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Cover picture

The governor who healed the sick (1640 A.D.)

Unable to attract apothecaries or physicians to the New World, John Winthrop, Governor of Massachusetts Colony (1630-49) sought advice by correspondence, performed apothecary's services in his own home for citizens of his colony.

One of a series: *A History of Pharmacy in Pictures*, presented by Parke, Davis & Company.

George A. Bender, Director Robert A. Thom, Artist

Management of childhood enuresis

What is enuresis?

Enuresis is repeated involuntary voiding of urine during the day or night in bed or into clothes. The commonest type is night-time wetting or nocturnal enuresis. Day-time wetting or diurnal enuresis is involuntary voiding while awake. Three subtypes of enuresis are described – nocturnal only, diurnal only and both nocturnal and diurnal. Some children with bedwetting do so even when they take a nap during daytime. A distinction is also made between "primary" and "secondary" enuresis. Primary enuresis is lifelong, whereas secondary is acquired after being dry for a minimum of 6 months. A child is not considered to have primary enuresis until 5 years of age but secondary enuresis can occur at any age. Nocturnal enuresis is commonly monosymptomatic with normal daytime urination or rarely polysymptomatic with daytime urinary urgency, frequency or other signs of unstable bladder.

How common is enuresis?

Primary nocturnal enuresis is estimated to be present in about 15% of 5 year olds, 9.8% of 7 year olds, 2% of 18 year olds and 1% of young adults. Prevalence in boys is twice that of girls. Often medical help is not sought in expectation of spontaneous remission, or because of social stigma.

What causes nocturnal enuresis?

The generally accepted cause is a delayed functional maturation of the central nervous system, which reduces the child's ability to inhibit bladder emptying at night. Lack of arousal to bladder distension and a pattern of uninhibited bladder contraction have been identified in these children. Parents often complain of difficulty in arousing the child from sleep when compared to their non-enuretic siblings. Sleep apnoea syndrome from upper airway obstruction is also associated with enuresis. There is a 70% chance of a child being enuretic if both parents have a history of bed-wetting and a 40% chance if one parent was affected. In isolated primary enuresis, there is no anatomical abnormality usually of the urinary tract but in polysymptomatic enuresis, functional bladder capacity may be less than that for the age of the child. Psychological factors do not cause primary enuresis, but it may lead to anxiety and low self-esteem as a consequence. In secondary enuresis, a source of psychological stress related to the family environment is possible. Bed-wetting occurs in previously dry children following sexual molestation.

Assessment of nocturnal enuresis

The history should include day and night-time voiding pattern. An organic cause should be excluded by a thorough neurological examination. If the history and examination are normal, urine analysis and culture would be sufficient, but further investigations such as ultra-sound scan and cystourethrogram are indicated if organic bladder pathology is suspected. It is important to know that enuresis may occur due to urinary tract infection (UTI), and that children with bed-wetting are more likely to develop UTI. Other treatable associations of enuresis should be looked for. For example, consti-pation will cause mechanical pressure on the bladder and lead to enuresis. History of snoring and enlarged adenoids will indicate sleep apnoea. Medications such as risperidone, lithium, theophylline and valproate are known to be associated with bed-wetting. Compulsive water drinking, diabetes mellitus and diabetes insipidus are other possible causes.

Pharmacological intervention

Two drugs are used extensively for enuresis – imipramine hydrochloride and desmopressin acetate (DDAVP).

Imipramine is a tricyclic antidepressant that offers two beneficial physiological effects – a direct anticholinergic action on bladder tone, and a decrease in the depth of sleep. In addition, it reduces anxiety. Successful management with imipramine is reported in 20% to 50% of children. Unfortunately, the relapse rate following discontinuation of the drug can be as high as 90%. Imipramine 25 mg to 50 mg is taken at bedtime. Children older than 12 years can be given 75 mg. The lowest possible dose should be used because of side-effects, which include dry mouth and constipation.

Desmopressin acetate (DDAVP) is a synthetic analogue of vasopressin and acts by reabsorbing water at the distal renal tubules. Desmopressin is available as tablets or as a nasal spray pump. Patients and families are advised about fluid restriction and should also be alerted to early signs of water intoxication. Desmopressin nasal spray is no longer recommended in primary nocturnal enure-sis because of the risk of hyponatremia, seizures and rarely death. The recommended dose taken at bedtime

is desmopressin is 200 to 600µg. The relapse rate on discontinuing medication is 90%.

