Chapter 6
Endocrine System

TABLE OF CONTENTS

High weighting

Chapter 6
Endocrine System

1 Antidiuretic hormone disorders

1.1 Diabetes insipidus

There are two types of diabetes insipidus:

1. ***Pituitray (cranial)***
   caused by insufficient levels of ADH
2. ***Nephrogenic***
   caused by kidney defects

Vasopresssin (antidiuretic hormone, ADH) and its analoge ***Desmopressin*** are used in the treatment of pituitary diabetes insipidus. Doses are tailored to produce slight diuresis every 24 hours to avoid water intoxication.

Desmopressin is more potent and has a longer duration of action than vasopressin. It is often used in the differential diagnosis of diabetes insipidus; failure to respond to a dose indicates nephrogenic diabetes insipidus.

Both pituitary and nephrogenic diabetes insipidus patients, can benefit from the paradoxical antidiuretic effect of ***thiazide diuretics***. ***Carbamazepine*** is sometimes useful in sensitising renal tubules to the action of remaining vasopressin.

1.2 Other uses

Desmopressin is sometimes used in ***haemophilia and Von Willebrands disease*** to boost factor VIII (8) concentration. It can also be used in the treatment of ***nocturnal enuresis***.

Vasopressin is used to control variceal bleeding in portal hypertension due to is vasoconstrictor effects. Oxytocin is another pituitary hormone indicated in obstetrics.

1.3 Desmopressin

Patients are advised to ***limit fluid intake*** to minimum from 1 hour before dose until 8 hours afterwards.

Intranasal desmopressin should not be given for nocturnal enuresis s there is an increased risk of hyponatraemic convulsions.

1.3.1 Common side effects

fluid retention, hyponatraemia on administration without restricting fluid intake (in more serious cases with convulsions), stomach pain, headache, nausea and vomiting

1.3.2 Hyponatraemic convulsions

Increased ***risk of hyponatraemic convulsions when taking desmopressin for nocturnal enuresis***. This can be ***minimised by avoiding fluid overload*** and stopping the medication during an episode of vomiting or diarrhoea (until fluid balance normal).

The risk can also be minimised by keeping to the recommended doses and by ***avoiding concomitant use of drugs which increase secretion of vasopressin*** (e.g. paracetamol, nicotine, and tricyclic antidepressants).

Increased risk in elderly patients — measure baseline serum sodium concentration, then ***monitor regularly*** during treatment; ***discontinue treatment if levels fall below baseline***.

1.3.3 Pregnancy

small oxytocic effect in third trimester; increased risk of pre-eclampsia (a disorder characterized by the onset of high blood pressure and a significant amount of protein in the urine).

2 CORTICOSTEROID RESPONSIVE CONDITIONS

2.1 CORTICOSTEROID REPLACEMENT THERAPY

The ***adrenal cortex*** normally ***secretes hydrocortisone (cortisol)*** which has ***glucocorticoid activity*** and some mineralocorticoid activity. It also secretes the ***mineralocorticoid aldosterone***.

In deficiency states, e.g. ***Addison's disease***, ***physiological replacement*** is best achieved with a ***combination of oral hydrocortisone and the mineralocorticoid fludrocortisone acetate***; hydrocortisone alone does not provide sufficient mineralocorticoid activity for complete replacement. Replacement therapy is given in 2 doses, the larger in the morning and the smaller in the evening, mimicking the normal diurnal rhythm of cortisol secretion.

In ***acute adrenocortical insufficiency***, ***hydrocortisone is given IV every 6 to 8 hours.***

In ***hypopituitarism***, ***oral hydrocortisone*** should be given as in adrenocortical insufficiency, a ***mineralocorticoid is not usually required*** as adrenal function is still present. ***Additional replacement therapy*** with levothyroxine sodium and sex hormones should be given as indicated by the pattern of hormone deficiency.

