overdosage (i.e 70 - 1200 mg over 2-12 days) and has also been used in thyrotoxic crisis. In one report of a patient who ingested 6 mg of thyroxine, plasmapheresis was of no significant pharmacokinetic or clinical benefit.
   c. Dantrolene has also been used successfully in a patient in whom the thyrotoxic crisis mimicked malignant hyperpyrexia.

REFERENCES
Chapter 5

DIABETES MELLITUS

Diabetes mellitus is a chronic disorder caused by an insulin deficiency or insulin resistance, which is characterised by an elevated plasma glucose concentration and long-term complications involving the eyes, kidneys, nerves and blood vessels.

Insulin is synthesised in the beta cells of the islets of Langerhans as a polypeptide precursor known as preproinsulin, which is converted to an 86 amino acid polypeptide called proinsulin. Proinsulin has only 5 - 10% of the activity of insulin in enhancing peripheral glucose uptake, although it may be more active than insulin in suppressing hepatic production of glucose. Proinsulin forms an equal amount of insulin and C peptide which are stored in membrane bound granules. Elevated glucose levels increase intracellular ATP which closes the pancreatic beta-cell ATP-sensitive K channels, prolonging depolarisation and allowing Ca$^{2+}$ to enter the cell which in turn causes the granules fuse with the cell wall and release equal amounts of insulin and C peptide to the exterior by exocytosis. Insulin is secreted into the portal system in the basal state at a rate of 0.5 to 1 U/hr increasing to 5 - 10 U during a meal. The insulin secretion is markedly reduced with exercise.

Insulin binds to its plasma membrane receptor and sets in motion the translocation of intracellular vesicles containing the transmembrane glucose transporter (GLUT-4) to the cell surface to fuse with the plasma membrane, increasing the number of GLUT-4 molecules in the membrane and thus the rate of glucose transport into the cell. Exercise also increases translocation of GLUT-4 containing vesicles to the cell membrane. Translocation of the GLUT-4 vesicles is inhibited in patients with type II diabetes and by TNF-α.

The total daily secretion of insulin is approximately 40 U/day (50% of which is removed by the liver). In normal man, fasting insulin levels range from 1 - 10 mU/L and peak at about 50 mU/L following a meal.

CLASSIFICATION

Type I diabetes (insulin-dependent diabetes mellitus or IDDM)

This condition is caused by an immunologically mediated destruction of the insulin-secreting islet cells (i.e. an insulitis), which results in an absolute insulin deficiency, a dependence on insulin therapy and a proneness to ketosis. It usually begins before the age of 40 and characteristically at around 14 years of age (i.e. at puberty). The plasma insulin and C peptide levels are low or unmeasurable and glucagon levels are elevated. Once the diagnosis is made, the patient usually requires insulin, although occasionally, following the resolution of an intercurrent illness, the patient may have a period of up to 1 year of normoglycaemia before insulin is required.

During this early or prediabetic phase of the illness, agents which provide an immune tolerance to the enzyme glutamic acid decarboxylase (GAD), in experimental studies, have arrested the autoimmune damage and prevented diabetes. Others have reported a reduction in the frequency of diabetes when BCG or complete Freund’s adjuvant are administered to
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patients late (i.e. 11 weeks) in the prediabetic phase (perhaps by channelling the immune response away from beta cell destruction).  

**Type II diabetes (non insulin dependent diabetes mellitus or NIDDM)**

This condition is associated with two defects, 1) insulin resistance and, 2) a relative insulin deficiency. Hyperglycaemia does not develop until a defect in the insulin secretion occurs. The glucose abnormalities are often mild and there is no proneness to ketosis. Most patients are obese and the diagnosis is often made in an asymptomatic individual on routine blood examination. The insulin levels are normal to high (but relative to the blood glucose level they are low) and there is an exaggerated glucagon response to ingested nutrients. If significant weight loss is able to be achieved, most patients are able to be managed by diet alone. Failing this, sulphonylureas are used although insulin may also be required.

**Other specific types (e.g. endocrinopathies, diseases of the exocrine pancreas)**

Diabetes may be caused by pancreatitis, haemochromatosis, hormonal disturbances (e.g. acromegaly, phaeochromocytoma, Cushing’s syndrome, endogenous glucocorticoid administration) drugs or stress.

**Gestational diabetes**

Gestational diabetes is a disorder of carbohydrate metabolism which has its onset during pregnancy and is due to the distinctive hormonal environment and metabolic demands of pregnancy. The disorder remits after parturition, although it is a risk factor for the development of type II diabetes in later years.

**CLINICAL FEATURES**

The clinical features are those which are associated with hyperglycaemia (e.g. glycosuria, polyuria, polydipsia, nocturia, polyphagia, weight loss, deterioration in consciousness), ketosis (e.g. Kussmaul breathing, sweet breath) and degenerative disorders (e.g. neuropathy, retinopathy, nephropathy). The degenerative disorders, which often present as late complications, are listed in Table 5.1.

**INVESTIGATIONS**

These include:

1. *Fasting or random blood glucose concentration ≥ 7 mmol/L*. The blood glucose levels vary depending on whether they are measured in venous plasma, capillary plasma, venous whole blood or capillary whole blood (e.g. whole-blood glucose levels may be of to 13% lower than plasma glucose levels). Ideally blood glucose levels should be measured on a venous plasma sample. This is all that is required to diagnose diabetes in routine clinical practice.

2. *Oral glucose tolerance test*. This is now no longer needed to diagnose diabetes in routine clinical practice. Before the test is performed the patient the patient must be in good health for at least 2 weeks prior to the test as an abnormal glucose tolerance test may be associated with many conditions (e.g. Table 5.2). Also the patient should ingest at least 150 g of carbohydrate for the previous 3 days (i.e. at least an extra three slices of bread per day if in doubt). For 8 hr before the test the patient should undergo an absolute fast (apart from water), with no alcohol, no smoking and no undue exercise. During the test the patient should lie in a semirecumbent position and not smoke. Venous blood samples are taken in the morning after the 8 hr fast, and again at 1 and 2 hr after 75 g of glucose (dextrose monohydrate not anhydrous dextrose) in 300 mL of water, ingested over 5 min (i.e. 300 mL of a 25% dextrose solution), or, in children, 1.75 g of glucose per kilogram (up to 75 g).
Table 5.1  Late complications of diabetes mellitus

**Atherosclerosis**
- Ischaemic heart disease, myocardial infarction (painless)
- Hypertension
- Cerebrovascular accidents
- Gangrene of limb, foot ulcers

**Retinopathy**
- Capillary microaneurysms, venous dilation
- Haemorrhages, waxy exudates
- New vessel formation, vitreous haemorrhages
- Fibrotic bands, retinal destruction, blindness

**Other ocular manifestations**
- Cataracts
- Horner’s syndrome
- Diplopia with sudden III, IV or VI cranial nerve palsies
- Argyl Robertson pupil
- Osmotic accommodation changes
- Arcus senilis, xantholesma

**Nephropathy**
- Chronic renal failure
- Nephrotic syndrome
- Papillary necrosis
- Preponderance for urinary tract infection

**Peripheral and autonomic neuropathy**
- Gastric stasis, diarrhoea
- Postural hypotension
- Foot ulcers
- Diminished sweating
- Bladder retention
- Neuropathic joints
- Impotence

**Skin lesions**
- Necrobiosis lipoidica (destruction of collagen)
- Lipodystrophy
- Moniliasis of nails
- Xantholesma

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*Guidelines for the diagnosis of abnormal glucose tolerance*¹³,¹⁴

1. *If symptoms of diabetes are present,*
   a. a fasting venous plasma glucose level of 7 mmol/L or greater is diagnostic of diabetes mellitus
   b. a plasma glucose level taken at least two hours after last eating of 11.1 mmol/L or greater is diagnostic of diabetes mellitus.
   c. if a random venous plasma glucose value lies in the uncertain range (i.e., 5.5 - 11.0 mmol/L), further investigations may be necessary.
2. If symptoms of diabetes are absent,
a. at least two test results with values in the diabetic range are desirable, from a fasting or a random sample, or from the oral glucose tolerance test.
3. Diagnostic values of the oral glucose tolerance test, these are shown in Table 5.3.

**Table 5.2. Causes of an abnormal glucose tolerance test**

<table>
<thead>
<tr>
<th>Prolonged inactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress within the previous 12 weeks</td>
</tr>
<tr>
<td>(e.g. myocardial infarct, stroke, trauma or surgery)</td>
</tr>
<tr>
<td>Stress within the previous 2 weeks</td>
</tr>
<tr>
<td>(e.g. fever, ‘flu’, gastroenteritis)</td>
</tr>
<tr>
<td>Starvation, recent weight loss, recent weight gain of more than 2 kg</td>
</tr>
<tr>
<td>Hypokalaemia</td>
</tr>
<tr>
<td>Hepatocellular disease</td>
</tr>
<tr>
<td>Endocrinopathies</td>
</tr>
<tr>
<td>hyperthyroidism, Cushing’s syndrome, acromegaly, phaeochromocytoma</td>
</tr>
<tr>
<td>Pyridoxine deficiency</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>oestrogens, ovulation suppressants, corticosteroids, cyclosporine</td>
</tr>
<tr>
<td>thiazides, frusemide, ethacrinic acid, phenothiazines, tricyclics</td>
</tr>
<tr>
<td>phenytoin, diazoxide, minoxidil, salicylates, nicotinic acid, salbutamol.</td>
</tr>
</tbody>
</table>

**Table 5.3 Diagnostic values of the 75 g oral glucose tolerance test**

<table>
<thead>
<tr>
<th>Glucose concentration (mmol/L)</th>
<th>Venous plasma</th>
<th>Capillary plasma</th>
<th>Venous whole blood</th>
<th>Capillary whole blood</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting value</td>
<td>≥ 7.0</td>
<td>≥ 7.0</td>
<td>≥ 6.1</td>
<td>≥ 6.1</td>
</tr>
<tr>
<td>2 hr after glucose load</td>
<td>≥ 11.1</td>
<td>≥ 12.2</td>
<td>≥ 10.0</td>
<td>≥ 11.1</td>
</tr>
<tr>
<td><strong>Impaired glucose tolerance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting value</td>
<td>&lt; 7.0</td>
<td>&lt; 7.0</td>
<td>&lt; 6.1</td>
<td>&lt; 6.1</td>
</tr>
<tr>
<td>2 hr after glucose load</td>
<td>7.8 - 11.0</td>
<td>8.9 - 12.1</td>
<td>6.7 - 9.9</td>
<td>7.8 - 11.0</td>
</tr>
</tbody>
</table>

While glucose intolerance is not the fundamental defect in diabetes mellitus, there is no suitable alternative to the oral glucose tolerance test as a screening test when glucose levels lie in an uncertain range; although HbA\textsubscript{1c} levels of > 7.0% may be useful in identifying patients with glucose intolerance who require treatment.\textsuperscript{15} It is believed that the degree of hyperglycaemia is relevant to the development of microangiopathy, as shown in the eye and kidney, and a 2 hr blood glucose greater than 11 mmol/L has been identified as the point above which the relative risk of retinopathy rises. Selection of the value of 11 mmol/L has also taken into account the observation that below a 2 hr concentration of 11 mmol/L, spontaneous remissions to normal glucose tolerance may occur in some people.\textsuperscript{15}
In one study of patients with type I diabetes between the ages of 13 and 39 years, where insulin was used to keep the preprandial blood sugar levels between 3.9 and 6.7 mmol/L and the postprandial level lower than 10 mmol/L, the onset of diabetic retinopathy, nephropathy and neuropathy was effectively delayed and the progression of microangiopathy was slowed, although there was a two-to-threefold increase in the incidence of severe hypoglycaemia.\textsuperscript{16}

**TREATMENT**

The main aim in the management of patients with diabetes mellitus is to minimise the impact of complications. In the short-term this means preventing the effects of insulin resistance, hypoinsulinaemia or hyperinsulinaemia (i.e. maintenance of normoglycaemia), and in the long term preventing the development and progression of vascular complications.

In type II diabetes if the glycemic goals are not met with a 3-month trial of diet and exercise, pharmacologic agents (e.g. sulfonylureas, metformin, acarbose, troglitazone, insulin) should be initiated.\textsuperscript{17} However, in one large study comparing conventional treatment (e.g. diet, exercise, weight reduction and tolerating blood glucose levels < 15 mmol/L) with an ‘intensive’ normoglycaemic strategy (e.g. using sulphonylureas supplemented with insulin to maintain premeal blood glucose between 4 - 7 mmol/L), while the ‘intensive’ normoglycaemic strategy affected diabetes-related events beneficially (i.e. improved microvascular outcomes), it did not change diabetes-related or all cause mortality (i.e. did not change macrovascular outcomes).\textsuperscript{18} However, in the group of obese type 2 diabetic patients treated with metformin, a lower diabetes mortality and all cause mortality was recorded compared to the conventionally treated group (although sulfonylurea-treated patients given metformin early had an increased diabetes and all cause mortality).\textsuperscript{19}

**Lifestyle**

Weight reduction, cease smoking, reduction in alcohol and regular exercise should be encouraged to improve glucose tolerance as well as to reduce the patients atherogenic risk.\textsuperscript{20}

**Diet**

An estimate is made of the total daily energy intake, based on ideal body weight, which ranges from 42 kcal/kg body weight (i.e. 175 kJ/kg) in an 18-year-old man to 30 kcal/kg body weight (140 kJ/kg) in a 75-year-old woman. The protein requirement is 0.9 g/kg, and the recommended carbohydrate content is 55 - 60% of total energy intake (although up to 85% has been prescribed). The remainder of the energy intake (i.e. 30-35%) usually consists of polyunsaturated fat. Refined sugars usually provoke postprandial hyperglycaemia and are not recommended.

As the average serve of most foods (e.g. one slice of bread) provides approximately 15 g of carbohydrate, the measure of an average serve of carbohydrate is 15 g. This is known as an ‘exchange’, which has replaced the 10 g carbohydrate ‘portion’. The partitioning of calories for each meal for type I diabetic patients depends upon lifestyles, and a typical pattern is 20% for breakfast, 35% for lunch, 30% for dinner and 15% for evening meal.

**Insulin**

There are three types of insulin preparations which are categorised according to their absorption characteristics: short-, intermediate- and long-acting (slow onset). Information concerning the duration of action and peak activity time of insulins (Table 5.4)\textsuperscript{21} should only be regarded as approximate, as there are large variations between and within individuals.\textsuperscript{1} In a recent study of subcutaneously injected regular insulin, the blood glucose began to decrease in 1 - 2 hr (range 0.5 - 2 hr), reached its nadir in 5.7 hr (range 4 - 8 hr) and had a total duration of
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16.2 hr (range 9 - 24 hr), values which are considerably longer than standard teachings. Furthermore, the larger the dose, the longer the peak effect and duration of insulin, and exercise and different subcutaneous sites cause variation in insulin absorption rates (e.g. the abdominal wall causes regular insulin to decrease 86% faster than from the leg and 30% faster than from the arm, and exercise reduces the insulin absorption time). Insulin lispro is a human insulin analogue (where the natural sequence of proline at position B28 and lysine at position B29 is reversed - which hinders the ability of insulin monomers to form dimers) which is absorbed subcutaneously more rapidly than regular insulin (causing an earlier plasma peak level, e.g. 40 minutes, compared to regular insulin e.g. 100 minutes) with a duration of action of about 3 hours compared with 5 hours for regular insulin.

<table>
<thead>
<tr>
<th>Table 5.4</th>
<th>Characteristics of currently available insulins</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-acting</strong></td>
<td><strong>Trade name</strong></td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>(hr)</td>
</tr>
<tr>
<td>Insulin soluble</td>
<td>Insulin-2</td>
</tr>
<tr>
<td>Insulin neutral</td>
<td>Actrapid</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td><strong>Trade name</strong></td>
</tr>
<tr>
<td>Insulin isophane</td>
<td>Isotard MC</td>
</tr>
<tr>
<td>Protaphane HM</td>
<td>6 - 12</td>
</tr>
<tr>
<td>Insulin zinc suspension</td>
<td>Lente MC</td>
</tr>
<tr>
<td>Monotard HM</td>
<td>6 - 14</td>
</tr>
<tr>
<td><strong>Slow-onset</strong></td>
<td><strong>Trade name</strong></td>
</tr>
<tr>
<td>Insulin zinc suspension</td>
<td>Ultralente MC</td>
</tr>
<tr>
<td>Ultratard HM</td>
<td>10 - 24</td>
</tr>
<tr>
<td>Insulin protamine Zinc</td>
<td>Protamine zinc MC</td>
</tr>
<tr>
<td>HOE 901</td>
<td>10 - 24</td>
</tr>
</tbody>
</table>

Conventional treatment involves 1 - 2 subcutaneous injections a day of intermediate-acting insulin, with or without addition of a short-acting insulin. Long-acting insulin may be used for baseline insulin requirements with the addition of a short-acting preparation before each meal.

Daily production of insulin in a standard non-diabetic adult is approximately 40 U/day, although only 50% enters the systemic circulation, as 50% of the insulin released into the portal system is removed by the liver. Therapy may begin with 20 U/day (25 - 30 U/day for obese patients) as a subcutaneous injection. Changes in insulin therapy should be by 5 - 10 U, after 3 - 5 days, and modified by blood sugar levels. If the blood sugar level is poorly controlled, then two-thirds of the injection may be administered before breakfast and one-third before supper (usually required if the total insulin dose is greater than 50 U/day). Other techniques to enhance blood glucose control involve multiple injections or continuous subcutaneous insulin infusions. Insulin should be reduced if exercise is anticipated.

Insulin resistance is defined as a state in which normal amounts of insulin (0.5 U/kg/day) produces a subnormal biological response. However, for most type 1 diabetes patients the total daily dose of insulin is 0.5 - 1 U/kg and most clinicians usually do not consider patients...
resistant to insulin until the dose exceeds 2 U/kg/day, although this clearly exceeds the amount required for physiological replacement.  

**Oral agents**

**Sulphonylureas**

The sulphonylureas act primarily by increasing the beta-cell sensitivity to glucose (by closing the ATP-sensitive K channels, decreasing the islet cell-membrane permeability to potassium, prolonging depolarisation and allowing more Ca to enter the cell), so that more insulin is released at every level of blood glucose. They do not increase the synthesis of insulin and therefore are of no value in type I diabetes.

Oral agents should be given to a type II diabetes patient when diet has failed. Alcohol may potentiate oral hypoglycaemics, whereas thiazide diuretics, and oral contraceptives have a hyperglycaemic effect (although the latter rarely disturb diabetic control). Long-acting sulphonylureas should only be used for patients under the age of 65 who have normal renal function. Treatment should be started with the minimum dose (Table 5.5). The average fall in fasting blood glucose is 25% (i.e. 3 mmol/L), ranging from 20% - 30% (i.e. 2.2 - 4.4 mmol/L). Secondary failure, defined as the recurrence of symptomatic hyperglycaemia (with fasting blood glucose concentrations of approximately 13.9 mmol/L), occurs in approximately 10% of patients per year, requiring additional therapy to improve glycaemic control.