Behavioural intervention

Two types of behaviour treatments have been used with success in nocturnal enuresis – enuresis alarm and dry bed training (DBT).

Enuresis alarm is a simple portable device where a buzzer sounds when an electrical circuit is completed by wetting. The old "bell and pad" has been replaced by a transistorised device, which the child wears on the body. The sound wakes the child who is now able to complete the emptying of bladder in the toilet. Over time, the child becomes conditioned to waking up when the bladder is full or to hold urine overnight to prevent activating the alarm. The disadvantage of the enuretic alarm is that they are time-intensive and require a high level of motivation and cooperation from the child and the family for 3 weeks, to 4 to 6 months. It is recommended that the child should continue to wear the alarm until dry at night for 4 weeks.

Dry bed training (DBT) involves waking the child at regular intervals in the night to pass urine, combined with praise for doing so. The interval between waking is gradually increased with the child learning to be dry at night. Empirical evidence shows that combined use of DBT and alarm to be the most effective intervention. Bladder-retention training is advocated especially when daytime wetting is also present. The training is based on the presumption that the child has a decreased functional bladder capacity. Retention training involves voluntary prolongation of interval between voiding to improve the holding capacity of the bladder. As the enuresis alarm is not freely available in Sri Lanka, DBT is a more rational intervention.

Some common sense approaches are useful even though there is no clear empirical evidence for their effectiveness. Parents should avoid criticising or punishing the child about the problem as this may cause anxiety, poor self-esteem and an inability to overcome the problem. Educate the parents that the child's problem is not purposeful. The child should discontinue taking fluids at least 1 to 2 hours before bedtime, empty the bladder before getting into bed, have easy access to a toilet in the night, and take responsibility in cleaning up.

Summary

Nocturnal enuresis should be treated because of its negative emotional and social implications for the patient. Assessment requires understanding of the pattern of bedwetting and exploration of both organic and non-organic causes. Pharmacological intervention is effective but not sustained after discontinuation. Behavioural methods achieve a better outcome long term but require a high level of motivation from parents and children.

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Prescribing in pregnancy

Introduction

Many women are exposed to drugs during pregnancy with or without their knowledge. With a few exceptions, most drugs are transmitted across the placenta to the foetus, and the prescriber should always consider the foetus as a potential recipient of drugs given to the mother.

Congenital malformations

A drug can have harmful effects on the foetus at any time during pregnancy. These effects may be of a structural or functional nature, and are called congenital malformations. Congenital malformations are defined as non-reversible functional or morphological defects that are present at birth. Some of these may not be detectable at birth, but only become evident later in life [1].

Teratogenicity

Teratogenicity is the presence of major congenital malformations. Some of these may be life-threatening, and others may require major surgery for survival. Some of these may cause serious cosmetic effects. The thalidomide induced deformities is an example of the latter. Substances that cause teratogenicity are called teratogens [1]. Panel 1 gives the factors that determine teratogenecity.

Panel 1. Factors that determine the effects of teratogens

- Dose of drug reaching the foetus
- Gestational age at exposure
- Duration of exposure
- Environmental factors
- Maternal factors such as nutrition, disorders and concurrent medications
- Genetic susceptibility of the foetus

Effect of gestational age at exposure to drug:

First trimester is the period of embryogenesis. From conception to 2 weeks there is a relative resistance to effects of drugs. This may be due to the absence of communication between the maternal and foetal tissue during this period. Exposure to a drug during this period produces an "all or none" effect. This means that the drug may have no effect on the foetus at all or have full effect and cause maximum harm. Weeks 4 through 10 is the most critical period in terms of drug effects on the foetus. Embryogenesis or organogenesis occurs during this period, and this is the most likely time for major congenital malformations to occur. Drugs that reach the embryo at this point in time may produce the following effects.

1. No effect
2. Abortion
3. Anatomical defect/s
4. Metabolic defect/s
5. Functional defects/s

Second and third trimesters are the periods of foetogenesis. During these periods drugs are less likely to be associated with major malformations, but they may influence neurological development, growth, physiological and biochemical functioning, and mental development of the foetus [1].