2.2 GLUCOCORTICOID THERAPY

When ***comparing corticosteroids***, it is important to remember that ***high glucocorticoid (anti-inflammatory) activity in itself is of no advantage unless it is accompanied by relatively low mineralocorticoid activity***. For example, mineralocorticoid activity of fludrocortisone is so high that its anti-inflammatory activity is of no clinical relevance.

2.2.1 Equivalent anti-inflammatory doses of corticosteroids

Betamethasone and dexamethasone have a ***long duration*** of ***very high glucocorticoid activity***, in conjunction with ***insignificant mineralocorticoid activity***. This makes them particularly suitable for ***high-dose therapy*** in conditions where fluid retention would be a disadvantage.

Prednisolone is the corticosteroid most commonly used by mouth for ***long-term disease suppression***, like ***prednisone*** it has predominantly ***glucocorticoid activity***. ***Deflazacort*** is derived from prednisolone and has a high glucocorticoid activity.

The **mineralocorticoid activity** of ***hydrocortisone***, and the resulting ***fluid retention,*** makes it ***unsuitable*** for ***disease suppression*** on a long-term basis. However, hydrocortisone can be used for ***adrenal replacement therapy***.

2.3 CORTICOSTEROIDS (HIGH RISK)

Corticosteroids are a class of steroid hormones that are produced in the adrenal cortex. Two main classes of corticosteroids are involved in a wide range of physiologic processes, glucocorticoids and mineralocorticoids.

Glucocorticoids *such as* ***cortisol*** *affect* ***carbohydrate, fat, and protein metabolism, and have anti-inflammatory, immunosuppressive, anti-proliferative, and vasoconstrictive effects.*** ***Mineralocorticoids*** *such as* ***aldosterone*** *are primarily involved in the* ***regulation of electrolyte and water balance****.*

2.3.1 Side effects

Mineralocorticoid side effects are most marked with fludrocortisone, and are significant with hydrocortisone, corticotropin, and tetracosactide. Mineralocorticoid actions are negligible with the high potency glucocorticoids, betamethasone and dexamethasone, and occur only slightly with methylprednisolone, prednisolone, and triamcinolone.

2.3.1.1 Mineralocorticoid side effects

- *hypertension*
- *sodium retention*
- *water retention*
- *potassium loss*
- *calcium loss*

2.3.1.2 Glucocorticoid side effects

- *diabetes*
- *osteoporosis (particularly in the elderly)*
- *high doses are associated with avascular necrosis of the femoral head*
- *proximal myopathy*
- *weakly linked with peptic ulceration*
- *psychiatric reactions may also occur*
- *high doses can also cause Cushing's syndrome, with moon face, striae, and acne; it is usually reversible on withdrawal of treatment*
- *weight gain / increased appetite*

2.3.2 Warning signs

(patients advised to report all to doctor immediately; patients undergoing prolonged steroid treatment (>3 weeks) should be given a steroid card; oral steroids are best taken as a single dose in the morning)

- *Paradoxical bronchospasm (constriction of the airways)*
- *Uncontrolled asthma (cough, wheeze, tight chest)*
- *Adrenal suppression (adrenal atrophy can develop and persist for years after stopping prolonged corticosteroid therapy; acute adrenal suppression can lead to hypotension or death, and occurs after abrupt withdrawal of prolonged treatment; signs include fever, nausea, vomiting, weight loss, fatigue, headache, muscular weakness)*
    - *prolonged corticosteroid therapy must be withdrawn gradually to prevent withdrawal or acute adrenal insufficiency*
    - *gradual withdrawal should be considered in those who have:*
        a) *received more than 40mg prednisolone (or equivalent) daily for more than one week*
        b) *been given repeat evening doses*
        c) *received treatment for more than three weeks*
- *Frequent courses of antibiotics and/or corticosteroids*
- *Immunosuppression (prolonged treatment increases infection risk, especially severe chicken pox or measles if not already immune, patients should avoid exposure to chickenpox, shingles, or measles; more serious infections e.g. TB and septicaemia, may reach an advanced stage before being recognised; fungal or viral ocular infections may be exacerbated; oral candidiasis can be avoided by rinsing thoroughly after using inhaled corticosteroids)*
- *Psychiatric reactions (linked to high doses and treatment withdrawal; aggravation of epilepsy or schizophrenia; euphoria, suicidal thoughts, nightmares, depression, insomnia; usually subside on reducing dose)*