The side-effects include rashes, pruritus, weight gain, hyponatraemia, adverse reaction to alcohol (disulfiram reaction), nausea, vomiting, cholestasis, haemolytic anaemia, bone marrow aplasia and hypoglycaemia.

<table>
<thead>
<tr>
<th>Table 5.5 Oral hypoglycaemic agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Acetohexamide</td>
</tr>
<tr>
<td>Chlorpropamide</td>
</tr>
<tr>
<td>Glibenclamide</td>
</tr>
<tr>
<td>Glipizide</td>
</tr>
<tr>
<td>Gliquidone</td>
</tr>
<tr>
<td>Tolazamide</td>
</tr>
<tr>
<td>Tolbutamide</td>
</tr>
<tr>
<td>Metformin</td>
</tr>
</tbody>
</table>

**Biguanides**

Metformin (dimethylbiguanide) acts as an hypoglycaemic agent by decreasing the hepatic glucose output, which is accounted for largely by the inhibition of hepatic gluconeogenesis. It also improves glycaemic control by increasing the efficiency of skeletal muscle glucose uptake (particularly at high doses), increasing the insulin-mediated glucose disposal and (by decreasing the patient’s appetite) reducing caloric intake. It is not effective in the absence of insulin. Metformin is usually reserved for the obese diabetic with poor dietary compliance, because, unlike insulin and the sulphonylureas, it is not likely to cause weight gain and results in a 10% - 20% reduction in plasma triglyceride levels. It is contraindicated in renal insufficiency (as it is excreted entirely by the kidneys), pregnancy, liver disease, alcoholism, and cardiopulmonary insufficiency (as tissue anoxia and cellular metabolism may promote the
Diabetes Mellitus

The fasting blood glucose levels fall on average by 2-3 mmol/L. The initial dose of metformin is 500 mg daily, which may be increased up to 1 g 8-hourly (Table 5.5). The side-effects include decreased appetite, nausea, diarrhoea, decreased plasma vitamin B12, lactic acidosis and rarely hypoglycaemia (i.e. hypoglycaemia is less likely than with sulphonylureas).

Metformin can be used alone or in conjunction with sulphonylureas, as it is well tolerated and improves glycemic control and lipid concentrations in patients with type II diabetes who are unresponsive to diet or sulphonylurea therapy (e.g. after a 6 month trial of monotherapy). If treatment targets are not achieved, insulin should be added or substituted.

Adjunctive drugs

α-glucosidase inhibitors

Acarbose (a complex oligosaccharide with a m.w. of 645.6 and a low systemic bioavailability) and miglitol reversibly inhibit intestinal α-glucosidases, impairing polysaccharide (but not monosaccharide) digestion and therefore carbohydrate absorption. While they reduce the postprandial blood glucose levels by up to 3 mmol/L, the fasting blood glucose levels and haemoglobin A1c may only fall slightly and the carbohydrate malabsorption often causes gastrointestinal problems of flatulence, diarrhoea and bloating.

Thiazolidinediones

The thiazolidinediones increase insulin sensitivity on glucose and lipid metabolism (they have no effect in the absence of insulin) in the adipose tissue and skeletal muscle. They also reduce hepatic glucose output and very-low density lipoprotein (VLDL) levels and increase high density lipoprotein (HDL) levels. The mechanism is distinct from metformin. These agents are believed to bind to and activate the gamma isoform of the peroxisome proliferator-activated receptor (PPARγ), which then binds to a specific region of DNA and regulates the transcription of many genes involved in glucose and fatty acid metabolism.

Troglitazone was the first agent of this class and was effective, but was withdrawn because of the side effect of severe and unpredictable hepatic failure. Rosiglitazone (2 mg twice daily) and pioglitazone (15 - 45 mg daily) are newer thiazolidinediones that have not been associated with hepatotoxicity and have been approved for use as monotherapy or in combination with sulfonylureas, metformin or insulin in patients with type 2 diabetes with inadequate glycaemic control. While rosiglitazone and pioglitazone have not been associated with hepatotoxicity, it is recommended that liver function tests be performed at baseline and 2-monthly for the first year of therapy and periodically thereafter. If the ALT increases more than three times normal during treatment then the drug should be discontinued.

Serotonergic drugs

The serotonergic drug D-fenfluramine reduces food intake and may be useful in the obese diabetic with poor dietary compliance. It also enhances glucose uptake into muscle and fat. Fasting blood glucose can fall by 2 - 3 mmol/L.

Recombinant human IGF-I

A moderate dose of (40 µg/kg/day) recombinant human IGF-I (rhIGF-I) when given as an adjunct to insulin therapy has been reported to reduce HbA1c levels. The proposed additional benefits of this treatment are to reduce retinopathy and nephropathy by reducing the circulating GH levels.

Islet transplantation

Islets (separated from the donor pancreas by gentle mechanical dissociation and purifed) have been transplanted successfully in animals and in humans (maintaining tight glycaemic
control for nine to 12 months after the procedure\textsuperscript{47} and may in future be used in the management of diabetic patients.\textsuperscript{48,49}

**Choice of agent**

There is little to choose between the oral hypoglycaemic agents, other than if the patient has significant renal failure, tolbutamide or tolazamide should be used. Chlorpropamide has the advantage of being able to be prescribed as a single daily dosage. Oral hypoglycaemic agents rarely cause hypoglycaemia; however, if they do, the patient should be admitted to hospital, because the hypoglycaemic episode is usually severe and prolonged. If hypoglycaemic agents do not control the blood glucose, insulin therapy should be considered.

**Biochemical monitoring**

Ideal control of blood glucose concentration, delays or prevents many of the long term complications of diabetes.\textsuperscript{50} For the type I diabetic patient, blood sugar levels are regularly measured to adjust the dose of insulin. Lipid studies should also be performed to assess the metabolic control of diabetic patients.

**Glycosylated (glycated or glyco) haemoglobin (Hb A\textsubscript{1c}).** Glycohaemoglobin is a compound which is formed by a non-enzymatic (and irreversible) interaction between glucose and the amino groups of valine and lysine residues of haemoglobin. The level of HbA\textsubscript{1c} increases during episodes of hyperglycaemia and for patients in whom blood sugar control may be less than ideal, a measurement of HbA\textsubscript{1c} indicates the degree of long term blood glucose control (i.e. the average ambient glycaemia over the preceding 4 - 5 weeks). The risk of microalbuminuria in patients with type I diabetes increases markedly when HbA\textsubscript{1c} levels are 8.1\% (which corresponds to an average daily blood glucose of 11.1 mmol/L)\textsuperscript{51} or greater, indicating that efforts to reduce diabetic nephropathy should focus on reducing the HbA\textsubscript{1c} levels below this threshold.\textsuperscript{52} For retinopathy the HbA\textsubscript{1c} threshold is slightly higher (8.5\% - 9\%).\textsuperscript{51} However, while non diabetic patients have HbA\textsubscript{1c} levels of up to 6\%, if diabetic patients have levels < 6\%, they have a high incidence of hypoglycaemic attacks.\textsuperscript{53,54,55}

**Advanced glycosylated end products-modified haemoglobin (Hb-AGE).** As blood glucose concentrations increase, glucose attaches non-enzymatically to the amino groups of many proteins to form glycosylated products (e.g. HbA\textsubscript{1c}). Some glycosylated products are degraded but those formed on collagen, DNA, or other long-lived macromolecules undergo further change to form advanced end-products (AGEs), which probably have a central role in the pathogenesis of diabetic complications.\textsuperscript{56} Measurement of Hb-AGE may provide a longer term measure of diabetic control as well as an index of the risk of diabetic complications.\textsuperscript{57}

Biochemical indices of metabolic control in patients with diabetes mellitus are listed in table 5.6,\textsuperscript{28} although these numerical targets may not be as important in the elderly as they are in the young.

<table>
<thead>
<tr>
<th>Table 5.6</th>
<th>Biochemical indices of metabolic control in diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Good</strong></td>
<td><strong>Acceptable</strong></td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L)</td>
<td>4.4 - 6.6</td>
</tr>
<tr>
<td>Postprandial blood glucose (mmol/L)</td>
<td>4.4 - 7.8</td>
</tr>
<tr>
<td>Haemoglobin A\textsubscript{1c} (%)</td>
<td>6.0 - 7.0</td>
</tr>
<tr>
<td>Total plasma cholesterol (mmol/L)</td>
<td>&lt; 5.2</td>
</tr>
<tr>
<td>Plasma HDL cholesterol (mmol/L)</td>
<td>&gt; 1.1</td>
</tr>
<tr>
<td>Plasma triglyceride (mmol/L)</td>
<td>&lt;1.7</td>
</tr>
</tbody>
</table>
Diabetic ketoacidosis is defined as a condition characterised by an absolute insulin deficiency (i.e. plasma insulin < 6 µU/mL) or relative insulin lack (plasma insulin level between 6 - 50 µU/mL when plasma glucose is > 14 mmol/L), in which ketone acids accumulate in blood to levels greater than 7 mmol/L, causing an acidaemia (pH < 7.25), or a decrease in serum bicarbonate to less than 10 mmol/L or both. When a relative insulin lack is present, an excess of counter-regulatory hormones of glucocorticoids, glucagon, adrenaline, noradrenaline, and growth hormone is also required to cause the ketoacidosis.

Aetiology

Ketoacidosis

The anticytolytic effects of insulin (e.g. inhibition of lipolysis, ketogenesis, gluconeogenesis, glycogenolysis, and proteolysis) are sensitive to low levels of insulin (i.e. 4 - 10 µU/mL), whereas the anabolic actions of insulin (i.e. lipogenesis, glycogenesis and protein synthesis) predominate with high insulin levels (i.e. 10 - 50 µU/mL).

Ketogenesis may be caused by an absolute insulin lack in the fasting state (e.g. the newly diagnosed type I diabetic patient, or the type I diabetic patient who has stopped his or her insulin therapy), or a relative insulin lack in the stressed state (e.g. the type I or type II diabetes patient who has a fixed insulin intake and an excess catabolic hormone secretion due to an acute illness, such as infection, myocardial infarction, stroke, post operative or trauma, or hormonal excess, such as Cushing’s disease, steroid therapy, phaeochromocytoma, sympathomimetic therapy). In both cases the excess FFA mobilisation and stimulation of ketogenesis causes ketoacidosis.

Hyperglycaemia

The normal glucose production by the liver in the fasting individual is approximately 50 mmol/hr/70 kg which rapidly increases to 100 mmol/hr/70 kg when insulin is withdrawn (although hepatic glucose production returns to normal when ketoacidosis develops). The total ECF glucose is 85 mmol/70 kg, which increases to 255 mmol/70 kg within 2 hr of insulin lack, increasing the ECF glucose from 5 mmol/L to 15 mmol/L.

Normal peripheral metabolism of glucose is 150 - 300 mmol/hr/70 kg, thus the hyperglycaemia of an absolute insulin lack is largely due to a reduction in peripheral glucose utilisation. In the patient who has a relative insulin lack, with hormonal excess or stress, stimulation of gluconeogenesis adds to the impairment of peripheral utilisation of glucose to cause hyperglycaemia.

Clinical features

The clinical features of diabetic ketoacidosis, and their causes are listed in Table 5.7. The hypotension is due to fluid loss (i.e. reduced preload) as severe ketoacidosis does not affect myocardial contractility. The abdominal pain associated with diabetic ketoacidosis is caused by a reversible autonomic neuropathy. It is generalised and usually occurs in the younger patient, abating after 4 - 6 h of treatment. Other causes of abdominal pain include pancreatitis, appendicitis or any acute abdominal disorder. The ketoacidotic patient is normally mildly hypothermic; if a pyrexia exists, sepsis should be suspected.

Investigations

These include:

1. Plasma biochemistry. Hyperglycaemia (usually between 30 - 40 mmol/L, although rarely it may vary from less than 11.1 mmol/L to greater than 55.6 mmol/L), hyponatraemia (i.e. plasma sodium < 135 mmol/L - due to hyperglycaemia induced ICF to ECF fluid shift, although severe hyponatraemia may be artifactual due to hyperlipidaemia), elevated anion gap,
hyperkalaemia, hyperlipidaemia (triglyceride concentration usually > 4.5 mmol/L) and hyperphosphataemia are the characteristic findings in a patient who has diabetic ketoacidosis.

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thirst, polyuria, blurred vision</td>
<td>Osmotic diuresis</td>
</tr>
<tr>
<td>leg cramps</td>
<td></td>
</tr>
<tr>
<td>Nausea vomiting, abdominal pain</td>
<td>Ileus, gastric stasis</td>
</tr>
<tr>
<td>Hypotension, tachycardia, dehydration</td>
<td>Fluid loss</td>
</tr>
<tr>
<td>Kussmaul’s breathing</td>
<td>Acidosis</td>
</tr>
<tr>
<td>Ketones on breath</td>
<td>Acetone</td>
</tr>
<tr>
<td>Drowsiness, coma</td>
<td>Hyperosmolality</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>Reduced metabolic rate</td>
</tr>
<tr>
<td>Warm dry skin</td>
<td>Peripheral vasodilation</td>
</tr>
</tbody>
</table>

2. **Blood gases.** The characteristic findings are an acidaemia, low bicarbonate and hypocapnia (i.e. a compensated metabolic acidaemia).

3. **Complete blood picture.** An elevated haemoglobin (due to haemoconcentration) and an elevated neutrophil count in the absence of infection often occur.

4. **Plasma ketones.** The plasma ketoacids (i.e. beta-hydroxybutyrate and acetoacetate, which usually exist in a ratio of 3:1, but may increase up to 9:1 with reduced redox states) normally are less than 1 mmol/L. During starvation they rise to 2 - 4 mmol/L and in ketoacidosis they are in excess of 5 mmol/L, rising up to 15 mmol/L, and almost totally account for the anion gap. As the major ketoacid is beta-hydroxybutyrate, this is often measured to assess the degree of ketoacidosis. Normally in sepsis and stress, the ketone levels are low.

Alcoholic ketoacidosis is the other common cause of ketoacidosis (starvation ketosis is not associated with an acidaemia), which usually follows 24 hr after a drinking binge, due to an excessive mobilisation of FFA. It never occurs in the absence of starvation and frequently is associated with vomiting and abdominal pain (75% have pancreatitis). In this disorder, on admission to hospital the blood glucose level is within normal limits in 75%, low in 15%, mildly elevated in 5% of cases; the level is almost never elevated above 17 mmol/L. The ketoacidosis is rapidly reversed with intravenous dextrose and thiamine.

5. **Plasma lactate.** This is elevated in the presence of shock or with alcoholic ketoacidosis.

6. **Blood, urine and sputum culture.** These are performed if the type I diabetic patient developed ketoacidosis during normal insulin administration.

**Treatment**

The fluid deficit in an adult is usually 3 - 8 L, sodium deficit 200 - 700 mmol, potassium deficit 20 - 700 mmol, phosphate deficit 50 - 80 mmol, calcium deficit 30 - 80 mmol and magnesium deficit 25 - 50 mmol. Central venous pressure measurements and right heart catheterisation and arterial pressure measurements may be required in the hypotensive elderly patient. Treatment requires, fluid resuscitation, insulin, potassium and general measures as outlined in Table 5.8.
Table 5.8 Treatment guidelines for adult diabetic ketoacidosis

Fluid
- 0.9% Saline; 1st litre over 30 min, 2nd litre over 1-2 hr
  (if blood pressure, or pulse have not improved, further saline requires close
  haemodynamic monitoring).
- 0.45% Saline is administered, 1 L/4 - 6 hr until the blood
  glucose is less than 15 mmol/L, thereafter
- 5% dextrose is administered, 1 L/6 to 8-hourly.

Insulin
- Loading dose of 20 U i.v., then 4 U/hr as an infusion using the sliding
  insulin scale outlined in Table 5.12.
  (If blood sugar not decreasing by > 2 mmol/L/hr the insulin rate is increased to 8 U/hr)

Potassium
- If plasma K is;
  > 5 mmol/L, no potassium
  4-5 mmol/L, administer potassium at 20 mmol/hr
  < 4 mmol/L, administer potassium at 40 mmol/hr

Other electrolytes
- Magnesium and phosphate deficits are corrected depending on the plasma levels.
  The calcium loss does not need to be replaced acutely.

General measures
- Continuous nasogastric aspiration if the patient is not conscious
  (to reduce the risk of aspiration)
- Urinary catheterisation in a patient who is not conscious
- Antibiotics, only in the presence of infection
- Low-dose heparin for the elderly

Insulin
The insulin infusion will normally decrease the blood glucose at a rate of 3 - 4 mmol/L/hr.
Insulin resistance occurs if shock or sepsis exists, thus effective resuscitation is required before
the maximum effect of insulin can be expected. Insulin has a half-life of 4 - 5 min, although
its biological half-life is 40 min. In a normal individual, fasting insulin levels range from 1 -
10 µU/mL, and insulin concentrations rarely exceed 50 µU/mL. With each 1 U/hr of insulin
infused, the plasma level rises by 20 µU/mL. Thus a bolus of 20 U given initially followed by
4 - 6 U hourly will produce insulin levels of 60 - 100 µU/mL. Glass and plastic surfaces of
infusion equipment bind approximately 20% - 30% of insulin. This is not a major problem
and while some clinicians infuse insulin with a protein carrier (e.g. 1 mL of 25% albumin), the
overall adsorption is only decreased by up to 10%, therefore 50 U of soluble insulin is
normally added to 0.9% saline up to 50 mL, and, using a plastic syringe pump, this solution is
infused until an effect is achieved.

Potassium
The reduction in potassium is due to an insulin effect and correction of the acidosis, both of
which cause a shift of potassium from the ECF to the ICF. While hyperkalaemia may be
present on admission, the patient is commonly depleted of potassium, and usually between
100 - 200 mmol of potassium is required in the first 24 hr. Potassium chloride (and
Diabetes Mellitus

Phosphate) are administered according to 2 hr monitored serum potassium levels, and usually at a rate of no greater than 40 mmol of potassium per hour.

Sodium bicarbonate

Due to the detrimental effects of sodium bicarbonate, it is not administered routinely, unless severe hyperkalaemia exists or unless a prolonged ketoacidosis has caused an excess renal loss of ketone salts (i.e. sodium or potassium beta-hydroxybutyrate and acetoacetate), producing a normal anion gap hyperchloraemic acidosis.