Of great importance is the fact that pregnancy is often not detected during the period of greatest potential risk. Therefore, caution should be observed in prescribing for all women of childbearing age. Since foetal ova may also be exposed to the drugs given to the mother, effects may be evident in future generations.

Mechanisms of teratogenicity

Mechanisms of teratogenicity are poorly understood. Some drugs may affect maternal receptors, causing indirect effects on the foetus whereas some others may have a direct effect on embryonic development, causing specific abnormalities. Yet others may affect foetal nutrition by affecting placental mechanisms [2].

Categorisation of drugs according to teratogenic risk

Drugs have been categorised according to their potential to cause teratogenicity. According to this classification each drug has been given a risk category. The USA Food and Drug Administration (FDA) classification is into Categories A, B, C, D, and X.

Category A

In controlled human studies no fetal risk has been shown. Drugs belonging to this category are preferred to other drugs.

Category B

No human data are available on risk of teratogenicity and animal studies show no foetal risk or they show a risk that human studies do not show.

Category C

No controlled studies on foetal risk are available for humans or animals, or fetal risk is shown in controlled animal studies but no human data are available.

Category D

Studies show foetal risk in humans. Should not be used unless benefits to foetus and mother clearly outweigh the risks.

Category X

Definite evidence of teratogenicity and foetal risk. Risk to foetus clearly outweighs any benefits.

The teratogenic effects of some drugs have been well established (panel 2). However, for many other drugs, the safety and efficacy profiles during pregnancy have not been established. This is mostly due to ethical constraints in conducting clinical trials during this period of vulnerability. As a result the same drugs and dosages given to non-pregnant adults are prescribed for pregnant women. This practice is far from ideal since pharmacokinetics (PK) and pharmacodynamics (PD) of drugs are altered with physiological changes inherent to pregnancy and can result in sub-therapeutic dosing or toxicity.

Panel 2. Some known teratogens and their effects

• Aminoglycosides (C)	VIII cranial nerve damage
• Androgens (X)	Masculinisation of female foetus
• ACE inhibitors	Renal tubular dysplasia, skull hypoplasia etc.
• Carbamazepine	Craniofacial abnormalities, neural tube defects
• Coumarine derivatives	Foetal warfarin syndrome
• Iodides	Goitre, foetal hypothyroidism
• Lithium	Ebstein anomaly, other cardiac defects
• Phenytoin	Foetal hydantoin syndrome
• Tetracycines	Permanent tooth discolouration, weakens foetal bones

Administering a drug effectively and safely to a pregnant woman could be a challenging task to the prescriber. To face these challenges better, the prescriber should be conversant with the principles of prescribing drugs in pregnancy.

Treatment recommendations

1. When prescribing for a woman of childbearing age, consider the possibility of pregnancy.
2. Discourage non-prescription drug use and self-medication.
3. During the first trimester of pregnancy avoid prescribing any drug unless it is absolutely necessary and confirmed to be beneficial.
4. Prescribe well tried drugs that have been safely used for a long time. Even though some newer drugs have claims of better specificity and lesser side-effects most of these drugs have not been tested during pregnancy.
5. Use the minimum effective dose.
6. Use monotherapy wherever possible.
7. Chronic maternal illnesses such as diabetes, hypertension, epilepsy, and asthma must continue to be treated throughout pregnancy. It is important to control these illnesses well during pregnancy to ensure maternal and foetal wellbeing. This should be explained to the pregnant woman as well as the family to ensure compliance.
8. Chronic diseases may often be safely managed during pregnancy with drugs that are not teratogenic. Some specific conditions are briefly discussed below.

Diabetes

Type 2 diabetes patients are managed on diet or given insulin if dietary therapy alone is inadequate. However the pregnant woman must be advised to continue the oral hypoglycaemic drugs until this change is made. Metformin and sulphonylureas are not known to be teratogenic and could be continued until the patient is changed to insulin. Otherwise, during the critical phase of organogenesis, the foetus would be exposed to hyperglycaemia with possible adverse effects.

Hypertension

Hypertension should be controlled optimally with suitable drugs. Angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, dihydropyridine calcium channel blockers, beta blockers and diuretics should be avoided.