2.3.3 Monitoring

- *blood pressure*
- *blood lipids*
- *serum potassium*
- *body weight and height in children and adolescents (growth can be slowed)*
- *bone mineral density*
- *blood glucose*
- *eye exam (for intraocular pressure, cataracts)*
- *signs of adrenal suppression*

2.3.4 Pregnancy and breastfeeding

The benefit of treatment during pregnancy and breast-feeding outweighs the risk; pregnant women with fluid retention should be monitored closely; treatment is required during labour.

2.3.5 Drug interactions

- *Metabolism of corticosteroids accelerated by carbamazepine, phenobarbital, phenytoin and rifamycins*
- *Corticosteroids may induce or enhance anticoagulant effect of coumarins*
- *High dose corticosteroid can impair immune response to vaccines; avoid concomitant use with live vaccines*
- *Corticosteroids can mask the gastrointestinal effects of NSAIDs (including aspirin); avoid concomitant use if possible and consider gastroprotection*
- *Hypokalaemia can be severe when given with other drugs that lower serum potassium e.g. loop and thiazide diuretics*
- *Effects of antihypertensive and oral hypoglycaemic drugs are antagonized by glucocorticoids*

3 DIABETES MELLITUS AND HYPOGLYCAEMIA

3.1 TREATMENT OF DIABETES

Patients with type 1 require administration of insulin. Patients with type 2 may be controlled on diet alone but may also require oral antidiabetics and/ or insulin.

Main aim is to alleviate symptoms and minimise the risk of long-term complications. Diabetes is a strong risk factor for **cardiovascular disease**, this **risk can be reduced** using an ACE inhibitor (also provide kidney protection to diabetics), and a lipid-regulating drug.

3.2 PREVENTING DIABETIC COMPLICATIONS

Optimal glycaemic control in both types reduces in the long term, the risk of microvascular complications

including neuropathy, retinopathy, and nephropathy (ACE and ARB may have a role).

HbA_{1c} (glycosylated haemoglobin) provides a good indication of glycaemic control over the previous 2-3 months, and should be measured every 3-6 months. Overall it is ideal to aim for HbA1c concentration of 59mmol/mol or less (reference range 20-42mmol/mol but not always achievable, plus results in increased risk of severe hypoglycaemic episodes in diabetics).

3.3 Diabetic Nephropathy

Tested for via urinary microalbuminuria, annual tests for urinary protein, and serum creatinine. Presence of nephropathy increases the risk of hyperkalaemia. All diabetic patients with nephropathy should be treated with ACE or ARB regardless of blood pressure; however, blood pressure should also be carefully controlled to minimise renal deterioration. ACE inhibitors can potentiate the hypoglycaemic effect of anti-diabetic drugs and insulin, especially during initial treatment and if renal impairment is present.

3.4 Diabetic Neuropathy

Treat **mild to moderate pain** with **Paracetamol or Ibuprofen**, whereas **Duloxetine** is effective for **painful neuropathy**. Amitriptyline or Nortriptyline (unlicensed) can be used if Duloxetine is ineffective. Gabapentin can also be used if all the above drugs are inadequate.

Evidence also supports the use of Tramadol, additionally morphine and oxycodone may also be used under specialist supervision. Gabapentin, Carbamazepine, and Capsaicin cream are also licensed for neuropathic pain.

3.5 Diabetic Emergencies

3.5.1 Hypoglycaemia (bsl < 3.5mmol/L)

Symptoms include: pale skin, feeling sweaty, tremor, rapid heart rate, confusion, aggression, fits, impaired consciousness

Restore blood glucose immediately; cooperative – oral glucose, unconscious – IV dextrose, unconscious or no IV access – Glucagon IM injection.