Other electrolytes

Phosphate and magnesium depletion may also occur in diabetic ketoacidosis. Intravenous phosphate is administered up to a rate of 4 mmol/hr, and intravenous magnesium up to a rate of 2 mmol/hr, with 6 to 8-hourly plasma levels guiding therapy.

Monitoring

The plasma glucose and potassium are monitored hourly if the plasma potassium is less than 3 or more than 6 mmol/L, otherwise they are measured 2-hourly for the first 6 hr and thereafter depending on the plasma levels. The acidosis is monitored by blood gases and anion gap levels.

Complications

The mortality associated with ketoacidosis is about 5% and often related to complications of, infection (i.e. pneumonia, pyelonephritis or septicaemia), ARDS, vascular thrombosis (gastrointestinal or cerebral) or myocardial infarction, rather than the ketoacidosis per se. Cerebral oedema associated with ketoacidosis, is often fatal and occurs usually in children rather than adults, and at a time when the biochemical defect is controlled. Its aetiology is largely unknown, although excessive hypotonic fluid, and bicarbonate administration have been incriminated.

Cerebral oedema associated with ketoacidosis, is often fatal and occurs usually in children rather than adults, and at a time when the biochemical defect is controlled. Its aetiology is largely unknown, although excessive hypotonic fluid, and bicarbonate administration have been incriminated.

In hyperosmolar states cerebral tissue has the capacity to accumulate osmotically active particles within the intracellular compartment and thereby, over a period of time, limit the osmotic effect and the volume change imposed. The nature and mechanisms by which these intracellular ‘idiogenic osmoles’ (which include myo-inositol, N-acetylaspartate, choline and taurine) accumulate and dissipate are not yet fully understood, although they appear to increase in concentration in a response to physiological conditions of hypertonicity (i.e. hyperglycaemia and hypernatraemia) rather than nonphysiological conditions of hypertonicity (i.e. glycerol or mannitol). They also accumulate more rapidly than they are dissipated. The formation of ‘idiogenic’ osmoles with prolonged hypertonicity, may provoke rebound cerebral oedema if the blood glucose is rapidly lowered below 14 mmol/L.

Treatment of cerebral oedema is largely preventative, by preventing excessive fluid administration and infusing dextrose solutions when the plasma glucose is 15 mmol/L or less. Otherwise cerebral oedema is treated by standard measures (e.g. mannitol, frusemide).

NONKETOTIC HYPERGLYCAEMIC COMA

Cause

This condition occurs characteristically in the elderly type II diabetic patient, and is usually precipitated by an intercurrent illness (e.g. pneumonia, meningitis, urinary tract infection, septicaemia). It has also been reported in nondiabetic patients with pancreatitis, burns, heat stroke, cerebrovascular accidents, myocardial infarction, septicaemia, thyrotoxicosis, acromegaly, corticosteroid therapy, l-asparaginase therapy, and with excess dextrose
administration during intravenous nutrition or peritoneal or haemodialysis. As the hyperosmolality is the predominant feature, and as ketones may be present and coma absent, some prefer to label the disorder the diabetic hyperosmolar syndrome.74

Clinical features
The clinical features include those caused by hyperglycaemia (e.g. polyuria, polydipsia, hypotension) and those caused by hypertonicity (e.g. coma). Patients with hyperosmolality are generally not comatose if the serum osmolality is less than 350 mosmol/kg,75 although attempting to correlate coma with osmolality is difficult, particularly when the permeant solute of urea may have a greater or lesser effect in determining its value, but has no effect on ICF fluid shift. If the effect of urea is removed and one calculates the ‘tonicity’, then patients with ‘tonicity’ values of greater than 320 mosmol/kg are often obtunded or comatose.76 Apart from coma a wide variety of other neurological abnormalities may also be present. For example focal seizures (generalised seizures may be due to cortical-vein thrombosis), epilepsia partialis continua, myoclonus, opsoclonia, coarse flapping tremor (i.e. asterixis), the posturing of paroxysmal ketogenic choreoathetosis and “fencing (stance) seizures”. Facial motor abnormalities have also been described including aphasia, facial muscle twitching and jerking.77 Transient and sustained hemiplegia has also been described, although the latter may indicate cerebral artery thrombosis.

Investigations
These include:
1. Plasma ketones. The patient has ketone levels no greater than the starvation range (i.e. 2 - 4 mmol/L) because the small amounts of circulating endogenous insulin, while not reducing the blood glucose levels, are sufficient to inhibit ketogenesis.
2. Plasma glucose. Patients who have symptoms have plasma glucose levels of 40 - 70 mmol/L (i.e. twice that seen with ketoacidosis).
3. Plasma osmolality. This is usually 350 mosmol/kg or greater.78,79
4. Plasma biochemistry. The initial biochemical findings in patients with diabetic ketoacidosis compared with nonketotic hyperosmolar coma, are listed in Table 5.9.8,80

Treatment
The sodium deficit is usually 400 mmol and the water deficit varies from 4 - 18 L.17 therefore fluid with a sodium content of approximately 60 mmol/L would seem to be ideal.20 Some of the water deficit may be predicted by correcting the serum sodium for normal glucose levels (for every 3 mmol/L elevation of glucose the serum sodium falls 1 mmol/L) and assessing the fluid required to correct the corrected sodium level back to normal.81 The aim is to decrease the osmolality by no greater than 2 mosmol/kg/hr and the serum glucose to no less than 10 - 15 mmol/L in 48 hr. Once this is achieved, 5% dextrose solutions are administered to maintain the serum glucose between 10 - 15 mmol/L for 24 hr, in an attempt to reduce the incidence of cerebral oedema (see above).72

An outline of fluid and electrolyte replacement, insulin therapy and general measures is shown in Table 5.10.23,36 Central venous pressure measurements and right heart catheterisation and arterial pressure measurements will be required in the hypotensive elderly patient. Blood glucose, potassium, sodium and osmolality are measured 2 hr. If the potassium is less than 3 or more than 5 mmol/L, then it is measured hourly.
### Table 5.9  Initial laboratory findings in diabetic ketoacidosis and nonketotic hyperosmolar coma

<table>
<thead>
<tr>
<th></th>
<th>Diabetic ketoacidosis</th>
<th>Nonketotic hyperosmolar coma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/L)</td>
<td>&lt; 40</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>Osmolality (mosmol/kg)</td>
<td>&lt; 330</td>
<td>&gt; 330</td>
</tr>
<tr>
<td>pH</td>
<td>&lt; 7.2</td>
<td>&gt; 7.2</td>
</tr>
<tr>
<td>$\text{HCO}_3^-$ (mmol/L)</td>
<td>&lt; 10</td>
<td>&gt; 15</td>
</tr>
<tr>
<td>Na⁺ (mmol/L)</td>
<td>&lt; 135</td>
<td>&gt; 135</td>
</tr>
</tbody>
</table>

### Table 5.10  Treatment guidelines for hyperosmolar nonketotic coma

**Fluid**
- 0.9% saline 1 L over 30 min
  - if still hypotensive and CVP (or wedge pressure) is low then
    - 0.9% saline 1 L over 30 min
- 0.45% saline is administered, 1 L/4 hr until the blood glucose is less than 15 mmol/L, thereafter;
- 5% dextrose is administered 1 L/8 hr.

**Insulin**
- 4 U/hr as an intravenous infusion until the blood sugar level is 15 mmol/L, then cease

**Potassium**
- If plasma K is;
  - > 5 mmol/L, no potassium
  - 4-5 mmol/L, administer potassium at 20 mmol/hr
  - < 4 mmol/L, administer potassium at 40 mmol/hr

**Other electrolytes**
- Magnesium and phosphate replacement are administered depending on the plasma levels.

**General measures**
- Continuous nasogastric aspiration if the patient is not conscious
  - (to reduce the risk of aspiration)
- Urinary catheterisation in a patient who is not conscious
- Antibiotics, only in the presence of infection
- Anticoagulation or low dose heparin

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**DIABETES MELLITUS IN THE SURGICAL PATIENT**\(^{82,83,84,85,86}\)

The risk of operation in diabetics is related mainly to cardiovascular complications (myocardial infarct, cardiac failure, stroke), infections and reduced rates of wound healing,\(^{15}\) rather than metabolic decompensation (i.e. hyperglycaemia and ketoacidosis), which are rare causes of morbidity and mortality.

Myocardial infarct, stroke and cardiac failure are responsible for 50% of deaths in diabetics in the postoperative period. Diabetic patients also often have renal insufficiency and require
Diabetes Mellitus

careful monitoring of fluids in the post operative period. The reasons to attempt to keep the blood sugar level between 7 - 10 mmol/L include suppression of ketoacidosis, hyperkalaemia and fluid loss, decreased protein glycosylation (which impairs wound healing, and which occurs when the plasma glucose level is greater than 11.1 mmol/L), and decreased hyperglycaemic interference of leucocyte chemotaxis, opsonisation and phagocytosis. 87,88

**Insulin-dependent diabetes mellitus**

_Elective surgery_

Ideally these patients are operated on in the morning. On the day of operation, an intravenous infusion of 5% dextrose is administered preoperatively and half their usual dose of insulin is given subcutaneously. The patient’s blood sugar should be monitored 2-hourly, unless it is greater than 20 mmol/L or less than 7 mmol/L, when it should be monitored hourly. Postoperatively, the remainder of the usual insulin dose is administered. If the patient is eating by the next day, the regular dose of insulin is administered. If the patient is not eating, the intravenous 5% dextrose should be continued. As the patient in the postoperative period will not be exercising and will have an increase in circulating catecholamines, cortisol and growth hormone due to the stress of surgery, and will receive a 5% dextrose infusion, the patient’s standard insulin dose is unlikely to be adequate and should be supplemented with regular dose of subcutaneous insulin adjusted from 4-hourly blood sugar levels (see Table 5.11 for an example).

**Table 5.11 Subcutaneous insulin sliding scale.**

<table>
<thead>
<tr>
<th>Blood glucose (mmol/L)</th>
<th>Subcutaneous insulin (Actrapid U)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4.0</td>
<td>0</td>
</tr>
<tr>
<td>4.1 - 6</td>
<td>2</td>
</tr>
<tr>
<td>6.1 - 8</td>
<td>4</td>
</tr>
<tr>
<td>8.1 - 10</td>
<td>8</td>
</tr>
<tr>
<td>10.1 - 12</td>
<td>12</td>
</tr>
<tr>
<td>12.1 - 14</td>
<td>16</td>
</tr>
<tr>
<td>&gt; 14.0</td>
<td>Notify doctor</td>
</tr>
</tbody>
</table>

_Emergency surgery_

If the patient is undergoing an emergency operation, an insulin infusion is used (Table 5.12) and adjusted on 2-hourly blood sugar levels. If emergency surgery is required in a ketoacidotic patient, then the fluid, electrolyte and insulin regimen required, is continued throughout the surgery. Close cardiovascular haemodynamic monitoring, using a right heart catheter, is necessary. Intraoperative and postoperative insulin is administered as an infusion, with the infusion rates being adjusted from the 2-hourly blood sugar levels (see Table 5.12 for an example). Usually, 0.5 mL of Actrapid (100 U/mL) is diluted in 49.5 mL of 0.9% saline to give 1 U/mL, and infused using a syringe pump which is accurate down to a flow rate of 0.5 mL/hr.
Diabetes Mellitus

Table 5.12  Intravenous insulin sliding scale

<table>
<thead>
<tr>
<th>Blood glucose (mmol/L)</th>
<th>Insulin infusion (Actrapid U/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4.0</td>
<td>0</td>
</tr>
<tr>
<td>4.1 - 6</td>
<td>0.5</td>
</tr>
<tr>
<td>6.1 - 8</td>
<td>1</td>
</tr>
<tr>
<td>8.1 - 10</td>
<td>2</td>
</tr>
<tr>
<td>10.1 - 12</td>
<td>3</td>
</tr>
<tr>
<td>12.1 - 14</td>
<td>4</td>
</tr>
<tr>
<td>14.1 - 16</td>
<td>5</td>
</tr>
<tr>
<td>&gt; 16.0</td>
<td>Notify doctor</td>
</tr>
</tbody>
</table>

Non insulin dependent diabetes mellitus

For both elective and emergency surgery, the oral hypoglycaemic agent is ceased on the day of surgery. During surgery and during the postoperative period, intravenous 5% dextrose is infused (50 g/8 hr) and subcutaneous insulin is administered using a sliding scale, with 4-hourly blood sugar levels to maintain the blood glucose level between 7 - 10 mmol/L.\(^87,88\) If the initial blood sugar is greater than 20 mmol/L, the patient is managed by an intravenous infusion of insulin which is varied according to a 2-hourly blood sugar level (Table 5.11). When the patient is able to eat the oral hypoglycaemic agent is readministered, although metformin is usually reintroduced 1-2 days later.

HYPERGLYCAEMIA DUE TO STRESS OR CRITICAL ILLNESS

Hyperglycaemia associated with insulin resistance is common in critically ill patients in the absence of a previous history of diabetes. Often the management of patients is to observe the blood glucose levels only (if less than 12.0 mmol/L) and treat the underlying condition in the belief that the patient will become normoglycaemic without a detrimental effect caused by the episode of hyperglycaemia.

However, in one study of mechanically ventilated critically ill patients admitted to a surgical intensive care unit (more than 60% of whom were post cardiopulmonary bypass patients) who received 200 - 300 g if glucose intravenously for the first day and 20 - 30 non nitrogen calories/kg per day (20 - 40 % as lipid) and 0.13 - 0.26 g N\(_2\) per kg per day either parenterally, enteralty or mixed thereafter (until discharge from the intensive care unit); an insulin infusion (up to 50 U/hr) to maintain the blood glucose between 4.4 - 6.1 mmol/L was associated with a reduction in morbidity (renal failure, infection, polyneuropathy, anaemia) and mortality (particularly in patients who remained in the ICU for > 5 days) when compared with an insulin infusion to maintain the blood glucose between 10 - 11.1 mmol/L if the blood glucose was > 12 mmol/L.\(^89\)

HYPOGLYCAEMIA

In health the plasma glucose level is regulated within narrow limits, with insulin countering postprandial hyperglycaemia and glucagon acting to counter hypoglycaemia. With severe hypoglycaemia, adrenaline, growth hormone and cortisol also act with glucagon to correct low plasma glucose levels.\(^90\)

Causes

The causes of hypoglycaemia are listed in Table 5.13\(^11,90,91,92,93\)
Table 5.13  Causes of hypoglycaemia

<table>
<thead>
<tr>
<th>Causes of Hypoglycaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Factitious</em> (due to elevated leucocyte count)</td>
</tr>
<tr>
<td><em>Starvation</em>, prolonged exercise</td>
</tr>
<tr>
<td><em>Insulinoma</em> (85% benign, 15% malignant)</td>
</tr>
<tr>
<td><em>Hepatic disease</em></td>
</tr>
<tr>
<td>Cirrhosis, acute hepatic failure</td>
</tr>
<tr>
<td><em>Endocrine disease</em></td>
</tr>
<tr>
<td>Addison’s</td>
</tr>
<tr>
<td>Anterior pituitary insufficiency (with reduction in GH, ACTH)</td>
</tr>
<tr>
<td>Hypothyroidism, phaeochromocytoma</td>
</tr>
<tr>
<td><em>Medication induced</em></td>
</tr>
<tr>
<td>Insulin, sulphonylureas, biguanides,</td>
</tr>
<tr>
<td>Pentamidine, octreotide, salicylates, alcohol</td>
</tr>
<tr>
<td>Quinidine, disopyramide, haloperidol</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors, ACE inhibitors</td>
</tr>
<tr>
<td>Sudden reduction in parenteral nutrition</td>
</tr>
<tr>
<td><em>Carcinomas</em></td>
</tr>
<tr>
<td>Primary hepatic carcinoma</td>
</tr>
<tr>
<td>Adrenal carcinoma, carcinoid</td>
</tr>
<tr>
<td><em>Renal failure</em></td>
</tr>
<tr>
<td><em>Shock, sepsicaemia</em></td>
</tr>
<tr>
<td><em>Metabolic disorders</em></td>
</tr>
<tr>
<td>Carnitine deficiency, Reye’s syndrome</td>
</tr>
<tr>
<td>Glycogen storage disease, hereditary fructose intolerance</td>
</tr>
</tbody>
</table>

Clinical features

The clinical features of hypoglycaemia relate to the effects of:

1. **Adrenergic stimulation.** Tachycardia, palpitations, diaphoresis, anxiety, tremor, hunger, nausea, irritability, and pallor, often occur when the plasma glucose levels fall below 2.2 mmol/L (40 mg/dL). Symptoms may be absent in diabetic patients who have severe autonomic neuropathy, or in those patients treated with a non-selective beta-blocker, due to a beta-2-adrenergic receptor blocking effect. The differential diagnosis of hypoglycaemia induced sympathetic stimulation include phaeochromocytoma, panic attacks and hyperventilation.

2. **Neurogycopenia.** Headache, blurred vision, paraesthesia, weakness, tiredness, confusion, dizziness, amnesia, incoordination, behavioural change, transient aphasia, hemiplegia, seizures, and coma, commonly occur with plasma glucose levels less than 2 mmol/L (36 mg/dL) and may cause cerebral oedema and permanent cerebral damage if prolonged. If seizures are prolonged and cerebral oedema develops, hyperthermia may be present, otherwise the patient is usually hypothermic.

Investigations

These include:

1. **Plasma glucose.** Most laboratories have their lower reference range limit for plasma glucose at 3.8 mmol/L (70 mg/dL). While a normal female may rarely have a fasting plasma glucose level down to 2.5 mmol/L (45 mg/dL) without any deleterious effect, a plasma glucose
level below 2.8 mmol/L (50 mg/dL) is significant and is sufficient to make the diagnosis of hypoglycaemia.\textsuperscript{92}

2. \textit{Plasma insulin:glucose ratio}. Because hypoglycaemia normally suppresses insulin secretion, the value of the ratio - plasma (insulin (µU/mL) x 5.5) : plasma (glucose (mmol/L) - 1.8), should be less than 50, except in patients who have an insulinoma or an overdosage of insulin or sulphonylureas.

3. \textit{Plasma C peptide, and proinsulin}. Fasting proinsulin and C peptide levels are elevated in patients who have an insulinoma or an overdosage of sulphonylureas. An increased ratio of proinsulin to insulin is also suggestive of an insulinoma. As plasma C peptide levels normally vary in parallel with the plasma insulin concentrations, C peptide levels are low with excess exogenous insulin administration. Serum levels of the sulphonylureas are elevated if hypoglycaemia is caused by these agents.

4. \textit{Prolonged 72 hr fast}: this is normally begun after the evening meal, thereafter the patient may only have water or other calorie-free caffeine-free drinks. Plasma is obtained 6-hourly for glucose, insulin and C-peptide levels for the first 24 hr then 4-hourly thereafter. The patient is monitored carefully for symptoms, with plasma being taken during symptoms, for, glucose, insulin and C peptide levels.