Patients must be treated with drugs safe for pregnant women such as methyldopa (Category A), hydralazine (Category B) and prazosin (Category B).

Antiepileptic drugs

All antiepileptic drugs are potentially teratogenic. Sodium valproate and phenobarbitone are the most teratogenic. But antiepileptic drugs should be continued in pregnant women with epilepsy, because the maternal, foetal and social harm due to uncontrolled epilepsy far outweigh any potential risks from antiepileptic drugs.

Migraine

Ergotamine and the triptans should be avoided throughout pregnancy. An acute attack of migraine should be treated with paracetamol. Non-steroidal anitiinflammatory drugs (NSAIDs) should be avoided. Use of beta blockers such as propranolol and metoprolol in late pregnancy may be associated with neonatal brady-cardia, hypoglycaemia and respiratory depression.

Asthma

Poorly controlled asthma can lead to foetal hypoxia. Asthma should be well controlled in pregnancy. The general principle is to use the lowest dose of the drugs that achieve good control. Corticosteroids and bronchodilators delivered via inhalers are preferred to oral drug administration for the management of chronic persistent asthma. An acute attack of asthma should be treated in the standard manner, but prolonged use of high dose oral corticosteroids is not recommended. Neonatal irritability and apnoea have been reported with theophylline when used in the third trimester of pregnancy.

Anticoagulation

Patients on warfarin should be converted to heparin during the first and third trimesters of pregnancy.

Diuretics

Diuretics should be avoided except for the treatment of cardiovascular disorders, such as pulmonary oedema and congestive cardiac failure. Diuretics are not recommended for the treatment of pregnancy induced hypertension because they can aggravate the characteristic maternal hypovolaemia.

Hyperthyroidism

Propylthiouracil is considered the first choice whereas carbimazole and methimazole are suitabale second-line agents. Radioactive iodine is contraindicated.

Dyspeptic symptoms and gastro-oesophageal reflux (heartburn)

Proton pump inhibitors such as omeprazole should be avoided. H2 receptor blockers are preferred. Ranitidine is preferred to cimetidine since the former has no antiandrogenic activity.

9. Acute maternal illnesses must be effectively managed.
10. Choice of anti-microbials may be made balancing efficacy with risk. Antibiotics should be used rationally and only when necessary. Antibiotic groups such as cephalosporins, macrolides and penicillins are preferred in pregnancy. Tetracyclines, sulphonamides, quinolones and aminoglycosides should be avoided.
11. For fever or pain, paracetamol is recommended. Salicylates and NSAIDs should be avoided since they affect maternal platelet function, increase pre- and post-partum haemorrhage, premature closure of the foetal ductus arteriosus, and delayed labour.

Checklist when prescribing a medicine in pregnancy

1. Non-pharmacological interventions: If safe and effective non-pharmacological measures are available they should be used instead of drug treatment at least until the end of the first trimester.
2. Risk/benefit analysis (Panel 3) What are the potential risks/benefits for mother and fetus of prescribing and not prescribing a given drug?
3. Education, documentation and communication: Has the education of the woman and her partner regarding risk/benefit been properly documented in the patient's notes? Have staff involved in obstetric management been informed?
4. Post-prescription follow up: What follow up should be done to monitor compliance, efficacy, adverse effects and dose alterations?
5. Delivery: Is change of drug or dose alteration indicated before delivery?

Panel 3. Risk/benefit analysis

	Foetus	Mother
Risk of prescribing		
Risk of NOT prescribing		

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Insulins in the State hospitals

Some information about the insulin preparations that are supplied to the State hospitals is given below for the benefit of the prescribers.

1. The preparations available

Presently 3 preparations are made available to hospitals.

i. Soluble insulin – rapid acting formulation. This is supplied as a regular stock item.

ii. Isophane insulin – intermediate acting formulation. This is supplied as a regular stock item.

iii. Pre-mixed – 30% soluble + 70% isophane biphasic insulin. This is supplied as a special item on a selected basis.

The preparation called lente insulin is no longer available in the State hospitals. It was discontinued nearly 3 years ago. We still see doctors writing "lente insulin" in prescriptions. It is likely that these patients are being given isophane insulin.

2. Labelling

The insulins are labelled poorly. The generic name was not found on the label in some of them. The Cosmetics Devices and Drugs Authority (CDDA) has pointed this out to the suppliers and is trying to put this right.