3.5.2 Diabetic Ketoacidosis (DKA) or HyperOsmolar Non-Ketosis (HONK)

Symptoms include: dehydration, acute hunger, thirst, abdominal pain, fruity smelling breath and urine if ketotic, rapid breathing, confusion, decreased consciousness, and arrhythmias due to hyper/hypo-kalaemia.

DKA is usually T1 and has a lower mortality than HONK. Hyperglcaemia >20mM with ketones present, ketones irritate vomiting centre which exacerbates DKA by increasing dehydration and loss of potassium.

HONK is mainly T2 and often occurs in undiagnosed patients. Severe dehydration due to hyperglycaemia >50mM; some insulin is present so minimal ketones present.

Both types are managed in essentially the same way.

1. Nasogastric Tube
   remove stomach contents to prevent aspiration
2. IV access
   IV insulin and fluids
3. LMWH
   hyperglycaemia increases clotting risk
4. Urinary catheter
   monitor fluids and for convenience of immobile pt
5. Sliding scale insulin
   tight glucose control and to prevent hypo
6. Fluid, potassium and phosphate replacement
   rehydration, maintain normal BP and electrolyte levels (insulin moves K+ and PO- from blood in to cells)
7. Consider abx
   if infection caused hyper

3.6 Insulins (High Risk)

1. ***Rapid***
   Used PRN, faster onset and shorter duration of action that 'short', should be injected immediately before or after eating
   e.g. Aspart (Novorapid), Glulisine (Apidra), Lispro (Humalog)
2. ***Short (neutral or soluble)***
   Used PRN, longer duration of action, should be injected 30 mins before eating
   e.g. Actrapid, Humulin S, Insuman Rapid
3. ***Intermediate***
   Usually BD, up to 16 hours duration, resuspend zinc-insulin particulate before injecting, never use IV as particulate may block a capillary
   e.g. Isophane/NPH (Insulatard, Humulin I, Insuman Basal)
4. ***Long-acting***
   For 24hrs cover, used at the same time each day
   e.g. Detemir (Levemir), Glargine (Absaglar, Lantus), Deglubec (Tresiba)
5. ***Biphasic***
   combination of shorter- and longer- acting insulins, more convenient but less control, need to

resuspend before injecting
e.g. Novomix 30, Humalog Mix 25, Humulin M3

3.6.1 Warning signs

- *Recurring episodes of hypoglycaemia e.g. sweating, palpitations, confusion, drowsiness*
- *Signs of diabetic ketoacidosis e.g. nausea, vomiting, drowsiness*
- *Any symptoms of liver toxicity, heart failure or pancreatitis e.g. jaundice, abdominal pain,*
- *Ulceration of foot tissue*

3.6.2 Interactions

- *Substances that may enhance blood-glucose-lowering activity (reduce insulin requirements) and increase risk of hypoglycaemia include oral antidiabetics, ACE inhibitors, MAOIs, salicylates, sulphonamide antibiotics*
- *Substances that may reduce blood-glucose-lowering activity (increase insulin requirements) include corticosteroids, diuretics, sympathomimetics (e.g. epinephrine, salbutamol, terbutaline), thyroid hormones, oral contraceptives (oestrogens, progestogens)*
- *Beta-blockers or alcohol may potentiate and/or weaken the blood-glucose-lowering activity of insulin*

3.7 Antidiabetic Drugs

3.7.1 Alpha glucosidase inhibitor (Acarbose)

Inhibits the breakdown of starch and sucrose to glucose, thus delaying absorption of sugar. Flatulence can lead to non-adherence but this S/E decreases with time. Should be taken with food.

3.7.2 Biguanide (Metformin)

NOW FIRST LINE TREATMENT FOR ALL PATIENTS!

Decreases gluconeogenesis and increases peripheral utilisation of glucose.

Contraindication

Use of general anaesthesia can cause ketoacidosis, suspend metformin on the morning of surgery and restart when renal function returns to baseline. Furthermore, iodinated contrast agents can cause renal failure and precipitate lactic acidosis, similarly suspend metformin prior to the x-ray and restart after 48 hours if renal function returns to baseline.