5. \textit{β-Hydroxybutyric acid}. The plasma β-Hydroxybutyric acid level is > 2.7 mmol/L in normal patients and < 2.7 mmol/L in patients who have excess insulin (e.g. insulinoma, insulin or sulfonylurea induced) at the end of a 72 hr fast.

6. \textit{The 6 hr glucose tolerance test}. This is a 6 hr extension of the glucose tolerance test, taking fasting and 30 min specimens of plasma glucose and insulin.

\section*{Treatment}

The standard treatment for hypoglycaemia is oral glucose or if the patient is unconscious, 50 mL of 50\% dextrose administered intravenously as a bolus (i.e. 25 g or 139 mmol, which will elevate the extracellular glucose acutely by 8 mmol/L/70 kg). Intravenous glucose is then infused at 4 - 5 mmol/hr (i.e. 40 mL of 20\% dextrose/hr), and blood glucose levels are measured 2 to 4-hourly. Glucagon 0.5 mg intramuscularly or intravenously may also be useful (the standard dose of 1 mg is often excessive and will produce nausea and vomiting 2 - 4 hr later in a significant number of patients\textsuperscript{95}).

If an insulinoma is responsible for the hypoglycaemia, it should be surgically removed. As octreotide is a potent inhibitor of insulinoma insulin secretion, it is used in cases of metastatic insulinomas.\textsuperscript{96} Octreotide (100 µg s.c. 6 - 12-hourly) has also been used successfully in cases of sulphonylurea overdose induced hypoglycaemia.\textsuperscript{97,98}

\section*{REFERENCES}

Diabetes Mellitus

Diabetes Mellitus

75. Arieff AI, Carroll HJ. Cerebral edema and depression of sensorium in nonketotic hyperosmolar coma. Diabetes 1974;23:525-531.
TRAINEE PRESENTATIONS

Each registrant has prepared a five minute talk and summary on the topics listed below. The summaries that were received in time for publication have been included (unedited).

1. Discuss the complications of intravenous hydrocortisone when used in the management of a patient with septic shock  
   Dr. T. Wigmore  
   page 57

2. Discuss the clinical features and management of a patient with pancreatic abscess.  
   Dr. C. Graves  
   59

3. Discuss the indications and complications of intravenous amiodarone.  
   Dr. D. Morgan  
   61

4. Compare and contrast the effects of inhaled no and nebulised prostacyclin in a patient with ARDS  
   Dr. J. Cohen  
   66

5. Discuss the indications for, mechanism of action and complications of intravenous mannitol.  
   Dr. P. Goldrick  
   69

6. Discuss the management of a patient who develops severe thrombocytopenia and acute mesenteric artery thrombosis five days following iv unfractionated heparin for an acute PE.  
   Dr. P. Liston  
   71

7. Discuss the indications and composition of lactate free dialysis.  
   Dr. D. Ghelani  
   74

8. Discuss the current indications and contraindications of intravenous lignocaine.  
   Dr. G. Brieva  
   76

9. Discuss the management of a one day post abdominal aortic aneurysm patient who has had an acute anterior myocardial infarct.  
   Dr. E. Trent  
   78

10. Discuss the management of a severely hypoxic patient who has been paralysed with suxamethonium whom you are unable to intubate or ventilate.  
    Dr. R. O’Connor  
    81

11. Discuss the management of a patient with severe verapamil overdosage.  
    Dr. P. Nelson  
    84

12. Discuss the clinical features and management of a patient with a sagittal sinus thrombosis.  
    Dr. B. Welch  
    86

13. Discuss the management of a patient with an acute central venous line candida septicemia and endophthalmitis who develops oliguria and a progressive rise in plasma creatinine.  
    Dr. H. Koelzow  
    89

14. Discuss the clinical features and management of a patient with diastolic heart failure.  
    Dr. B. O’Brien  
    92

15. Discuss the indications and complications of intravenous octreotide  
    Dr. S. Morphett  
    94

16. Discuss the aetioloogy and management of a patient with hepatopulmonary syndrome and portopulmonary hypertension.  
    Dr. C. Allen  
    97

17. Discuss the causes and treatment of torsades de pointes.  
    Dr. M. McNamara  
    100
18. Discuss the indications for and mechanism of action of intravenous activated protein C in a septic patient.  
   Dr. S. Sturland 104

19. Discuss the management of a patient with methyl alcohol poisoning.  
   Dr. A. Dennis 108

20. Discuss the indications for inhaled antibiotic therapy and what antibiotics have been used.  
   Dr. M. Saxena 111

21. Discuss the indications for and complications of intravenous calcium chloride during a cardiac arrest.  
   Dr. O. Sheffer

22. Describe the method used and the indications for the positions of insertion of an intercostal drain.  
   Dr. U. Kadam

23. Discuss all the methods used to improve the likelihood of a successful cannulation of a central vein.  
   Dr. S. Wilson

24. Discuss the indications and complications of intravenous calcium chloride.  
   Dr. S. Hockley

25. Define and list the causes and management of a ventilator associated pneumonia.  
   Dr. K. Deshpande

26. Discuss the clinical presentation and management of a patient who has an acute Budd-Chiari syndrome.  
   Dr. C. Bradford

27. Discuss the causes, clinical features diagnosis and management of a patient with an acute viral encephalitis.  
   Dr. C. Cody

28. Discuss the clinical features and management of a patient who has an acute acalculus cholecystitis.  
   Dr. D. Charlesworth
DISCUSS THE COMPLICATIONS OF INTRAVENOUS STEROIDS WHEN USED IN THE MANAGEMENT OF A PATIENT WITH SEPTIC SHOCK

Dr. T. Wigmore, Intensive Care Unit, Westmead Hospital, NSW

The use of steroids in septic shock was originally contemplated due to their well known anti-inflammatory properties. They have been shown to inhibit inducible NO synthesis, prevent leucocyte aggregation and adhesion induced by exotoxin. In addition they decrease platelet activating factor, tumour necrosis factor and interleukin-1 release and prevent prostaglandin generation through induction of phospholipase A2 inhibitor.

In consideration of the complications of steroids in septic shock it is important to distinguish between the early practice of giving large doses of steroids and that more recently adopted of giving “physiological doses”.

Initial trials were conducted with ‘industrial’ doses of corticosteroids. An early report by Schumer suggested that treatment with either dexamethasone or methylprednisolone dramatically improved survival in patients with septic shock. As a result the administration of 2g of methylprednisolone became the defacto standard of care for proven or suspected septic shock during the late 1970s and early 1980s. In 1984 however Sprung et al showed that although a transient survival benefit was afforded to patients randomised to receive either dexamethasone or methylprednisolone, the improvement was not durable and the hospital mortality rates were similar for both groups.

A subsequent multi-centre RCT by Bone et al showed an increased mortality in the steroid group. Two meta-analyses of corticosteroid treatment were published in Critical Care Medicine in 1995, both showing increased mortality in the steroids group. Below is a list of the side effects found.

1. Significant increased mortality in patients with overwhelming infection RR 1.13
2. Trend towards increased mortality in the subgroup with septic shock RR 1.07
3. Trend towards increased mortality overall RR 1.10
4. Increased gastrointestinal bleeding RR 1.17
5. 3 studies reported increased hyperglycaemia in the steroid group (although hyperglycaemia was not defined)
6. One study reported increased blood urea in the steroid group
7. Two double blind studies reported a trend towards increased cause-specific mortality in patients receiving corticosteroids (RR 1.7, No overall increase was found in the meta-analyses).

More recent studies have concentrated on the use of physiological doses of corticosteroids (200mg per day of hydrocortisone with some recommending the addition of 50 µg of fludrocortisone), particularly in functionally hypoadrenal patients (as classified in the recent Annane et al paper). Annane et al found an improvement in 28-day survival in patients with relative adrenal insufficiency who were treated with corticosteroids according to the above regimen. (although the statistics performed to show this are hugely complex and a more simple analysis would not appear to be so conclusive.) Interestingly Bollaert et al also showed a trend towards improved survival in patients treated this time with 300 mg of hydrocortisone irrespective of response to a corticotropin test. In neither paper was there an excess of adverse events, suggesting that the earlier observed side effects with the use of steroids were related to dosage.
References
DISCUSS THE CLINICAL FEATURES AND MANAGEMENT OF A PATIENT WITH PANCREATIC ABSCESS

Dr. C. Graves. Division of Critical Care, Royal Brisbane Hospital, Queensland

The Atlanta classification defines pancreatic abscess as “a circumscribed collection of pus, containing little or no pancreatic necrosis, which arises as a consequence of acute pancreatitis or pancreatic trauma”.

Incidence reported at 1-5% following acute pancreatitis and is often associated with gastrointestinal fistulas, pseudoaneurysms and not uncommonly with multi-organ dysfunction.

Microbiology may be mono-microbial (~50%) or poly-microbial (~50%). Culturing E. coli (35-50%), Klebsiella spp. (13-25%), Enterococcus spp. (7-28%), Staphylococcus spp. (14-36%) and occasionally Streptococcus spp., Bacteroides spp. and Candida spp. (all <9%). Infection is the result of translocation of bacteria across damaged bowel and secondary haematogenous spread.

Mortality has previously been reported as high (20-60%) due to lack of standard nomenclature and subsequent inclusion of infected pancreatic necrosis. Currently, treated pancreatic abscess has a mortality of 2-14% due to multi-organ failure, septic shock or haemorrhage. Treated infected pancreatic necrosis has a mortality of 20-40%. Infected pseudocysts have the least mortality.

Presentation is heralded > 4 weeks after the onset of acute pancreatitis by persistent or worsening pain and localised tenderness (80-100%), fever esp. if > 39.5C (50-100%), nausea, vomiting and an abdominal mass (22-85%). There may be an associated left sided pleural effusion or an enlarging spleen secondary to splenic vein thrombosis.

Diagnosis is dependent on clinical vigilance and suspicion and confirmed by rapid-infusion contrast CT scanning.

Management involves:
1. Supportive care and early recognition of complications.
2. Broad spectrum antibiotics.
3. Drainage
   a) Endoscopic stenting is an emerging treatment modality with ~9% in-hospital patient mortality which is comparable to surgical drainage and involves an average of two ERCP procedures.
   b) Percutaneous radiological drainage has an increasing role in selected patients (i.e. single abscess, no loculations and an adequate window for drainage). Advantages include being minimally invasive and it may provide definitive treatment. If not resolved by 7-10 days a repeat CT scan is indicated and surgery or a second catheter considered. Complications include pancreatic (cutaneous or gastrointestinal) fistulas, empyema or bleeding. Requires Surgical and Radiological liaison.
   c) Surgical management is the mainstay for patients with multi-organ dysfunction or those unsuitable for percutaneous drainage or for complications of drainage. Complications include fistulas and post-operative bleeding.
4. Nutrition is by enteral (jejunal) feeding or TPN and avoidance of recommencing oral intake too early.

References
DISCUSS THE INDICATIONS AND COMPLICATIONS OF INTRAVENOUS AMIODARONE

Dr. D. Morgan. Intensive Care Unit, Royal Perth Hospital, Newcastle, WA

Description

- Amiodarone has been described as a class III (drugs that slow the flow of potassium into heart cells and prolongs the duration of the action potential) antiarrhythmic drug but in reality its effects extend across multiple mechanisms of action including effects on sodium, potassium, and calcium channels; as well as α and β adrenergic blocking properties.
- When given intravenously, amiodarone has little class III effect; the major action is on the AV node, causing a delay in intranodal conduction and prolongation of refractoriness

Indications (Supraventricular arrhythmias)

- **AF**
  - **Incidence**
    - General population
      - Overall 1-2%
      - < 60 years old 0.4%
      - > 60 years old 2-5%
      - AMI 10-15%
      - ↑ Mortality risk due to decreased LV function
      - CCF 40%
      - Critically Ill 15%
      - 3-5% Non cardiothoracic major surgery
      - Usually reflects a combination of
        - Cardio-respiratory disease
        - Adrenergic stress
  - **Conversion**
    - Spontaneous
      - 60-65% at 24hours
    - Amiodarone
      - 72-82% at 24 hours
    - Compared with other anti-arrhythmic drugs
      - Of equal efficacy
  - **Post CABG Prophylaxis**
    - Incidence
      - CABG 30%
      - Post valvular surgery 50%
    - Prophylactic amiodarone use
      - Reduces the rate of post CABG AF by ~ 50%
    - Possible role in poor risk patients
      - Large left atrium
      - Advanced age
      - Low ejection fraction
- **High Dose Amiodarone**
  - 3 gram per day (125 mg/hr)
  - Conversion at 24 hours
    - Placebo: 64%
    - Amiodarone: 92% (p=0.0017)
  - Crossover
    - 85% of those not converting to placebo converted with high dose amiodarone
    - All patients not responding to amiodarone where still in AF at one month

- **WPW**
  - Safe choice in antidromic conduction

- **Unstable SVT**
  - In patients with severely impaired heart function IV amiodarone is preferable to other antiarrhythmic agents for atrial tachyarrhythmias

- **Paediatric SVT**
  - Amiodarone is safe and effective

**Indications (Ventricular Arrhythmias)**

- **Stable VT**
  - Listed on the 2000 ILCOR guidelines as a first line option for the “Stable Ventricular Tachycardia Algorithm”
  - Class IIb (possibly helpful)

- **Unstable VT**
  - Patients with CCF and depressed myocardial function should be treated cautiously with antiarrhythmic therapy
  - In patients with severely impaired heart function IV amiodarone is preferable to other antiarrhythmic agents for ventricular tachyarrhythmias
  - Amiodarone has the least additional impairment on LV function and has shown to be effective in treating haemodynamically unstable VT and VF
  - The negatively inotropic and vasodilatory effects of amiodarone are dose and rate dependent

- **Cardiac Arrest**
  - ILCOR Guidelines for pulseless VT or VF
    - 300 mg IV push
    - 150 mg second dose IV push
    - Maximum dose 2,200 mg over 24 hours
    - Class IIb evidence (possibly helpful)
  - ARREST Trial
    - (Amiodarone in out-of-hospital Resuscitation of REfractory Sustained ventricular Tachyarrhythmias trial)
      - Adults with non-traumatic out-of-hospital cardiac arrest were eligible for inclusion if VF or pulseless VT was present were then randomly assigned to receive either amiodarone I.V. 300 mg or placebo (diluent).
      - Total patients: 504
        - Amiodarone: 246
        - Placebo: 258
The majority of patients in both groups were male, ≥65 years, and presented with ventricular fibrillation as the initial cardiac arrest rhythm.

Survival to hospital admission
- Amiodarone 44%
- Placebo 34% (P = 0.03)

But survival to hospital discharge was similar
- Amiodarone 13.4%
- Placebo 13.2%

Hypotension (the need for vasopressor infusions) and bradycardia (the need for chronotropic therapy) were significantly more common in the amiodarone group (59% vs. 48% and 41% vs. 25%, respectively).

There are some limitations to the wider applicability of this study. It took place in Seattle and King County, Washington, where response times are extraordinarily short (dispatch to arrival of first responder was 4.3 min).

Many would argue that an intervention that has been shown to improve survival to hospital admission, but not to hospital discharge neurologically intact, should not be adopted without data on long-term outcome.

**ALIVE Trial**

(Almiodarone versus Lignocaine in Prehospital Refractory Ventricular Fibrillation Evaluation)

- Enrolled patients between November 1995 and June 2000
- Amiodarone vs. lignocaine
  - Amiodarone 5mg/kg and 2.5 mg/kg
  - Lignocaine 1.5 mg/kg and 1.5 mg/kg
- Total patients enrolled 347 (no difference in baseline characteristics)
  - Amiodarone 180 patients
  - Lignocaine 167 patients
- Average time to drug therapy 25 minutes
- Endpoints
  - Primary
    - Survival to admission to hospital
      - Amiodarone 22.7%
      - Lignocaine 11.0% (p = 0.009)
    - Survival rates much higher if patients received treatment in under 25 minutes
    - Lower survival rates to hospital when compared with ARREST trial (44% vs. 23%)
  - Secondary
    - Hospital discharge
      - Amiodarone 5%
      - Lignocaine 3% (P=0.34)

In comparison with the Seattle study, the mean interval to first defibrillation was 2.5 minutes longer and the interval to study drug administration was 4 minutes longer.

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COMPLICATIONS

• **Adverse Effects**
  
  - The most common adverse effect seen with intravenous amiodarone during controlled and open-label clinical trials were
    - **Hypotension** 16%
      - If hypotension does occur, slow the infusion rate. In addition, standard supportive therapy may be required, including the use of vasopressor drugs, positive inotropic agents, and volume expansion.
      - **Bradycardia** 4.9%
      - **Liver function test abnormalities** 3.4%
      - **Cardiac arrest** 2.9%
      - **VT** 2.4%
    - Like all antiarrhythmic drugs, amiodarone I.V. may exacerbate or precipitate arrhythmias.
    - Proarrhythmia, primarily torsades de pointes, has been associated with amiodarone I.V. prolongation of the QTc interval to 500 ms or greater.
    - Although QTc prolongation occurred frequently in patients receiving amiodarone I.V., the frequency of torsades de pointes or new-onset VF was <2%.
    - Patients should be monitored for QTc prolongation during infusion with amiodarone I.V.
      - **Congestive heart failure** 2.1%
      - **Cardiogenic shock** 1.3%
      - **AV block** 0.5%
  
• **Drug Interactions**
  
  - Caution should be used when using amiodarone with drugs that have either antiarrhythmic, vasodilatory or myocardial depressant properties.
  - Conversely, drugs producing a significant effect on amiodarone pharmacokinetics include phenytoin, cimetidine, and cholestyramine.

• **Contraindications**
  
  - Intravenous amiodarone is contraindicated in patients with
    - Known hypersensitivity
    - Cardiogenic shock
    - Marked sinus bradycardia
    - Second- or third-degree AV block unless a functioning pacemaker is available.

References


COMPARE AND CONTRAST THE EFFECTS OF INHALED NO AND NEBULISED PROSTACYCLIN IN A PATIENT WITH ARDS

Dr. J. Cohen. Intensive Care Unit, Royal Brisbane Hospital, Queensland

Nitric Oxide

Nitric Oxide (NO) is a colourless, almost odourless gas that is slightly soluble in water. Environmental NO arises from combustion processes (fossil fuel combustion and tobacco smoke) and lightning. Atmospheric concentrations of NO usually range between 10 and 500 parts per billion (ppb) but can exceed 1.5 parts per million (ppm) in areas of heavy traffic.

Endogenous NO arises from the action of the enzyme Nitric Oxide Synthase (NOS) on L-arginine, producing L-citrulline and NO. Three NOS isoforms have been identified, and classified according to the tissue in which they were first observed, and their regulation of activity.