3. Sources

These are genetically engineered insulins having 100 units per ml.

4. Cost

The State spends between Rs.430 to 450/= per vial of soluble and isophane insulin. The pre-mixed vials cost about Rs.565/=.

Medical officers conducting diabetic clinics need to be careful about prescribing insulins. Aspects of compliance have to be gone into. Recently I came across a patient who produced 6 unused insulin vials prescribed over several months. This patient was not using the insulin although she collected them from the diabetic clinic.

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Modern management of thyroid replacement therapy

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Summary

Hypothyroidism is a common and chronic condition. Finding a high concentration of thyroid stimulating hormone in a symptomatic patient confirms the diagnosis and a cause is usually readily found. Lifelong thyroxine therapy relieves symptoms and restores 'normal' thyroid function. Commencing thyroxine can aggravate cardiac disease but is relatively free of adverse effects. The concentration of thyroid stimulating hormone is used to monitor therapy.

Key words: hypothyroidism, pregnancy, thyroid stimulating hormone, thyroxine.

(Aust Prescr 2008; 31: 159-61)

Introduction

Hypothyroidism is a common condition with an annual incidence of 3.5/1000 in women and 0.6/1000 in men.[1] The prevalence increases with age. In areas without iodine deficiency the common causes of chronic hypothyroidism are autoimmune thyroid disease, thyroidectomy, radiotherapy (both radioiodine therapy and external beam radiotherapy), congenital disorders and disorders of thyroid hormone metabolism. Secondary hypothyroidism occurs with some pituitary and hypothalamic diseases.

Diagnosis

Patients may not present with the typical clinical features of hypothyroidism. They may have vague symptoms such as tiredness.The diagnosis can be made by finding a persistently elevated serum concentration of thyroid stimulating hormone (TSH).The serum free thyroxine (fT4) concentration will be low. Measuring triiodothyronine (fT3) adds little to the diagnosis or monitoring of hypothyroidism.

In secondary hypothyroidism the pituitary fails to produce TSH appropriately so measurement of TSH is unhelpful. The diagnosis is suggested by a low fT4 and features of pituitary disorder.

In subclinical hypothyroidism the TSH is elevated (usually to 5-10 mlU/L) but the fT4 is normal. The typical symptoms of hypothyroidism are often absent.

The cause of primary hypothyroidism in an adult will usually be determined from a history of thyroidectomy or radiotherapy or finding high titres of antithyroid antibodies (thyroid peroxidase, antimicrosomal or antithyroglobulin antibodies). The use of lithium and iodine-containing preparations (such as amiodarone) can cause a drug-induced hypothyroidism.

Providing patients with a copy of the laboratory results which confirm their need for thyroxine often proves helpful for the patient and future treating doctors.

Treatment

Primary hypothyroidism is treated by giving the patient replacement thyroxine, usually for life. Liothyronine rarely needs to be used unless there is life-threatening hypothyroidism. Alternative sources of thyroid hormones such as thyroid extracts should be avoided.

Thyroxine dose

Thyroxine has a half-life of 7-10 days but a much longer biological effect. Once-daily dosing is appropriate. The dose is dependent on body weight and age. Children require larger doses of thyroxine per kg body weight than adults who require approximately 1.6 microgram/kg/day.[2] Most adults will maintain euthyroidism with a dose of thyroxine of 100-200 microgram/day. There may be a decline in thyroxine requirements in the elderly.

Both brands of thyroxine currently available in Australia come from the same supplier and are identical. Concerns regarding the bioavailability of different preparations are not relevant in Australia.

Thyroxine tablets should be kept dry and cool and in their original container.[3] Recent advice to refrigerate thyroxine tablets increases the likelihood of moisture causing deterioration in the medication. A month's supply can be kept at room temperature.[4]

Starting thyroxine

The rate of introduction of thyroxine should be determined by the duration of the hypothyroidism and the presence (or risk) of coronary disease or heart failure. Otherwise healthy patients who have recently undergone

thyroidectomy or radioiodine treatment for thyrotoxicosis can immediately start at or just below their predicted daily replacement dose of thyroxine 100-200 microgram.