Side Effects

GI disturbances are initially common, especially at high doses. Dose titration may improve tolerability.

3.7.3 Sulphonylureas (Gliclazide, Glipizide, Glibenclamide, Glimepiride, Tolbutamide)

Increases insulin secretion from the pancreas.

Should be taken with food. May cause hypoglycaemia and weight gain. Blood dyscrasias are rare, and hypersensitivity is common in the first 6-8 weeks of therapy.

3.7.4 Thiazolidinedione (Pioglitazone)

Reduces peripheral insulin resistance.

Side effects include, GI upset, weight gain, oedema, hypoglycaemia, anaemia, headache, visual disturbances, arthralgia, haematuria, impotence, liver toxicity.

Liver toxicity: discontinue treatment if symptoms of liver dysfunction occur e.g. severe GI upset, fatigue, jaundice, or dark urine.

MHRA/CHM advice

Pioglitazone cardiovascular safety

Risk of heart failure increases when pioglitazone is combined with insulin. Patients should be closely monitored; treatment should be discontinued if any sign of deterioration in cardiac status occurs e.g. shortness of breath, fatigue, oedema, and irregular heartbeat.

Pioglitazone: risk of bladder cancer

A small increased risk of bladder cancer is associated with pioglitazone use. However, the benefits of pioglitazone continue to outweigh the risks. Before treatment patients should be assessed for risk factors e.g. un-investigated macroscopic haematuria, age, smoking status, exposure to chemotherapy agents. Treatment should be reviewed after 3–6 months and any haematuria, dysuria, or urinary urgency during treatment should be reported promptly.

3.7.5 Meglitinides (Nateglinide, Repaglinide)

Stimulate insulin secretion.

Should be taken 30 mins before main meals. May cause hypoglycaemia, hypersensitivity and GI upset.

3.7.6 DPP 4 inhibitors (Alogliption, Linagliptin, Saxagliptin, Sitagliptin, Vidagliptin)

Inhibits DPP4 enzymes that break down incretins. Incretins are produced by the gut in response to food and trigger insulin secretion and lower glucagon secretion.

Side effects include, hypoglycaemia, URTI, GI upset, peripheral oedema and pancreatitis. Rare reports of liver dysfunction with Vildagliptin.

Pancreatitis: discontinue treatment if severe abdominal pain, nausea, and vomiting persists

Liver toxicity: discontinue treatment if symptoms of liver dysfunction occur e.g. severe GI upset, fatigue, jaundice, or dark urine

3.7.7 SGLT2 inhibitors (Canagliflozin, Empagliflozin, Dapagliflozin)

Inhibit SGLT2 in the renal tubules to reduce glucose reabsorption and increase glucose excretion.

Associated with volume depletion, therefore any hypovolaemia needs to be corrected before treatment. Consider interrupting treatment if symptoms of hypovolaemia occur i.e. postural hypotension and dizziness. Increased risk exists with the elderly, concomitant antihypertensive use, cardiovascular disease, GI illness and complicated UTI.

Side effects include, constipation, thirst, nausea, lower UTI, hypoglycaemia, and polyuria.

MHRA/CHM advice

Risk of diabetic ketoacidosis

Serious and potentially life-threatening cases of DKA have been reported in patients taking SGLT2 inhibitors. Patients should be advised on how to recognise the signs and symptoms of DKA. Treatment should be discontinued if DKA is suspected, and prompt medical attention must be sought.

Increased risk of lower-limb amputation (mainly toes)

Canagliflozin may increase the risk of lower-limb amputation (mainly toes). Preventive foot care is important for all patients with diabetes. Patients are advised to stay well hydrated, carry out routine preventive foot care, and to seek medical advice promptly if they develop skin ulceration, discolouration, or new pain or tenderness.