Constitutive neuronal NOS was initially described in neuronal tissue; Inducible NOS (iNOS) is expressed in a variety of inflammatory cells; and constitutive endothelial NOS was initially described in vascular endothelial cells.

NO for medical administration is supplied in pressurised cylinders and requires specialised apparatus to ensure accurate delivery and monitoring.

Mechanism of action

NO activates soluble guanylate cyclase, which catalyses the conversion of guanosine 5 triphosphate to cyclic 3’:5’ GMP (cGMP). cGMP activates a variety of intracellular protein kinases to relax smooth muscle, inhibit leukocyte adhesion, platelet adhesion, and cellular proliferation. The action of cGMP is limited by phosphodiesterases which convert cGMP to GMP.

Effects in Lung Injury

Selective vasodilation of ventilated areas, resulting in improved ventilation/perfusion matching. May lead to improved right ventricular performance, with improvements of RV ejection fraction and reduced RV end diastolic and systolic volumes. Decrease in pulmonary artery pressures and pulmonary vascular resistance. Rapid uptake and inactivation by hemoglobin prevents systemic effects.

Decrease in pulmonary capillary pressure and pulmonary transvascular albumin flux, caused partly by effect on pulmonary venous resistance. May promote resolution of pulmonary oedema.

Improvement in arterial oxygenation demonstrated in a number of human and animal studies, with reduction in shunt fraction and improved FiO₂/PO₂ ratios.

Bronchodilator activity, although appears to be mild in studies of human volunteers.

Interaction with pulmonary surfactant in animal models suggest it may reduce surfactant production and reduce its efficacy.

Human trials suggest that about 50% of patients with ARDS will respond to inhaled NO therapy, but no outcome benefit in terms of mortality or reduced ventilatory time has been demonstrated.

Metabolism

Half life of NO in vivo is only a few seconds as it is rapidly inactivated by binding to haemoglobin, with subsequent release of NO₃. Approximately 90% of NO is absorbed during a steady state inhalation. Almost 70% of the inhaled gas appears within 48hrs as NO₃ in the
urine. The remaining 30% is recovered as NO₂ in the oral cavity through secretion from the salivary glands. NO₂ is also partly converted to nitrogen gas in the stomach and some NO₂ in the intestine is reduced to ammonia, reabsorbed, and converted to urea.

Toxicity
Reaction with haemoglobin results in the production of methaemoglobin (Fe³⁺ haemoglobin). Most of the methaemoglobin created is reduced back by NADH cytochrome b₅/cytochrome b₅ methaemoglobin reductase within erythrocytes.
NO reacts with oxygen to produce NO₂. High levels of NO₂ in animal models (> 10ppm) induced pulmonary oedema, alveolar haemorrhage, changes in surfactant surface tension, intrapulmonary accumulation of fibrin, neutrophils, and macrophages, and death.
NO stimulates cGMP formation within platelets and can inhibit platelet function and augment the bleeding time.
Sudden discontinuation of NO therapy may lead to severe rebound hypoxia and right ventricular failure.

Prostacyclin
Prostacyclin (PGI₂) is a member of the prostaglandin family of lipid mediators derived from arachidonic acid and is synthesized predominantly by endothelial cells, including the pulmonary vascular endothelium.

Supplied as a powder which must be dissolved in the glycine buffer provided by the manufacturer before use. After reconstitution it is stable for up to 12 hours at room temperature, and 48 hours if refrigerated. The solution must be protected from light to prevent photodegradation. Administration is via a standard nebuliser over 20 – 30 minutes at flow rates of 8l/min.

Mechanism
In contrast to NO, PGI₂ activates adenylate cyclase to produce adenosine-3,5-cyclic monophosphate. The result is similar in producing smooth muscle relaxation. PGI₂ is also the most potent known inhibitor of platelet aggregation, and has been shown to stimulate the release of NO from endothelial cells.

Effects in Lung Injury
Production of selective pulmonary vasodilation in a similar manner to NO. Has been shown to decrease pulmonary artery pressures, with significant increases in PaO₂/FiO₂ ratios. Efficacy compared to INO appears similar, with one study showing both agents producing a 7% decrease in measured shunt and comparable improvements in PaO₂. However PGI₂ produced a greater decrease in PVR than NO. Further studies have suggested that NO may produce a greater oxygenation benefit than PGI₂, and that PGI₂ may generally only be effective in patients with ARDS caused by extrapulmonary disease. Percentage of responders appears similar to NO, with about 50% of patients showing an oxygenation benefit. No data on outcomes is available.

Metabolism
PGI₂ is spontaneously hydrolysed at neutral plasma pH to its inactive metabolite, 6-keto-prostaglandin-f₁. In vitro half life is approximately 6 minutes. Inhaled PGI₂ is not metabolised within the lung to any significant extent. Systemic absorption can be determined by measurement of serum 6-kpf levels.
Toxicity and side effects

No known toxic metabolites. Rebound phenomena may be potential hazard, but there are no case reports. Produces platelet inactivation, but a study in post operative cardiac patients failed to show any clinically significant bleeding problems.

REVIEW

<table>
<thead>
<tr>
<th>Nitric Oxide</th>
<th>Prostacyclin</th>
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<tr>
<td>Similar response rates (50%)</td>
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<tr>
<td>Selective pulmonary vasodilator</td>
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<tr>
<td>Enviromental Gas</td>
<td>Arichadonic acid derivative</td>
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<tr>
<td>Requires specialised delivery apparatus</td>
<td>No specialised equipment needed.</td>
</tr>
<tr>
<td>Activates guanylate cyclase</td>
<td>Activates adenylate cyclase</td>
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<tr>
<td>Platelet inhibitor</td>
<td>Profound platelet inhibitor</td>
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<td>Mild bronchodilator on bronchial tone</td>
<td>Conflicting reports on effect</td>
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<tr>
<td>Reduction in transvascular albumin flux</td>
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<tr>
<td>May produce greater improvement in PaO2</td>
<td>May produce greater decrease in PVR</td>
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<tr>
<td>May be ineffective in intrinsic ARDS</td>
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<tr>
<td>Produces methaemaglobinaemia</td>
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<tr>
<td>Has toxic metabolites</td>
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<tr>
<td>Rebound phenomena demonstrated</td>
<td>Rebound phenomena not documented</td>
</tr>
<tr>
<td>Cheaper</td>
<td>More readily available</td>
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<tr>
<td>No outcome benefit demonstrated</td>
<td>Data on outcome benefit lacking</td>
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References

DISCUSS THE INDICATIONS FOR, MECHANISM OF ACTION AND COMPLICATIONS OF INTRAVENOUS MANNITOL

Dr. P. Goldrick. Intensive Care Unit, Townsville Hospital, Queensland

Mannitol is a low MW alcohol (MW182). It presents as a 10% solution (549mosmol/l) or a 20% solution (1098mosmol/l). Administered IV it is not metabolised. It is freely filtered in the kidneys, with little re-absorption. The elimination T1/2 is 70min.

PROPOSED INDICATIONS AND MECHANISMS OF ACTION

1. Effects on intracranial pressure (ICP) & cerebral blood flow (CBF)
   1. Immediate Effect: (15-30 mins) increase in cerebral blood flow (CBF) to a increase in circulating volume, improved viscosity, and a reduction in ICP mediated by vasoconstriction of pial arteries.
   2. Delayed effect. Reduction in brain mass osmotic shrinkage and reduced CSF formation (onset 30-60min and lasts up to 6hrs)
   3. Scavenging free hydroxyl radicals

Indications
   (i) Management of raised ICP in traumatic brain injury (TBI)
   A bolus dose of IV mannitol (0.25-1.0 g/kg) may be effective in management of raised ICP in the context of TBI with evidence transtentorial herniation. Need maintain euvolemia & serum osmolarity less than 320mosmoles [Level 2 Evidence].
   (ii) Reduction infarct size & improvement outcome in stroke (No conclusive evidence).
   (iii) Improving neurosurgical field access with reduction in brain mass
   (iv) Management of raised ICP in acute hepatic encephalopathy.
   (v) Reduction in cerebral oedema associated with DKA

2. Renal Effects
   Increased renal blood flow and GFR (via renal vasc resistance-direct & Indirect effects via changes in circulating volume & blood viscosity)
   Diuretic/natriuretic-osmotic (30%filtered H2O, 15% filtered Na)
   Dissipation of medullary hypotonicity
   Scavenging free radicals
   Post op cadaveric renal transplant oliguria – probable some benefit in graft protection.
   Contrast nephropathy, oliguric renal failure, peri-operative renal protection (major vasc. surgery) and myoglobinuric nephropathy diuretic effect established BUT no level 1 or 2 data for outcome.

3. Reduction of raised Intra-ocular pressure (IOP)

4. Ciguatera poisoning. A dinoflagellate toxin that accumulates at the top of the food chain from algae near dead corals and causes acute Na channel block axonopathy characterised by GI, CVS, neurologic symptoms. Mannitol has been accepted as the treatment of choice in CP, on the basis of reversal of Na channel block & reduced neuronal oedema. Not borne out by only prospective controlled trial.
3. Complications of IV Mannitol Therapy
1. Circulatory overload and acute pulmonary oedema
2. Uremic renal failure and dehydration
3. ↑ renal oxygen demand
4. Osmotic nephrosis: reversible vacuolisation of renal tubules with high dose mannitol
5. Electrolyte abnormalities, K (↓), Mg (↓), Na (↓ or ↑)
6. Agglutination with red cell transfusion
7. Rebound ↑ ICP
8. Accumulation in cerebral tissues after breakdown of BBB with theoretical risk of reverse osmotic effect
9. Irritant to tissues/veins
10. Crystallises at low temperatures

References
1. MIMS Annual 2001
DISCUSS THE MANAGEMENT OF A PATIENT WHO DEVELOPS SEVERE THROMBOCYTOPENIA AND ACUTE MESENTERIC ARTERY THROMBOSIS FIVE DAYS FOLLOWING IV UNFRACTIONATED HEPARIN FOR AN ACUTE PE

Dr. P. Liston. Intensive Care Unit, Liverpool Hospital, NSW

The following issues are identifiable
1. Acute PE, and its cardiorespiratory complications.
2. Heparin-induced thrombocytopenia (HITS) such that they have a thrombotic tendency and the need for alternative anticoagulation for the treatment of PE.
3. Acute mesenteric artery thrombosis with ischaemic gut and possible hypovolaemia, sepsis and septic shock.
4. The patient needs urgent surgery which will be complicated by thrombocytopenia and the medical condition.

HITS and its treatment
Thrombocytopenia is a well recognised complication of heparin therapy. HITS is an immune mediated disorder that classically occurs 4-10 days after commencement of therapy. IgG & IgM antibodies are provoked by the complex of heparin & platelet factor 4 on the platelet surface. This complex binds to the platelet surface and leads to further activation of the platelet with further release of PF4 creating a positive feedback loop. This leads to removal of platelets from the circulation & thrombosis. (Another form of thrombocytopenia can also occur with an earlier, transient lesser drop in platelet count, which is of no clinical consequence). The drop in platelet count is rarely below 20,000 & mostly about 60,000 so spontaneous bleeding is unusual. Surgical bleeds occurs in counts < 50,000.

Treatment
1. Stop heparin
   avoid LMWH as it may cross react with heparin induced antibodies.
   Don’t recommence UFH until antibodies are cleared & then for only short period.
   Don’t give warfarin until thrombocytopenia has resolved
2. Obtain diagnosis
   Thrombocytopenia in setting of heparin > 4 days
   Serotonin release assay ( the gold standard )
   Heparin induced platelet antibody assays (HIPAA)
3 Commence alternative anticoagulation (as patients at risk for thrombosis, but in this case defer in the presence of the need for urgent surgery)
   Danaparoid: a heparinoid that inhibits factor Xa
   BUT difficult to monitor, long TI/2, can’t reverse it.
   2500U bolus then infusion (400U decreasing to 200 U/hr )
4. Prevention
   judicious use of UFH or substitution where appropriate
   limit use of < 5 days and starting warfarin early
5. Other
   TEDs & calf compressors
**Ischaemic / infarcted gut & sepsis diagnosis & treatment**

Unfortunately the signs & symptoms of dead gut appear late in the course of the illness therefore delays in diagnosis & treatment are often inevitable.

acute abdo pain, bloody diarrhoea, fever, tachycardia, hypotension, abdo tenderness, decreased bowels, abdo distension. Peritonism often occurs later when the ischaemia becomes transmural.

AXR is often normal early on, later it may reveal distension, later perforation

**Ischaemic gut can lead to**
- respiratory failure from abdo pain & distension
- cardiovascular instability
- renal dysfunction from dehydration & sepsis
- haematological disorders
  - anaemia from haemolysis, thrombocytopenia, coagulopathy
- infection

Treatment should be directed at treating the ischaemic gut urgently
- resuscitation and correction of the above organ-system failures
- antibiotics
- urgent surgical consult &: preparation for surgery

- Decision to operate is based on clinical suspicion as there is no specific test for detecting ischaemia (except angiography)

**Place of Angiography**
- if the diagnosis is recognised early angiography may be useful to both confirm diagnosis & treat the occlusion (esp in the setting of HITS)
- if peritonitis is present then angio will only delay definitive treatment
- Also false positive/false negative results can confuse the issue.
- But advantages are that it is widely available, narrowing can be treated angiographically (treat spasm with papaverine, and clot can be treated with selective injection of thrombolytic)
- complications include reaction to contrast, renal impairment, bleeding

**Definitive Surgery**
- Failure of angiography should lead to surgery
- examination of the bowel, assessment of viability
- vascular reconstruction depends on
- surgical skill
- presence of viable bowel
- non viable bowel should be resected
- stoma formation
- leave abdo open
- second look after 24 hows

**Thrombocytopenia and bleeding in surgery**
- platelets should be given depending on the platelet count and on the amount of bleeding
- recommencement of alternative anticoagulation regimes 24 hrs after surgery (danaparoid)
References
2. Evans J. List the clinical features and management of a patient with HIT. ASCICM 1997 Handbook
DISCUSS THE INDICATIONS AND COMPOSITION OF LACTATE FREE DIALYSIS

Dr. D. Ghelani, Intensive Care Unit, Queen Elizabeth Hospital, SA

Renal replacement therapies in ARF have three major aims; detoxification, fluid elimination and compensation of acidosis. In CRRT, the physical properties of haemofiltration, haemodialysis or haemodiafiltration are therefore used. Three different forms of substitution fluids have been used for haemofiltration. However, acetate-buffered substitution fluids should not be used as they provide lower haemodynamic stability & poor control of acidosis. In present day technique, lactate-buffered or bicarbonate-buffered (lactate free) substitution fluids are used.

Up to 1000 mmols/day of bicarbonate is removed by CVVHDF and this needs to be replaced to ensure acid-base balance. Commercially available solutions are lactate buffered, which is converted to bicarbonate on equimolar basis under physiological conditions. The lactate buffer has advantage of greater stability over a physiological bicarbonate buffer. Lactate buffered solutions may lead to daily lactate load of 800-1300 mmol which needs to be converted to bicarbonate by liver.

**Composition of dialysate fluids:**

<table>
<thead>
<tr>
<th></th>
<th>Lactate Buffered Solution</th>
<th>Bicarbonate Buffered Solution*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mmol/L)</td>
<td>142</td>
<td>142</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>103</td>
<td>109</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.0</td>
<td>1.66</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
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<td>0</td>
</tr>
<tr>
<td>Magnesium (mmol/L)</td>
<td>0.75</td>
<td>0.66</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.6</td>
<td>10</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>44.5</td>
<td>3</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>0</td>
<td>33</td>
</tr>
</tbody>
</table>

* Initial solution has sodium concentration of 109 mmol/L, with no bicarbonate ions. Hundred (100) mL of NaHCO₃ (8.4%) is added immediately before use to form a buffered normotonic solution. The ready mixed solution is prepared in bags made of special plastic sheering to prevent evaporation of CO₂. To avoid precipitation of calcium & magnesium carbonate, the concentration of these electrolytes is reduced. Phosphate is not included in the solutions.

**Indications of Lactate free Dialysis:**

To date only few studies have compared different buffers used in substitution fluids. From these data, following conclusions can be drawn:

1. Control of uraemia within 48 hours with both buffered patients in acutely ill ARF patients is same.
2. There was no difference in haemodynamic and other parameters (drop in MAP, need for positive inotropic agents) between the groups with different buffers.
3. Sufficient control of acidosis was achieved with either bicarbonate or lactate-buffered solutions.

In critically ill patients, the physiological capacity of lactate metabolism allows either lactate or bicarbonate buffered solutions without any adverse events.

However, hyperlactataemia may result in patients with severely impaired lactate metabolism or high existing lactate levels. Lactate accumulation can be associated with alteration in
NADH:NAD ratio, increased protein catabolism, increased urea generation & myocardial depression. Therefore, only bicarbonate buffered (Lactate free) solutions are indicated for:
1. Concomitant Liver failure
2. After Liver transplantation
3. Lactic acidosis

References
DISCUSS THE CURRENT INDICATIONS AND CONTRAINDICATIONS OF INTRAVENOUS LIGNOCAINE

Dr. G. Brieva, Intensive Care Unit, John Hunter Hospital, Newcastle, NSW

Lignocaine is a group lb anti-arrhythmic and a local anaesthetic agent of the amide type. By blocking the Na/K influx to the cells, it decreases the refractory period on the AV node and Purkinje fibers, reduces the action potential duration and decreases the automaticity and the membrane responses both in the Purkinje fibers and in the neural conduction pathways. On the ECG these effects will reduce the Q-Tc, evidence of shortened repolarization. Intravenous doses are based on weight and depending of the indication, usually between 1 and 2 mg/kg as a bolus, however doses up to 4 mg/Kg have been used in status epilepticus. Following initial bolus, maintenance is indicated and plasma levels must be obtained.

**Current Indications.**
- Serious ventricular arrhythmias (VT/VF)
- Digitalis-induced ventricular tachyarrhythmias
- Routine prophylactic use of lidocaine for the treatment of acute myocardial infarction (AMI) is NOT recommended, with the possible exception being situations in which a defibrillator is unavailable.

**Not approved reported uses**
- Aortocoronary bypass surgery: prior to clamp release reduces the rate of reperfusion VF.
- Asthma: attenuate reflex bronchoconstriction following inhalational histamine challenge in patients with bronchial hyperreactivity.
- Cough suppression: during cataract surgery.
- Adjunctive therapy for decompression illness.
- Diabetic Neuropathy: effective in reducing painful symptoms.
- Chronic intractable hiccups.
- Infusion-related pain: reduces the incidence of pain associated with propofol.
- Reduces the intracranial pressure increment during endotracheal suctioning.
- Liver function assessment: Principal lidocaine metabolite (MEGX) predicts morbidity and mortality related to liver disease.
- Peripheral angiography-related pain.
- Postoperative pain control.
- Refractory pruritus.
- Pulmonary artery catheterisation: decreases the risk of mechanically-induced arrhythmias.
- Seizures: reported effective in the treatment of refractory status epilepticus.
- Tinnitus Aurium: can improve or abolish tinnitus.