Elderly patients and those with known heart disease should start with a daily dose of thyroxine 25 microgram for 3-4 weeks with a reassessment of their condition before further increments of 25 microgram every 3-4 weeks until the predicted dose is reached. Worsening symptoms of coronary disease or heart failure should be controlled before increasing the dose of thyroxine and a dose reduction may be necessary while cardiac disease is stabilised.

For patients between these two extremes, a starting dose of 50 microgram/day is reasonable. This is increased at intervals of 3-4 weeks until the predicted dose is reached.

Patients should feel some symptomatic improvement within two weeks of starting thyroxine. It may take 3-4 months for the full benefit of the drug to become apparent and for the TSH to normalise.

Monitoring and dose adjustment

In primary hypothyroidism the TSH alone can be used to monitor therapy. The aim should be to maintain the TSH at the lower end of the normal range (0.4-5 mlU/L). Symptoms may be best relieved when the TSH is at the lower end of this range. It takes at least four weeks for the TSH to stabilise after a change in thyroxine dose and so any testing of TSH should be done at least 4-6 weeks after the change. At the start of treatment a patient does not need measurement of their TSH until they have been on their predicted dose of thyroxine for 4-6 weeks (unless symptoms of thyrotoxicosis dictate otherwise). Repeat testing every six weeks is appropriate until the dose is stabilised, however if the patient is approaching euthyroidism and is feeling well this interval can be increased. After the dose is stabilised an annual TSH measurement is usually adequate monitoring unless a problem arises.

When the thyroxine dose is in the range of 100-200 microgram/day, variable daily dosing may be necessary to achieve euthyroidism. Considering the total weekly dose is helpful when changing the dose. For example, 100 microgram/day (700 microgram/week) may be inadequate to control the TSH but 125 microgram/day (875 microgram/week) may be too much. A dose of 800 microgram/week can be taken as 100 microgram/day five days a week and 150 microgram/day two days a week. Variable daily dosing removes the need for patients to cut thyroxine tablets.

Problems

If taken correctly, thyroxine should enable patients to lead a normal life. However, there are some common problems which can affect management.

Persistently elevated TSH

Poor adherence is the most likely explanation of TSH remaining above the normal range. I advise patients to decant a week's supply of thyroxine into a separately labelled bottle and refill the bottle on the same day each week. If the patient discovers they have missed one (or more) doses they can take the missed doses in conjunction with their usual dose over the next few days.

The absorption of thyroxine may be reduced by cholestyramine, colestipol, aluminium hydroxide, ferrous sulfate and possibly fibre. Two hours should elapse between use of thyroxine and these drugs.

Symptoms do not respond to thyroxine

Hypothyroidism is often discovered on biochemical testing after patients present with non-specific complaints. While it is likely that symptoms such as muscle aches and pains, dry skin and dry hair and menstrual irregularity may respond to thyroxine, other symptoms such as lethargy, tiredness and fatigue, weight gain and depressive symptoms may have other causes. It is helpful to consider if the patient's symptoms are likely to be due to hypothyroidism before prescribing thyroxine and to tell them if you suspect that some of their symptoms are unlikely to respond. There is no proven benefit in adding liothyronine to the treatment of patients who have persistent symptoms despite taking thyroxine.

Secondary hypothyroidism

If there is pituitary or hypothalamic disease, TSH is unreliable for diagnosing and monitoring thyroid function and fT4 should be used instead. A low fT4 will be found in secondary hypothyroidism and treatment should aim to maintain fT4 within the reference range.

Most patients with secondary hypothyroidism will be hypogonadal and many will also be cortisol deficient. It is extremely important to consider cortisol deficiency before starting treatment with thyroxine in patients with pituitary and hypothalamic disease as its use will speed the metabolism of cortisol and can induce an adrenal crisis.

When commencing thyroxine in secondary hypothyroidism it is therefore safest to also treat the patient with a corticosteroid (for example prednisone 5 mg daily). Subsequently, cortisol reserve can be assessed with an early morning cortisol measurement. A morning cortisol less than 100 nmol/L always indicates the need for ongoing steroid replacement. Results greater than 500 nmol/L indicate adequate reserve and values in between may require provocation tests.[5]

Drug-induced hypothyroidism

Lithium and iodine are the common causes of drug-induced hypothyroidism. Amiodarone, iodine-containing contrast media and kelp tablets are common sources of large doses of iodine.