3.7.8 Glucagon-like peptide receptor agonist (Exenatide, Albiglutide, Dulaglutide, Liraglutide, Lixisenatide)

AKA Incretin mimetics, they bind to and activate the GLP-1 receptor mimicking the activity of normal incretins; increasing insulin secretion and slowing gastric emptying.

Side effects include GI upset, headaches, weight loss, and pancreatitis.

Pancreatitis: discontinue treatment if severe abdominal pain, nausea, and vomiting persists

Exenatide can cause severe pancreatitis (sometimes fatal), but has been reported rarely. Patients or their carers are advised to seek prompt medical attention if symptoms such as abdominal pain, nausea, and vomiting develop; discontinue permanently if pancreatitis is diagnosed.

Missed doses

NEVER administer a missed dose after a meal!!

Albiglutide, Liraglutide, and Dulaglutide: administer missed dose only if there are at least three days until the next scheduled dose

Exenatide: leave the missed dose and continue with the next scheduled dose

Lixisenatide: administer missed dose 1 hour before next meal

3.8 Treating Type 2 Diabetes (NICE 2017)

1. Metformin monotherapy
   a. If contraindicated or not tolerated, initial treatment with one of the following:
      - A gliptin (DPP4 inhibitor)
      - Pioglitazone
      - A sulfonylurea
2. Metformin dual therapy with a gliptin, or pioglitazone, or a sulfonylurea
   a. For people in whom metformin contraindicated or not tolerated:
      - A gliptin plus pioglitazone, or
      - A gliptin plus a sulfonylurea, or
      - Pioglitazone plus a sulfonylurea

4 Osteoporosis

Osteoporosis commonly occur is in postmenopausal women and in those taking long-term oral corticosteroids. Other risk factors for osteoporosis include low body weight, cigarette smoking, excess alcohol intake, lack of physical activity, family history of osteoporosis, and early menopause. Those at risk should maintain an adequate intake of calcium and vitamin D. To reduce the risk of osteoporosis doses of oral corticosteroids should be as low as possible and courses of treatment as short as possible.

Calcitonin decreases blood calcium concentrations, and is involved with parathyroid hormone (PTH) in the regulation of bone turnover and the maintenance of calcium balance. Teriparatide is a recombinant form of PTH, intermittent use activates osteoblasts which leads to an overall increase in bone. Cinacalcet sensitises Ca^{2+} receptors of the parathyroid gland to reduce PTH levels. Denosumab is a human monoclonal antibody that inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption.

4.1 Bisphosphonates

e.g. alendronate and risedronate

Mechanism of action
These are absorbed onto bone crystals and slow down the rate of bone turnover.

Osteonecrosis of the jaw
The risk is substantially greater for patients receiving intravenous bisphosphonates. Patients should have a dental check-up before treatment, receive routine dental check-ups, maintain good oral hygiene, and report any oral symptoms such as dental mobility, pain, or swelling, non-healing sores or discharge to a doctor and dentist during treatment.

Atypical femoral fractures
Rare risk, mainly in mainly in patients receiving long-term treatment. Patients should be advised to report any thigh, hip, or groin pain during treatment with a bisphosphonate

Osteonecrosis of the external auditory canal
Very rare risk of benign idiopathic osteonecrosis of the external auditory, mainly in patients receiving long-term therapy. Patients should be advised to report any ear pain, discharge from the ear, or an ear infection during treatment with a bisphosphonate.

4.2 Strontium ranelate

Mechanism of action
Stimulates bone formation and reduces bone resorption

Cautions
Associated with an increased risk of serious cardiovascular disease, including myocardial infarction, and the risk should be assessed before treatment and regularly during treatment

Severe allergic reactions
Severe allergic reactions, including drug rash with eosinophilia and systemic symptoms (DRESS), have been reported. DRESS starts with rash, fever, swollen glands, and increased white cell count, and it can affect the liver, kidneys and lungs; DRESS can also be fatal. Treatment should be discontinued, and patient should consult GP immediately.

Counselling
Avoid food for 2 hours before and after taking granules, particularly calcium-containing products e.g. milk, and antacids containing aluminium and magnesium hydroxides.