**Contraindications**
- Hypersensitivity to lignocaine or amide type of local anaesthetics

**Precautions**
- Adams-Stokes syndrome
- Advanced Heart failure
- Severe degree of SA, AV or intraventricular block
- Hepatic disease
- Hypovolaemia
- Renal disease
- Shock
- Sinus bradycardia
- Wolff-Parkinson-White syndrome
References
DISCUSS THE MANAGEMENT OF A ONE DAY POST ABDOMINAL AORTIC ANEURYSM PATIENT WHO HAS HAD AN ACUTE ANTERIOR MYOCARDIAL INFARCT

Dr E. Trent. Intensive Care Unit, Royal Perth Hospital, WA

Risk /benefit situation.
- Risk of bleeding from surgical site if treated conventionally for MI
- Risk of death from MI if not treated
The aggressiveness of treatment will depend on the clinical severity of the myocardial infarction and surgery related factors.

Confirm diagnosis: History, examination, ECG, cardiac enzymes, ECHO (RWMA).
⇒ Acute Reperfusion is ultimate goal - restore flow.

GENERAL PRINCIPLES OF MANAGEMENT IN THE POST-SURGICAL SETTING

Optimise the myocardial supply and demand
- Increase Myocardial Oxygen supply: Increase O2 delivery (flow x O2 content)
  1. Increase diastolic BP if low, CPP = DBP-LVEDP
  2. Transfusion if Hb < 100. (80g/l some)
  3. Decrease heart rate - analgesia, beta-blockers
  4. Reperfusion is ultimate goal - restore flow
  5. Maintain adequate oxygenation
- Decrease myocardial demand
  1. Good analgesia
  2. Decrease Heart rate, contractility
  3. Decrease afterload
  4. Treat fever

Initial MI therapy: Aim to relieve ischaemic pain, assess haemodynamic state and correct abnormalities present
1. Oxygen, analgesia- morphine, monitoring in appropriate environment, i.e. continuous ECG, SPO2, U/O, NIBP +/- arterial pressure, PAC depending on circumstances and pre-existing monitoring
2. Aspirin as soon as possible after the symptoms (2) or Clopidogrel if aspirin not tolerated
3. Intravenous nitroglycerine if ischaemic pain present + for control hypertension and symptoms of heart failure. No convincing evidence for prophylactic nitrates or continued therapy for 4-6 weeks
4. Beta-blocker: metoprolol or atenolol if no contraindications according to haemodynamic state. (Multiple studies support) Many high-risk vasculopathic patients would have been started on peri operative beta blockage.

Reperfusion therapies
Liase with the surgical team about how aggressively you can anticoagulate. Aggressiveness of treatment approach depends to some extent on nature of the operation, other peri operative surgical complications and on the stability of the patient. In an unstable patient with cardiogenic shock you would accept a higher bleeding risk for the benefit of reperfusion.
Aspirin/clopidogrel ⇒ heparin ⇒ GIIbIIIa inhibitors?
1. Primary percutaneous coronary intervention (PCI): therapy of choice with better outcome than thrombolysis (ACC/AHA) in STEMI - consult cardiologists in this peri operative scenario

Issues in this AAA repair patient one-day post op:

- Availability in hospital
- Access (if through the groin with graft in abdominal aorta), alternative through arm arteries.
- Anticoagulants for PCI: GIIbIIIa, heparin and risk of bleeding at AAA graft site and epidural space if epidural in situ. Interventional cardiologists in my hospital (RPH) have performed PCI with stenting in this situation with aspirin, clopidogrel, minimal heparin (2500u) and without GIIbIIIa inhibitors and would use femoral access past the new aortic graft.

2. PCI not available or surgical intervention indicated on angiogram; consider CABG consult cardiothoracic surgeons.

3. Thrombolysis is contraindicated one- day post operatively.

Anticoagulation issues

1. Heparin infusion: Suggestive but no definitive evidence of benefit post PCI. ACC/AHA currently recommends as class one evidence. Limits re-thrombosis on an ulcerated plaque. Use for 48hours only unless other reasons to continue like high risk of VT.

2. IV, SC Heparin or LMWH in patients not receiving reperfusion therapy

3. Epidural analgesia sited for post op analgesia may need consideration- epidural haematoma risk versus benefit of good analgesia. Consult anaesthetists - Removal first then anticoagulate may be the best option.

Early risk stratification

High-risk features are older age, previous MI, low BP, tachycardia, heart failure, and anterior MI - so this patient is high risk

Patients with none of these features are considered low risk

Further medical therapy

Depends on the response to the initial regimen ⇒ relief of pain and reduction in ST elevation AND the current haemodynamic profile

1. ACE inhibitors should be given to all patients without a contraindication after first 24 hours. Caution is necessary with hypotension. HOPE trial - all Caucasian patients might benefit from chronic therapy. ATII receptor blockers should not be considered a first line alternative to an ACE unless not tolerated

2. IV/Oral beta-blocker should be continued or begun if no contraindications

3. Statin therapy may benefit all patients not just those with LDL cholesterol > 3.2mmol/L. Benefit within 24-96 hours so begin immediately. Probably via antiinflammatory and lipid lowering effects.

4. DVT prophylaxis

5. No calcium channel blocker has been shown to reduce mortality in acute MI- restrict to certain settings

6. Anticoagulation if chronic AF or left ventricular thrombus

Complications

1. Cardiogenic shock: supportive care, dobutamine, vasopressors, IABP- Consider abdominal stent and risk with IABP: Aortic surgical graft - probably OK if balloon above upper
anastomosis. Endovascular stent may be different because of the spikes into the arterial wall.

2. Arrhythmias: Don’t use antiarrhythmics prophylactically. May be needed to revert or prevent recurrence of SVT and VT. AV nodal and IV Conduction abnormalities may be seen in ST elevation anterior MI’s. Symptomatic bradycardia’s may need temporary pacing

3. Post MI ischaemia in the setting where you have elected not to do PCI - Reconsider revascularisation options.

4. Surgical Bleeding - stop heparin, transfuse, support

Discharge planning

1. Depends on the surgical management and complications and the STEMI management

2. Risk stratification - evaluation of LV function (reduced EF is one of the major predictors of future cardiac events) 2D echo, exercise test if no PCI or CABG performed - timing differs between centres and in different circumstances

3. Lifestyle changes; dietary modification, exercise, smoking cessation, weight loss in obese patients, reducing emotional stress, multifactorial cardiac rehabilitation, treatment of hypertension and diabetes (tight sugar control DIGAMI study).6

References

1. ACC/AHA guidelines for the management of patients with AMI, Circulation 1999; 119:228S


3. Effects of an angiotensin-converting-enzyme Inhibitor, ramipril, on cardiovascular events in high risk patients NEJM 2000; 342:145

4. Effect of carvedilol on outcome after myocardial infarction in patients with left ventricular dysfunction: CAPRICORN. Lancet 2001; 357:1385

5. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high risk individuals: a randomised RPCT. Lancet 2002; 360:7


General references

7. Up-To-Date 2003 11.1

DISCUSS THE MANAGEMENT OF A SEVERELY HYPOXIC PATIENT WHO HAS BEEN PARALYSED WITH SUXAMETHONIUM WHOM YOU ARE UNABLE TO INTUBATE OR VENTILATE

Dr. R. O'Connor, Intensive Care Unit, Port Macquarie Hospital, Port Macquarie, NSW

This is a life threatening emergency. Call for assistance immediately.

While rare in the operating theatre setting (incidences quoted in the literature range from 1:1,000 in the audit by Parmet et al,1 to 0.2-1:10,000) inability to intubate may occur in 0.5-1% of patients requiring invasive airway management in the Emergency Department or Intensive Care Unit. This is due to a variety of patient and ergonomic factors. Up to 15-20% of these will be difficult to ventilate by bag and mask.

There are four management options:-
• Cricothyrotomy, either surgical or needle;
• Tracheostomy; or
• Insertion of a laryngeal mask airway to enable ventilation and subsequent endotracheal intubation.
• Insertion of a Combitube to enable ventilation.

Cricothyrotomy

The two key problems associated with this procedure are obtaining access and maintaining it. The anatomy may be difficult to identify due to body habitus or pathological factors (e.g. haematoma, abscess, tumour, oedema, neck scarring). Access may be limited by distended veins.

The surgical approach is simple in concept - incise the skin and cricothyroid membrane, dilate the entry wound with the scalpel handle or a set of artery forceps and insert a tracheostomy or endotracheal tube. Experienced operators can place an airway in less than 30 seconds. Haemorrhage and misplacing the tube are potential significant complications.

Needle puncture can be performed even more rapidly, but has several disadvantages. Large bore IV cannulae are prone to kink. Needle movement can be difficult to prevent, leading to bleeding or even posterior tracheal wall perforation.

To maintain adequate oxygenation through such narrow tubes, high pressure (jet) ventilation is required. A jury-rigged jet ventilation system can be assembled from an IV ‘pump’ giving set. The pump chamber is cut and one end placed over the common gas outlet of the anaesthetic machine. Breaths are delivered by hitting the oxygen flush button.

Catheter migration can then cause pneumothorax or massive subcutaneous emphysema. If there is no route for exhalation (e.g. complete upper airway obstruction) gas trapping can lead to haemodynamic compromise.

More complex needle-based approaches rely on percutaneous dilation using the Seldinger technique. A variety of cricothyrotomy kits are available in which a single dilator is passed before the airway tube over the guidewire. Care must be taken to ensure that the end of the guidewire remains intratracheal. In any case, cricothyrotomy is a temporising step until a definitive airway can be established. This is usually a tracheostomy.
Tracheostomy

There have been case reports of the successful use of percutaneous dilational tracheostomy to securing the airway in an emergency situation, e.g Dob et al. This appears to be a very useful technique, provided the operators are sufficiently skilled.

Most of the time though, tracheostomies are going to be performed by surgeons under somewhat more controlled conditions. The potential for morbidity remains high, both in the short (bleeding, pneumothorax, air embolism) and long term (granuloma, tube malposition, obstruction, disconnection).

It has been estimated that emergency surgical airways have an overall 30% complication rate.

The Laryngeal Mask Airway

The ordinary LMA and the intubating laryngeal mask (Fastrach) have been reported to provide good conditions for ventilating and enabling endotracheal intubation in a wide variety of difficult situations. The main advantage of these devices are that they are relatively easy to place.

If cricoid pressure has been applied, briefly releasing it at the time of insertion may increase the likelihood of successful placement. Endotracheal tubes can then be inserted either blindly, or assisted with a bougie, tube changer or fibreoptic bronchoscope.

The size 4 LMA will take up to a size 6 microlaryngoscopy tube.
The size 5 LMA can be used with a 7 or 7.5 ETT.

The LMA is less likely to be useful in the clinical situation described above, for the following reasons:

- In patients with periglottic or subglottic pathology causing their airway problems, the LMA is unlikely to effect an improvement in the ability to ventilate.
- The risk of aspiration is greatly increased if inspiratory pressures greater than 20 cm water (oesophageal opening pressure) are required using the LMA. Therefore, it is less likely to be useful in patients with poor lung compliance.

The Combitube

This is a double lumen, double cuffed tube which can be blindly inserted into the oesophagus. It is designed to prevent or limit aspiration and facilitate ventilation by the arrangement of side holes proximal to the tracheoesophageal cuff) which can be positioned either in the esophagus or in the trachea, serving to seal these structures. It has been used as an aid to endotracheal intubation.

Problems with this device include the potential for soft tissue injury and even oesophageal perforation. Most of the literature discussing the Combitube comes from Europe and the U.S. The product doesn’t seem to be uniformly available in Australasia. It therefore has all the disadvantages of the LMA with the addition of lack of familiarity.

Conclusions

In the scenario initially outlined, placing a laryngeal mask airway and seeing if ventilation is possible is a valid first move in some cases. Most medical staff involved in acute care settings are familiar with the use of the LMA.

Unfortunately, far fewer are proficient in establishing surgical airways which seems to be the most appropriate initial manoeuvre in this clinical context. This may change with more systematic and extensive training in airway management.
SUMMARY
Discuss the management of a severely hypoxic patient who has been paralysed with suxamethonium whom you are unable to intubate or ventilate.

- ‘Can’t intubate can’t ventilate’ (CICV) scenario relatively rare but significantly higher incidence in ICU or Emergency Department population (0.5-1%) compared to the operating theatre (1:1,000 - 0.2:10,000) for a wide variety of reasons.

- Calling an arrest or getting assistance by other means is a good opening gambit.

- Cricothyrotomy best next move in the setting of CICV + severe hypoxia.
- The operator should use the technique they are most familiar with in this crisis situation.

- Both surgical and needle crics are not without potential morbidity.

- Attempting to place an LMA or Combitube to restore ventilation and therefore buy time another option, but unlikely to succeed with periglottic or diffuse pulmonary pathology.

Tracheostomy is the definitive airway option, but ideally awaits a more controlled situation than that given above

References

General References
DISCUSS THE MANAGEMENT OF A PATIENT WITH SEVERE VERAPAMIL OVERDOSAGE

Dr. P. Nelson, Intensive Care Unit, Royal Perth Hospital, WA

Diagnosis
1. History
2. Clinical features:
   - **Cardiovascular**
     - Hypotension
     - Bradyarrhythmias (blockade of AV nodal conduction)
     - Asystole
   - **Central nervous system**
     - Lethargy, slurred speech, confusion, drowsiness, coma
     - Respiratory arrest
     - Seizures
   - **Gastrointestinal**
     - Nausea, vomiting
     - Ileus, obstruction
     - Bowel ischaemia, infarction
   - **Metabolic**
     - Hyperglycaemia (decreased insulin release)
     - Lactic acidosis

Management
1. General management
   - Airway, breathing, circulation
   - Gastric lavage (if <1 hour post ingestion)
   - Activated charcoal
   - Consider whole-bowel irrigation and repeat doses of activated charcoal*
     (*if sustained-release preparation)
   - IV calcium chloride if critical
   - ICU admission; ECG monitoring
   - Exclude other poisons (e.g. paracetamol, aspirin)
2. Arrhythmias
   - Asymptomatic: Supportive measures
   - Symptomatic: Atropine, isoprenaline, pacing
3. Hypotension
   - Arrhythmias as above
   - 10ml 10% calcium chloride or 30ml 10% calcium gluconate over 5 minutes
     (Repeat doses as necessary every 15-20 minutes up to 4 times)
   - Glucagon, 2-5mg IV over 5 min, repeat doses or infusion
   - Dopamine, dobutamine, noradrenaline
4. Central nervous system
   - Seizures: Phenytoin, benzodiazepine, or phenobarbitone
5. Other
   - Insulin-dextrose (hyperinsulinaemic euglycaemia): not yet proven
References
DISCUSS THE CLINICAL FEATURES AND MANAGEMENT OF A PATIENT WITH A SAGITTAL SINUS THROMBOSIS

Dr. B. Welch, Intensive Care Unit, Mackay Base Hospital, Queensland

Thrombosis of the venous sinuses is an uncommon cause of cerebral infarction relative to arterial disease but is an important consideration because of its potential morbidity. When occlusion of venous sinus occurs, resulting venous congestion can lead to infarction. Venous infarcts are frequently haemorrhagic and commonly occur within the white matter or at the grey-white matter junction.1,2

CLINICAL FEATURES

Uniform age distribution in men with sagittal sinus thrombosis (SST), although 61% of women with SST aged between 20-35 years. This may be related to pregnancy and use of oral contraceptives.

**Symptoms:**
- Headache, may be thunderclap headache3
- Nausea and vomiting
- Confusion
- Focal or generalised seizures

**Signs:**
- Weakness of lower extremities with bilateral Babinski signs or unilateral hemiparesis or paraplegia.
- There may be a rapid development of stupor and coma.
- When SST occurs as a complication of bacterial meningitis, nuchal rigidity with Kernig's and Brudzinski’s signs may be present.

AETIOLOGY OR POSSIBLE ASSOCIATED FACTORS

**Hypercoagulability**
- Pregnancy, puerperium, oral contraceptives4
- Antiphospholipid syndrome5
- Protein S and C deficiencies6,7
- Anti thrombin III deficiency
- Lupus anticoagulant autoimmune diseases
- Haematological conditions, thrombotic thrombocytopenic purpura, polycythaemia vera, etc
- Nephrotic syndrome, dehydration
- Inflammatory bowel syndrome
- Drugs: Tamoxifen, steroids

**Stasis of local bloodstream**
- Complication of septic meningitis, HIV8
Abnormality of vessel wall
- Trauma (even minor head trauma)\(^9\)
- Neurosurgical procedures (dural tap)

25% of cases unknown aetiology.

SPECIAL INVESTIGATIONS

CT scan
- Infarction that does not respond to an arterial distribution. In absence of haemorrhagic component may delay demonstration of infarct 48-72 hours.
- Empty delta sign \(^{10,11}\) on contrast as enhancement of the collateral veins in SSS walls surrounding a non-enhanced thrombus in the sinus - frequently absent.

MRI
- Infarct not typical of expected arterial occlusion.
- MR venography
- Single-slice phase-contrast angiography

Carotid Arteriography

Lumbar Puncture
- Helpful in meningitis, but otherwise not performed, risk of herniation with large lesion.

MANAGEMENT
a. Fluids - N Saline
b. Elevate head 30\(^\circ\)-40\(^\circ\)
c. Treat seizures- Phenytoin, Diazepam, Lorazepam
d. Anticoagulation
   - Heparin infusion \(^\frac{1}{2}\)
   - LMWH\(^{12}\)
   - Thrombolytic therapy - micro-catheter technique

=> Followed by Warfarin, depending on aetiology if permanent risk factor- lifelong anticoagulation

e. Surgical thrombectomy- Only in severe neurological\(^{13}\) deterioration combined with local infusion of TPA
f. Appropriate antibiotics for meningitis cases.

PROGNOSIS
- Mortality in recent studies varies between 6 and 20%, including residual focal neurological deficits.
- \(\pm\) 30-80% patients have\(^{14}\) a full recovery, but is improved with new diagnostic techniques. Frequency of long-standing epilepsy is low, suggesting longterm anticonvulsant not necessary.

References
DISCUSS THE MANAGEMENT OF A PATIENT WITH AN ACUTE CENTRAL VENOUS LINE CANDIDA SEPTICAEMIA AND ENDOPHTHALMITIS WHO DEVELOPS OLIGURIA AND A PROGRESSIVE RISE IN PLASMA CREATININE

Dr. H. Koelzow, Intensive Care Unit, Royal Prince Alfred Hospital, NSW

The management of this patient involves the treatment of the candida septicaemia and resuscitation to prevent / treat acute renal failure.