5 Sex hormone responsive conditions

5.1 HRT

Hormone replacement therapy (HRT) with small doses of an oestrogen (together with a progestogen in women with a uterus) is appropriate for alleviating menopausal symptoms such as vaginal atrophy or vasomotor instability, and may also diminish postmenopausal osteoporosis. Clonidine may be used to reduce vasomotor symptoms in women who cannot take an oestrogen.

HRT increases the risk of venous thromboembolism, stroke, endometrial cancer (reduced by a progestogen), breast cancer, and ovarian cancer.

Risk of breast cancer
Increased risk within 1-2 years of starting treatment; risk is related to duration of use but disappears within 5 years of stopping.

Risk of endometrial cancer
Risk depends on the dose and duration of oestrogen-only HRT; risk is eliminated if a progestogen is given continuously.

Risk of ovarian cancer
Long-term use associated with an increased risk, this excess risk disappears within a few years of stopping.

Risk of venous thromboembolism
Increased risk of DVT and pulmonary embolism especially in the first year of use. In women who have predisposing factors i.e. family history of DVT or obesity, it is prudent to review the need for HRT. Travel involving prolonged immobility further increases the risk of deep vein thrombosis; can be reduced with exercise or compression hosiery.

Risk of stroke
Risk increases with age; therefore, older women have a greater absolute risk of stroke.

Risk of coronary heart disease
HRT does not prevent coronary heart disease. There is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause.

Reason to stop immediately
Combined hormonal contraceptives or hormone replacement therapy (HRT) should be stopped, if any of the following occur:

- sudden severe chest pain
- sudden breathlessness (or cough with blood)
- unexplained swelling or severe pain in one leg
- severe stomach pain
- serious neurological effects including severe, prolonged headache, sudden partial or complete loss of vision, sudden disturbance of hearing, bad fainting attack, unexplained epileptic seizure or weakness, motor disturbances, very marked numbness suddenly affecting one side or one part of body
- hepatitis, jaundice, liver enlargement
- blood pressure above systolic 160 mmHg or diastolic 95 mmHg
- prolonged immobility after surgery or leg injury
- detection of a risk factor which contra-indicates treatment

5.2 Clomifene (anti-oestrogen)

Stimulate ovulation; are used in the treatment of female infertility.

Clomifene should not normally be used for longer than 6 cycles due to an increased risk of ovarian cancer.

5.3 Male sex hormone responsive conditions

Androgens (testosterone) cause masculinisation; they may be used as replacement therapy in castrated adults and in those who are hypogonadal due to either pituitary or testicular disease.

Anti-androgens inhibit the effects of testosterone. Cyproterone acetate used in the treatment of severe hypersexuality and sexual deviation in men. Dutasteride and finasteride is used in benign prostatic hyperplasia to reduce prostate size.

6 Thyroid disorders

Antithyroid drugs

Carbimazole is the most commonly used drug. Propylthiouracil should be reserved for patients who are intolerant of carbimazole or for those who experience sensitivity reactions to Carbimazole. Both drugs act primarily by interfering with the synthesis of thyroid hormones. Radioactive iodine is contraindicated in pregnancy.

6.1 Carbimazole

Neutropenia and agranulocytosis

Risk of bone marrow suppression:

1. Patient should report symptoms and signs suggestive of infection, especially sore throat
2. A white blood cell count should be performed if there is any clinical evidence of infection
3. Carbimazole should be stopped promptly if there is clinical or laboratory evidence of neutropenia

6.2 Thyroid hormones

Levothyroxine and Liothyronine

For initial dosing, baseline ECG is valuable because changes induced by hypothyroidism can be confused with ischaemia. If diarrhoea, nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain develops, reduce dose or withhold for 1–2 days and start again at a lower dose.

Liothyronine

Patients switched to a different brand should be monitored as brands may not be bioequivalent and dose adjustment may be necessary. Thyroid status may need reviewing; if patient is taking Liothyronine long-term, thyroid function test should to be repeated 1–2 months after any change in brand.