As part of the treatment of the infection, the catheter should be removed, because it serves as a persistent nidus of infection and this is especially important for candida infected catheters. Most studies show that outcome is improved if the catheter is promptly removed.¹

Major complications of catheter related infections include septic shock, supplicative thrombophlebitis, metastatic infection and endocarditis. In this patient ocular involvement has already occurred. Small white retinal exudates appear in about 10% of patients with candidaemia. Retinal detachment, vitreous abscess and extension to the anterior chamber may occur over the following weeks. Antifungal treatment for patients with central venous catheter candidaemia is either fluconazole (400 mg/day) or amphotericin B (0.5 mg/kg daily).² The preferred treatment for endophthalmitis is intravenous amphotericin B with or without flucytosine and should be continued for 2 weeks after the patient becomes afebrile. Vitrectomy may be necessary for a vitreous abscess and the injection of amphotericin B into the vitreous humor can also be helpful. Regular fundoscopy should be performed to ensure that retinal lesions resolve completely.

The commonest and most serious unwanted effect of amphotericin B is renal toxicity, with some degree of reduction in renal function occurring in more than 80% of patients. There are three liposome-encapsulated forms of amphotericin available with a significantly lower degree of nephrotoxicity and unchanged antymycotic action: Liposomal amphotericin B, Amphotericin B lipid complex and Amphotericin B colloidal dispersion. As this patient already demonstrates signs of renal impairment one of these formulation should be chosen for the antifungal treatment.

The incidence of nosocomial bloodstream infections caused by Candida species has risen 5 to 10 fold in the past 20 years and candidemia currently accounts for 10 to 15% of hospital acquired infections of the bloodstream.³ A recent cohort analysis found a very high mortality of 60% and a high likelihood of associated multiple organ failure. These patients were also more likely to have underlying renal failure at baseline.⁴ This has already occurred in this patient who suffers from oliguria and progressive rise plasma creatinine. Aggressive resuscitation needs to be implemented as soon as possible in order to prevent acute renal failure and other organ dysfunction. The first step is restoration of intravascular volume which should be done with monitoring of intraarterial and central venous pressure. Mean arterial blood pressure should be maintained above 70 mmHg (higher in the presence of premorbid hypertension) to guarantee adequate renal perfusion. If this is unable to be achieved with fluid resuscitation alone, LV preload and CO should be assessed with a pulmonary artery catheter or PICCO and optimized using the appropriate inotropes and / or vaspressors. Unfortunately therapy with dopamine, frusemide, mannitol, calcium channel blockers, growth factor etc have not been shown to be beneficial in preventing or treating renal failure. Frusemide might convert oliguric into polyuric renal failure if used after adequate fluid resuscitation, but has no effect on mortality or duration of renal failure. If despite these measures renal failure progresses renal replacement therapy should be commenced early. The management of this patient involves the treatment of the candida septicaemia and resuscitation to prevent / treat acute renal failure.
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References
DISCUSS THE CLINICAL FEATURES AND MANAGEMENT OF A PATIENT WITH DIASTOLIC HEART FAILURE

Dr. B. O’Brien, Intensive Care Unit, The Alfred Hospital, Victoria

Diastolic cardiac failure means clinical heart failure in the presence of a normal ejection fraction (EF). This is postulated to result from slow or incomplete relaxation of the heart in diastole, impairing the organ’s filling. It probably contributes to the symptoms of over 50% of elderly patients with heart failure. The existence of diastolic failure as a specific entity remains controversial, however.

The symptoms of dyspnea on exertion, productive cough, reduced exercise tolerance, orthopnea/nocturnal dyspnea and fatigue are typical of heart failure. Physical findings of dependent edema, crepitations on auscultation, a raised jugular venous pulse and tachypnea are expected. Those who recognise diastolic failure (DF) as a clinical entity cite the results of studies on a subgroup of heart failure patients with a normal EF – this is DF by definition. Epidemiologically, such studies suggest that DF is more commonly encountered in the elderly, diabetics, those with hypertension and in females than is systolic failure (SF). Those affected have less severe limitations to their exercise tolerance, and a better quality of life than those with SF, though both are worse than in age-matched controls. DF and SF do not differ in regard to findings on clinical examination, or measurement of central venous or pulmonary capillary wedge pressures (CVP and PCWP), and measures of neuroendocrine activation are also similar (eg plasma levels of norepinephrine and natriuretic peptides). Thus the diagnosis is problematic, especially since many patients with heart failure are managed through primary care, and are identified and treated according to clinical findings.

In terms of routine monitoring of venous and pulmonary pressures, both forms of heart failure involve increased left ventricular end diastolic pressure (LVEDP), and thus of CVP and PCWP also. Echocardiographic findings of increased left ventricular mass/volume ratio, normality of EF, low end-systolic (LVESV) and end-diastolic volumes (LVEDV) and slow diastolic filling are typical of DF in contrast to SF. Many derived variables are suggested to distinguish DF and SF, but the usual criterion for inclusion in studies has been clinical heart failure with an EF above 50%. On exercise testing such patients were found to have a significantly higher pulse pressure than healthy controls or those with SF.

The optimum treatment of the DF patient is not established. It is suggested that the routine use of diuretics may be harmful and that they should be used with greater caution in DF than in SF lest preload be dangerously reduced. The heart with SF is relatively preload insensitive, tolerating diuresis well. Drugs that improve ventricular relaxation – positive lusitropes – are suggested to be appropriate agents for DF. Studies are underway to evaluate Perindopril and Candesartan, and it is believed that the renin-angiotensin-aldosterone axis will be a major target of therapy. Calcium channel antagonists and phosphodiesterase inhibitors may also prove to be useful, while exercise and magnesium supplementation are advocated without compelling evidence. There are no well-conducted trials in the literature on the effects of drugs on patients with pure DF. The best recommendations at present are that hypertension and ischemia be controlled, sinus rhythm maintained and circulating volume optimized, by avoiding salt intake, using diuretics or fluids. Interestingly, though caution regarding diuretic use is emphasized by many authors, in the most cited study on DF all patients were treated with furosemide. The critical care management of DF has not been investigated. The titration of standard therapy of diuretics, inotropes and vasodilators against measured variables – cardiac output, blood pressure, respiratory rate and oxygenation, etc – appears reasonable. This is common critical care practice.
Many experts are sceptical about the concept of DF. Some point out that this distinction between subtypes of heart failure is simplistic, as “a heart that cannot fill cannot empty, and vice versa”, while the architecture of failing hearts varies widely. One study on those diagnosed with DF suggested that they had been mostly misdiagnosed, and had other illnesses which explained their symptoms. Others have suggested that transient systolic dysfunction or mitral regurgitation explains the phenomenon, though this seems unlikely. Finally there is a view that the changes of DF are part of the normal ageing process, and that they don’t constitute a genuine disease entity.

Overall, it seems likely that diastolic dysfunction contributes to the illness of many people with cardiac failure, though presumably SF and DF may overlap in many individuals. The best treatment has not been established, and until a distinction in therapy for these subtypes of heart failure can be made, the usefulness of separating DF from SF will probably remain contentious. Though patients with DF and SF are not easily distinguished, there is as yet little evidence that the distinction is critically important. Ongoing trials may provide an evidence base to resolve this issue.

References
DISCUSS THE INDICATIONS AND COMPLICATIONS OF INTRAVENOUS OCTREOTIDE

Dr. S. Morphett, Intensive Care Unit, Royal Hobart Hospital, Tasmania

Introduction
Octreotide is a peptide and cyclic analogue of the hormone somatostatin. Somatostatin is actually a multigene family of peptides with two important bioactive products – somatostatin-14 and somatostatin-28. (14 and 28 amino acids respectively).\(^1\) Somatostatin has widespread and diverse effects that are mediated through specific membrane receptors, of which there are five subtypes.\(^2\) All five subtypes mediate their effect via modulation of adenylate cyclase activity, reducing intracellular cAMP, an effect which is G-protein linked.

The spectrum of activity of somatostatin includes:
- CNS modulation of neurotransmission
  - Inhibition of release of growth hormone and thyrotropin
- GIT inhibition of glandular secretion
  - Inhibition of release of vasoactive intestinal polypeptide and gastrin
  - Inhibition of exocrine and endocrine functions of the pancreas (including inhibition of insulin and glucagon production).
  - Decrease in neurotransmission and smooth muscle contractility.
- Other
  - Inhibition of function of activated immune cells
  - Antimitotic activity

Octreotide was developed as a longer acting analogue of somatostatin with particularly potent inhibition of growth hormone release.

Indications
The indications for the use of octreotide intravenously are essentially in the management of acute upper gastrointestinal haemorrhage. There are two areas to be considered – Oesophageal variceal and non-variceal bleeding.

Acute oesophageal variceal haemorrhage:
In this setting, octreotide decreases portal and intravariceal pressures by blocking the release of vasodilator substances such as glucagon. The dose used in relevant trials involves an initial bolus dose, usually 50 mcg, followed by an infusion of 25 – 50 mcg/hr for 2 – 5 days.

Octreotide has been shown to be effective in the initial control of variceal bleeding and in the prevention of re-bleeding, when compared to placebo. It appears to be more effective than vasopressin and have fewer complications, in a recent meta-analysis.\(^3\) A different meta-analysis confirmed the effect on initial bleeding (compared to placebo) but questioned the size of the effect and found no effect on number of patients re-bleeding.\(^4\) Neither meta-analysis found a decrease in overall mortality with the use of octreotide/somatostatin, compared to placebo. The beneficial effect of octreotide appears to be about equivalent to that of sclerotherapy.

Where possible, emergency endoscopic treatment remains the definitive therapy (banding is superior to sclerotherapy). The combination of octreotide with endoscopic treatment is better than either approach alone. (In stopping bleeding and reducing re-bleeding) This was confirmed in a recent meta-analysis\(^5\) and has been recomended in a recent review.\(^6\) There is a trend towards decreased mortality with the combined approach.
Octreotide for acute non-variceal upper gastrointestinal bleeding:

Octreotide can be useful in this situation. It has been studied in a well-conducted meta-analysis. It included 1829 patients from 14 trials (12 using somatostatin and 2 using octreotide) The relative risk for continued or repeat bleeding if somatostatin/octreotide was used was 0.53 (95% CI 0.43-0.63).

In subgroup analysis, the effect was most pronounced on stopping initial bleeding, rather than preventing re-bleeding and was also more pronounced if the bleeding was from peptic ulcer disease.

There was a trend towards a decrease in need for surgery with somatostatin/octreotide but no difference in transfusion requirements. Mortality was not an endpoint. Of note is that octreotide was used in only 2 of the studies, which had conflicting results.

Complications

Octreotide is generally well tolerated with less side-effects than other vasoactive infusions used in the above settings, such as vasopressin. Problems are as might be expected from the drug’s spectrum of activity.

- Hypo/hyper-glycaemia – suppresses glucagon more than insulin, therefore might expect hypoglycaemia, but clinically may see either. Insulin requirements in diabetic patients may fluctuate widely.
- Gastrointestinal side effects – include anorexia, nausea, vomiting, abdominal bloating and pain and may cause steatorrhoea.
- Cholelithiasis – very unlikely to be a problem with short term use.
- Rarely – acute pancreatitis, bradycardia, hypersensitivity.
- Drug interactions – decreases absorption of cyclosporin, potentially precipitating transplant rejection.

Summary

An intravenous infusion of octreotide is effective in stopping acute oesophageal variceal haemorrhage, both in combination with endoscopic therapy, or alone if this is not available. It does not alter mortality. It is also useful in stopping bleeding in non-variceal upper gastrointestinal haemorrhage and is used in our unit if the patient has continued or re-bleeding on proton pump inhibitors.

Octreotide is generally safe and well tolerated.

Other indications:

Octreotide may be used subcutaneously for therapy in acromegaly, high output fistulae or “short gut” syndromes, VIPomas, preparation for pancreatic surgery, AIDS associated diarrhoea, carcinoid and a variety of other endocrine tumors.

References

DISCUSS THE AETIOLOGY AND MANAGEMENT OF A PATIENT WITH HEPATOPULMONARY SYNDROME AND PORTOPULMONARY HYPERTENSION

Dr. C. Allen, Intensive Care Unit, Royal Perth Hospital, WA

High flow hyperdynamic circulation – imbalance between vasoconstrictors and vasodilators, and other mediators synthesised or metabolised by the liver

Pulmonary Consequences:
1. Hepatopulmonary Syndrome
2. Portopulmonary Hypertension

Hepatopulmonary Syndrome:
1. Liver disease
2. arterial hypoxaemia
3. intrapulmonary vascular dilatations

Liver Disease: portal hypertension (almost always); cirrhotic (10-20% develop HPS), non-cirrhotic (relatively rare)

Arterial Hypoxaemia: definitions vary, room air \( p_aO_2 \) < 70 mmHg, \( p_{A-a}O_2 > 20 \) mmHg
  - co-morbidities must be considered (important in 20–30% of HPS cases)
  - response to 100% may be useful

Intrapulmonary vascular dilatations: contrast ECHO or \( ^{99m}TcMAA \)~>6%

Aetiology:
Almost any liver disease, cirrhotic or non-cirrhotic causing portal hypertension may give rise to HPS

Pathophysiology:
  1. Pre-capillary/capillary dilations (ventilation with excess perfusion) and
  2. Anatomic shunting important (perfusion with no ventilation)
Relative importance of these factors varies

Cause of these abnormalities uncertain, possibilities include
  1. failure of liver to clear circulating pulmonary vasodilators
  2. production of a circulating vasodilator

Increasing evidence that nitric oxide may play a central role in pathogenic vasodilatation
  • benefit from methylene blue on pulmonary pressures and oxygenation
  • variety of animal experimental work implicating NO

Treatments:
No medical therapies demonstrated to be of sustained benefit
  - some evidence that methylene blue has short-lived benefit after single dose infusions
  - case reports of improvement with: long-term high-dose aspirin, almitrine bismesylate, indomethacin, garlic
  - supplemental oxygen, suggested 24 hours/day, 1–3 L/min
  - coil embolotherapy if discrete arteriovenous communications identified
  - TIPSS (case reports mixed, controversial)

Liver Transplantation (OLT)
  - HPS once considered to be a relative contra-indication
  - now a recognised indication in many transplant centres
  - HPS resolves in 62–82% of cases of successful OLT, resolution of hypoxaemia may take up to 15 months
  - outcome likely to be poor if room air \( p_aO_2 < 50 \) mmHg AND Shunt fraction > 20%
mortality is higher (20–30% @ 1 year) than in transplanted patients without HPS (~10% @ 1 year).

Inhaled NO may improve hypoxaemia immediately post OLT (atelectasis, fluid overload, pneumonia).

**Portopulmonary Hypertension (PPH)**

1. Pulmonary arterial hypertension (mean PAP > 25 mmHg), usually RV systolic pressure > 50 mmHg.
2. Portal Hypertension.
3. PCWP < 15 mmHg, Pulmonary vascular Resistance (PVR) > 120 dynes•cm⁻⁵.

*May occur in up to 20% with advanced liver disease and portal hypertension.*

**Aetiology:**
Complex interaction of: hyperdynamic high flow circulation, excess central volume, non-embolic pulmonary vasoconstriction/obliteration.
Portopulmonary hypertension strictly only refers to the last process (rare @ ~4%).

**Pathology:**
Medial & intimal hypertrophy (reversible?), endothelial proliferation, thrombotic/fibrotic change (irreversible?).
Indistinguishable from Primary Pulmonary Hypertension histopathological changes.

**Treatments:**
Epoprostenol (PGI₂)
- Potent pulmonary and systemic vasodilator, synthesised by pulmonary endothelium.
- Improves pulmonary haemodynamics short and long term.
- Disadvantages: continuous central vein infusion, splenomegaly, thrombocytopenia, cost, side-effects.
Liver Transplantation
- PPH is a relative contraindication to OLT if mean PAP > 35 mmHg or PVR > 250 dynes•cm⁻⁵.
- PGI₂ often needed before and after OLT (duration unclear).
- Recurrence/progression of PPH may occur despite OLT.

Pulmonary Vasodilators
- Bosentan (non-specific endothelin receptor antagonist).
- Oral mononitrates.
- PGI₂ analogues.
- Inhaled NO.

**References**

DISCUSS THE CAUSES AND TREATMENT OF TORSADES DE POINTES

Dr. M. McNamara, Intensive Care Unit, Royal Adelaide Hospital, SA

DEFINITION
Polymorphic QRS complexes that change in amplitude and cycle length, appearing as oscillations around the baseline. Associated with long QT by definition.

ELECTROCARDIOGRAPHIC RECOGNITION
Ventricular tachycardia - rates of 200 to 250/min
QRS complexes of changing amplitude appear to twist around the isoelectric line
Long QT on ECG documented previously QTc >0.46 men >0.47 women.
The U wave also can become prominent.
Torsades de pointes often reverts spontaneously to the basal rhythm, but may terminate with a period of ventricular standstill, a new attack of torsades de pointes, or ventricular fibrillation.
Ventricular tachycardia that is similar morphologically to torsades de pointes but occurs in patients without Q-T prolongation, whether spontaneous or electrically induced, should be classified as polymorphic ventricular tachycardia, not as torsades de pointes. Can be treated as VT - without restrictions on QT prolonging antiarrhythmics.

CAUSES

Congenital long Qt
Jervell and Lange-Nielsen syndrome
sensorineural deafness
autosomal recessive
Romano-Ward syndrome
normal hearing
autosomal dominant
Sporadic form
normal hearing
nonfamilial

Acquired long Qt
Drugs (see table below)
Electrolyte abnormalities (hypokalaemia, hypomagnesaemia)
Severe bradycardia (especially complete heart block)
Cerebrovascular disease (SAH, ischaemic stroke)
Cardiac pathology [heart failure, ischaemia, myocarditis, MVP]
Idiopathic
Some drugs associated with QTc prolongation

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**Risk Factors for Drug Induced Torsades de Pointes**

Risk factors for the development of drug-induced Torsades de Pointes have been identified (Roden, 1998):

- Female gender
- Hypokalemia, hypomagnesemia
- Bradycardia
- Diuretic use
- Recent conversion from atrial fibrillation
- Congestive heart failure or cardiac hypertrophy
- Rapid intravenous infusion, high doses or longterm usage of drugs prolonging QT
- Baseline ECG showing QT prolongation, T wave lability
- ECG during drug therapy showing marked QT prolongation, T wave lability, T wave morphologic changes

**TREATMENT**

- As with any arrhythmia an immediate decision must be made on urgency of treatment.
- Rapid assessment, attention to ABCs and DC cardioversion remain the treatments of choice for the unstable patient.
- DC cardioversion may be successful initially but is rarely effective unless other treatments are instituted as well.
- In all patients with torsades de pointes, administration of class IA, possibly some class IC, and class III antiarrhythmic agents (amiodarone and sotalol) can increase the abnormal Q-T interval and worsen the arrhythmia.
Treatment of acquired long QT Torsades
Patients with the acquired form of long QT commonly develop torsades de pointes during periods of bradycardia or after a long pause in the R-R interval

- Determine and correct or remove cause of long QT
- Intravenous magnesium is the initial treatment of choice for torsades de pointes due to an acquired cause 1g -2g boluses
- Potassium infusion 0.5meq/kg over 90 mins used effectively for quinidine induced QT prolongation
- Temporary ventricular pacing at a rate of 90-110 bpm is effective in >90% patients with drug induced torsades.
- Isoprenaline infusion, given cautiously because it can exacerbate the arrhythmia, can be used until pacing is instituted.
- Lignocaine, mexiletine and phenytoin have been used successfully
- Potassium channel openers may be useful.

Treatment of Congenital Long QT associated Torsades.
Patients with Congenital Long QT commonly develop ventricular tachyarrhythmias during periods of adrenergic stimulation such as fright or exertion.
Torsades de pointes due to the congenital long Q-T interval syndrome is treated with
- beta blockade,
- surgical sympathetic interruption
- pacing
- implantable defibrillators
- ECGs taken on close relatives can help secure the diagnosis of long Q-T syndrome in borderline cases.
Often a combination of the above is required.

References
2. Irwin and Rippes Intensive Care Medicine 4th Ed Lippincott Raven
SUMMARY

DISCUSS THE CAUSES AND TREATMENT OF TORSADES DE POINTES

DEFINITION
Polymorphic VT Preceded by long QT often in excess of 0.6s

CAUSES

*Congenital Long Qt*
- Jervell and Lange-Nielsen AR - Sensorineural deafness
- Romano Ward AD - Normal Hearing
- Sporadic Form Non familial with normal hearing

*Acquired Long Qt*
- Drugs
- Electrolyte abnormality (hypokalaemia, hypomagnesemia)
- Severe bradycardia (especially complete heart block)
- Cerebrovascular disease (SAH, ischaemic stroke)
- Cardiac pathology [heart failure, ischaemia, myocarditis, MVP]
- Idiopathic

TREATMENT

Is Rhythm Stable or Unstable (Hypotensive, obtunded or not)?
- Unstable - DC Cardioversion + ABC
- Stable - Depends on cause of underlying prolonged QT

*Congenital long QT*
- Beta Blockers
- QT interval shortening drugs - phenytoin
- Cervicothoracic sympathectomy
- Permanent pacemaker/AICD

*Acquired lone QT*
- Treat underlying cause - remove precipitating factors
- Correct electrolyte abnormalities
- Remove drugs causing long QT
- Intravenous magnesium 1g -2g boluses
- Isoprenaline infusion whilst awaiting pacing wire
- Atrial or ventricular overdrive pacing
  - Ventricular pacing at 90-110 beats per minute
  - Effective in >90% patients

References
2. Irwin and Rippes Intensive Care Medicine 4th Ed Lippincott Raven
DISCUSS THE INDICATIONS FOR AND MECHANISM OF ACTION OF INTRAVENOUS ACTIVATED PROTEIN C IN A SEPTIC PATIENT

Dr. S. Sturland, Intensive Care Unit, The Royal Brisbane Hospital, Queensland

The systemic inflammatory response and procoagulant state that arises during sepsis is associated with an extensive endovascular injury. This can result in a distributive shock state with regional microthrombosis and organ ischaemia leading to overt organ dysfunction (i.e. severe sepsis).1 As part of the body’s natural defence, the vitamin K-dependant serine protease – protein C – binds to thrombomodulin and becomes activated.

Activated protein C has anti thrombotic, anti inflammatory and profibrinolytic effects designed to counter the microvascular injury. Indeed a deficiency in protein C is associated with increased morbidity and mortality and is seen in the majority of patients with severe sepsis.2,3 In cases of severe sepsis it is postulated that the activation of protein C may be impaired by generalised endothelial dysfunction and down regulation of thrombomodulin by inflammatory cytokines. As a result administration of activated protein C may be more effective.

MECHANISM OF ACTION

Drotrecogin alfa (activated) or recombinant human activated protein C (APC) acts in a similar manner to the endogenous vitamin K-dependant serine protease, acting as an antithrombotic, anti-inflammatory and profibrinolytic agent;

Antithrombotic action

APC acts by proteolytic inhibition of the coagulation factors Va and VIIIa.5 This has the effect of reducing thrombin formation and hence reducing the formation of fibrin from fibrinogen. It also reduces the ability of thrombin to stimulate multiple inflammatory pathways.6

Profibrinolytic action

Plasminogen-activator inhibitor 1 (PAI-1) is released from platelets and the endothelium when they are stimulated by thrombin acting to suppress fibrinolysis. APC acts to directly inactivate this compound. APC also prevents the activation of “thrombin-activatable fibrinolysis inhibitor –TAFI” which also acts as a powerful endogenous anti-fibrinolytic.7 As a result of the above two mechanisms APC acts to preserve or restore microcirculatory blood flow, preventing ischaemia-reperfusion injury and subsequent organ dysfunction.

Anti-inflammatory action

Aside from reducing the inflammatory effects initiated by thrombin as above, it intervenes with leukocyte action specifically;APC reduces the production inflammatory cytokines (i.e. tumour necrosis factor, interleukin –1 and interleukin-6) by monocytes. It binds selectins and as a result prevents the rolling migration of monocytes/neutrophils along the injured endothelium. It also reduces activation of nFKB (a nuclear transcription factor) in target cells, essentially preventing DNA from unwinding from its histone proteins, reducing the cellular output of inflammatory cytokines, adhesion molecules and enzymes. Indeed Japanese research has qualitatively measured the inhibition of cellular nitric oxide synthase by APC in septic animal models.8 It is suggested that no one factor is responsible for the clinical effect of APC and that a synergy of all of its complex mechanisms is the reason why it has shown benefit where so many other narrowly targeted therapies have failed.
INDICATIONS FOR THE USE OF APC

Worldwide use of APC follows the publication of the PROWESS trial (Protein C Worldwide Evaluation in Severe Sepsis). In this trial investigators used three specific entry criteria as described below:

1. Presence of a known/suspected infection i.e.:
   - presence of white cells in a normally sterile body fluid
   - perforated viscus
   - radiographic evidence of pneumonia associated with purulent sputum
   - syndrome associated with a high risk of infection (i.e., ascending cholangitis or meningococcemia)

2. Presence of at least three SIRS criteria i.e.:
   - Core temperature >38 C or <36 C
   - Elevated heart rate (>90 beats/min)
   - Respiratory rate >20 breaths/min or PaCO2 <32 mmHg or mechanical ventilation for acute respiratory process
   - WBC >12000 or <4000 or >10% immature neutrophils

3. Dysfunction of one or more organ systems i.e.:
   - Cardiovascular: systolic BP of < 90 mmHg or mean BP < 70 mmHg for > 1 hr despite adequate fluid resuscitation or the use of vasopressors to maintain this.
   - Renal: urine output of <0.5 ml/kg body weight despite adequate fluid resuscitation
   - Respiratory: Pa:Fi O2 ratio of <250 in the presence of other dysfunctional organ systems or <200 if alone
   - Hematologic: platelet count of <80000 or a 50 % decrease in the preceding 3 days
   - Metabolic: pH <7.30 or base deficit >5.0 mmol/L with plasma lactate level >1.5 times upper limit

Patients were deemed eligible if they met the criteria within a 24 hour period, and after enrolment treatment had to begin within 24 hours. There was therefore a maximum of 48 hr between diagnosis and treatment. Although baseline APACHE II scores were recorded and subsequently to classify sub group analysis, there was no criteria based on entry APACHE II score. The US FDA has subsequently also used the APACHE II score AS AN EXAMPLE only of people who may benefit from APC therapy and not as guidelines.

AUSTRALIAN CLINICAL GUIDELINES

An Australian Clinical Advisory Board has been formed in conjunction with Eli Lilly in order to provide guidelines for the responsible use of APC. Its members are Prof M Fisher, Prof I Clarke, Dr R Barnett, Dr G Dobb, A Prof A Bell, A Prof J Lipman, A Prof R Bellomo, Dr P Thomas, A Prof D Bihari, A Prof D Tuxen

The Board recommends the use of APC “in patients with severe sepsis who are at a higher risk of death as defined by their response to antibiotics and resuscitation over 4 hours, and who have persistent multi-organ failure or an APACHE II of >25”. Added to this are the absolute and relative contra-indications published by Eli Lilly.
ABSOLUTE CONTRA-INDICATIONS
- Active internal bleeding
- Recent (within three months) haemorrhagic stroke
- Recent (within three months) intra-cranial or intra-spinal surgery, or severe head trauma requiring hospitalisation
- Trauma patients with increased risk of life-threatening bleeding
- Patients with an epidural catheter
- Patients with intracranial neoplasm or mass lesion

RELATIVE CONTRA-INDICATIONS
- Concurrent heparin therapy >15 U/kg/hr
- Platelet count of <30000 (even post transfusion)
- Recent (within 6 weeks) GI bleed
- Recent administration (within 3 days) of thrombolysis
- Recent administration (within 7 days) of aspirin >650 mg or other platelet inhibitors
- Recent (within 7 days) of oral anticoagulants or GPIIbIIIa inhibitors
- Recent (within 3 months) ischaemic stroke
- Patients with intracranial arteriovenous malformation
- Known bleeding diathesis except for coagulopathy of sepsis
- Chronic severe hepatic disease
- Any other condition in which the physician thinks bleeding likely
- Conditions increasing the risk of bleeding (i.e., Within 12 hours of major surgery)
- HIV infection with CD4 count of < 50/mm
- Chronic renal failure with dialysis
- Acute pancreatitis with no established source of infection

In summary, the clinical use of APC will become dependant on the recommendations of The Australian Clinical Advisory Board in conjunction with clinical judgment and observation. As experience with this drug grows, so will our ability to tailor its use appropriately.

References
DISCUSS THE MANAGEMENT OF A PATIENT WITH METHYL ALCOHOL POISONING

Dr. A. Dennis, Intensive Care Unit, St Vincent’s Hospital, Victoria

Methyl alcohol poisoning requires high degree of suspicion as it may not be recognized, or presentation may be delayed especially when it occurs in combination with ethanol intoxication. Poisoning may also occur in a paediatric setting with accidental ingestion. Ingestion results in metabolic acidosis, blindness and death. Complications are due to:
- the chemical itself
- its metabolites
- concurrent administration of other chemicals
- and their metabolites

BACKGROUND

Pharmacology
It is a common industrial solvent, antifreeze and is used in paints and paint removers.
Synonyms: methyl alcohol, carbinol, colonial spirit, columbian spirit, methylol, methyl hydrate, wood alcohol, wood naphtha, wood spirit, methyl hydroxide, pyroxylic spirit, RCRA waste number U154, meths

Molecular formula: CH₃OH

Pharmacokinetics

Absorption - rapidly absorbed from stomach, small intestine and colon.
Distribution – throughout total body water including transfer via placenta to fetus.
Metabolism – metabolism occurs predominately in the liver (97%) via the same enzymes that metabolize ethanol. These are alcohol dehydrogenase and aldehyde dehydrogenase which degrade methyl alcohol to toxic intermediates – formaldehyde and formic acid.

- Step 1 Methyl alcohol → Formaldehyde (alcohol dehydrogenase – rate limiting step)
- Step 2 Formaldehyde → Formic acid (aldehyde dehydrogenase - rapid)
- Step 3 Formic acid → formate (pH dependent)
  → CO₂ + H₂O (folate-dependent - slow)

The rate of oxidation of methyl alcohol is independent of its concentration in the blood however the rate is only 1/7th that of ethanol and complete oxidation occurs over days.
Excretion – renal

Pharmacodynamics

Toxicity
- Dose 15mls for blindness
- 70-100mls death

Mechanism of toxicity
Early manifestations are due to methyl alcohol and late manifestations are due to formic acid.

1. Formic acid causing
- An increased anion gap metabolic acidosis (severity ∞ acidosis) in combination with lactic acidosis (reduced tissue perfusion) and ketosis
inflammation followed by atrophy of retinal ganglion cells leading to blurred vision, diplopia, blindness
pancreatic necrosis

2. Respiratory acidosis secondary to intoxication – death is most often due to respiratory failure

Principles of treatment
- treat acidosis
- inhibition of further methyl alcohol metabolism thereby reducing the concentrations of formic acid and formaldehyde. This is achieved with ethanol which acts as a preferential substrate for alcohol dehydrogenase thereby effectively inhibiting the metabolism of methyl alcohol.
- Haemodialysis should be considered if patient has persistent acidosis or methyl alcohol blood concentration > 500mg/L

MANAGEMENT
1. Immediate Resuscitation
   A
   B
   C  IV access, IV fluids,
      Observation of vomitus, urine, faeces,
      Investigations - screening and specific
      FBE, U+E/Cr, LFTs, ABGs, INR/APTT, glucose, ECG, CXR
      Blood ethanol and methyl alcohol levels

2. Short term
   a. History/examination/review of investigations – assist in establishing a diagnosis and an estimate of chemical(s) and dosage taken.
      Metabolic acidosis and elevated serum osmolality in association with visual disturbances is highly suggestive of the diagnosis of methyl alcohol poisoning.
      Respiratory acidosis and abdominal pain, in addition to non-specific symptoms/signs (headache, vertigo, vomiting, mild CNS depression) are also common features.
      Visual disturbances, persistent metabolic acidosis and blood methyl alcohol level > 200-300mg/L require specific intensive treatment with ethanol and levels > 500mg/L usually require additional treatment with haemodialysis.
   b. Prevention of further drug absorption – due to rapid absorption from GIT, prevention of absorption is usually not possible.
   c. Removal of absorbed drug
      Renal elimination – alkalinization of urine enhances formic acid excretion
      Extracorporeal – haemodialysis for persistent acidosis and/or methyl alcohol level >500mg/L.
   d. Administration of antidote/competitive substrate → ethanol
      Ethanol \( \text{CH}_3\text{CH}_2\text{OH} \)
      Indicated for patients with visual disturbances or a methyl alcohol level exceeding 200-300mg/L.
      Acts as a competitive substrate for the metabolic enzymes due to its 100 fold increased affinity for alcohol dehydrogenase compared with that of methyl alcohol.
Adult dosage:

Loading dose  
IV  10mls/kg 10% ethanol (in 5%dextrose)  
Oral 1ml/kg 95% ethanol

Infusion  
IV  1.5ml/kg/hr 10% ethanol  
(3.0ml/kg/hr 10% ethanol during haemodialysis)

Aim for blood alcohol concentration of 1-1.5g/L (20-30mmol/L)

SE – drunkenness, ataxia, nausea, sedation, hiccups, hypoglycaemia

Continue ethanol administration until all clinical signs have resolved and methyl alcohol levels < 200mg/L.

Other agents

4-methylpyrazole – inhibitor if alcohol dehydrogenase. Not registered in Australia. It has increased half life compared with ethanol, is simpler to use with a single 20mg/kg dose however is expensive.

Folate supplementation – assists in metabolism of formic acid to CO₂ & H₂O

50mg IV Q4H

e. Level of care/Level of monitoring – if significant ingestion then ICU management is the appropriate level of care.

3. Long term

Prevention

References

DISCUSS THE INDICATIONS FOR INHALED ANTIBIOTIC THERAPY AND WHAT ANTIBIOTICS HAVE BEEN USED

Dr. M. Saxena, Intensive Care Unit, St George Hospital, NSW

Inhaled bronchodilators and steroids have transformed the management of asthma since their introduction. The concept of inhaled antibiotics is an attractive one, both in terms of the prophylaxis and the treatment of lung infections, but, at present, there are many technical and efficacy issues which need further attention before their use can be recommended. There is some objective evidence emerging for their usage in the outpatient setting, but as yet data is lacking to support their use in intensive care units.

Current indications for nebulized antibiotic therapy include:

Over time patients with cystic fibrosis inevitably become colonized with Pseudomonas Aeruginosa and this is associated with a gradual decline in FEV₁ and an increased mortality. A recent randomized controlled clinical trial of 320 patients with cystic fibrosis and chronic colonization with Pseudomonas Aeruginosa demonstrated a significant benefit with nebulized Tobramycin as compared to placebo. Patients were randomized to receive nebulized tobramycin or saline for 28 days on treatment and then followed with 28 days off treatment. This cycling was repeated 3 times giving a total duration of therapy of 6 months. The benefits included an absolute improvement in FEV₁ of 11% in the treatment group (<1% with placebo) and a significant reduction of hospital days and parenteral antibiotic usage. A subsequent open label study of the above groups provided further support for the use of nebulized tobramycin. Importantly there was no associated ototoxicity or nephrotoxicity.

Two studies support the use of inhaled antibiotic for chronically colonized non cystic fibrosis bronchiectasis. A small randomized and controlled study of 1 year of treatment with nebulized ceftazidine and tobramycin vs placebo demonstrated a reduction in both the frequency and duration of hospital admissions. 1/7 patients were hospitalized in the treatment group, whereas all 8 of the placebo group required hospitalization during the study. In a further study of 74 patients randomized to receive tobramycin or placebo, the treatment group had reduced sputum density, a third had pseudomonas eradicated (vs none in the placebo arm) and 62% had an “improved medical condition” (vs 38% in placebo).

In these outpatient groups the benefit of eradication and hence blunting the associated decline in respiratory function needs to be balanced against the pathogenicity of resistant bacteria that may emerge with treatment. Hence longer term data would be useful.

There is not currently enough evidence to support the usage of nebulized antibiotic therapy in the prophylaxis or treatment of ventilator associated pneumonia, although this would appear an interesting area for future research. In the past “oropharyngeal atomization” with non absorbable polymixins have attempted to eradicate the gram negative flora that come to colonize the oropharynx in intubated patients and, hence prevent ventilator associated pneumonia. Although early studies showed promise, this was not borne out subsequently. More recently an uncontrolled study of nebulized gentamycin vs nebulized amikacin (9 courses for 14 to 21 days) demonstrated a decrease in sputum volume, eradication of gram negatives in most cases and decreased levels of inflammatory cells in sputum. A further trial of nebulized tobramycin vs placebo on top of standard parenteral therapy (iv beta lactam and tobramycin) for ventilator associated pneumonia showed no difference between the groups.

Other uses of inhaled antibiotic include the role of nebulized pentamidine for Pneumocystis Carinii infection complicating HIV and also tribavarin in children with respiratory syncitial virus infection.
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