All forms of drug-induced hypothyroidism will usually resolve on withdrawal of the drug. Thyroxine can be used to control symptoms if required while recovery occurs. Lithium- and amiodarone-induced hypothyroidism are managed with thyroxine. The ongoing need for the lithium or amiodarone should be considered, but they can be continued if necessary.

Pregnancy and lactation

Thyroxine requirements increase by 25-30% during pregnancy with increased requirements seen as early as the fifth week of pregnancy.[6] Children born to women whose hypothyroidism was inadequately treated in pregnancy are at increased risk of neuropsychological impairment.[7]

I advise women taking thyroxine who are planning to conceive to increase their dose of thyroxine by 30% at the confirmation of the pregnancy. TSH should be monitored every 8-10 weeks during pregnancy with further dose adjustments as necessary. The thyroxine dose returns to the pre-pregnancy dose after delivery whether the mother is breastfeeding or not.

Transient hypothyroidism

Some patients have transient hypothyroidism so it is appropriate to consider withdrawing the drug. For example, women who develop hypothyroidism in the postpartum period (postpartum thyroiditis) may not require long-term thyroxine replacement. In some patients a clear cause of hypothyroidism is not established, but the cause will often have been the hypothyroid phase of subacute (de Quervain's) thyroiditis or possibly iodine-induced hypothyroidism. Other patients may ask if they can stop thyroxine therapy.

If treatment is stopped it usually takes four weeks for the TSH to rise, but it can be tested earlier if symptoms occur. The onset of symptoms and a rising TSH show an ongoing need for thyroxine and patients can immediately recommence their previous dose.

Subclinical hypothyroidism

Some patients have an elevated TSH, but a normal concentration of fT4. The need for treatment is debatable. I consider treating patients who have had an elevated TSH for over six months with persistent symptoms which may be due to hypothyroidism, and also patients who have antibodies suggesting autoimmune thyroid disease. After a 3-6 month trial I continue treatment if there has been a substantial symptomatic improvement, or stop and reassess symptoms and TSH after 4-6 weeks to determine if there is an absolute need for ongoing thyroxine replacement. Patients with a modestly elevated TSH and positive thyroid antibodies have a 5% per year chance of developing overt hypothyroidism.[1] Pregnant women and those considering pregnancy should be treated.

Addison's disease

Addison's disease and autoimmune hypothyroidism occasionally occur together. This is a rare but dangerous association. Increased pigmentation, postural hypotension and possibly weight loss may suggest the additional diagnosis. As in secondary hypothyroidism, give steroid replacement before introducing thyroxine to avoid inducing an adrenal crisis.

Thyroid cancer

Some patients with differentiated thyroid cancer are given thyroxine at a higher dose to suppress TSH (to less than 0.1 mlU/L) with minimum elevation of fT4. This helps prevent recurrence of the cancer.

Conclusion

Treatment of hypothyroidism is usually a lifelong necessity. Determining the cause will detect those patients who need only transient treatment. Except for those patients with or at risk of known cardiac disease, the elderly and those with long-standing symptoms, thyroxine can usually be commenced at or near a full replacement dose. The dose is adjusted to keep the concentration of TSH within the normal range.

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Non-invasive ventilation

History of ventilation

The first artificial ventilation of a human being was performed during the polio epidemic in Denmark in the 1940s where the hospitals were overwhelmed with patients needing ventilatory support. They were hand ventilated round the clock by medical staff and students. To cope with the situation negative pressure tank ventilators were put to use. During the first half of the 20th century negative pressure non-invasive ventilation was the main means of providing ventilation. It gradually went out of use in the 1960s when invasive positive pressure ventilation was introduced.

Invasive vs non-invasive (NIV) ventilation

In invasive ventilation the ventilatory support is delivered through an endotracheal (ET) tube, whereas in non-invasive ventilation, it is delivered by techniques that do not require an ET tube. It is usually by a nasal or face mask. Nasal masks are more tolerable to patients, but require a cooperative patient to keep the mouth closed for ventilation to be effective. This type of ventilation offers a number of advantages, such as the delivery of precise oxygen concentrations and separate inspiratory and expiratory tubing that minimise rebreathing. Patient disconnection can be readily detected because monitoring and alarm features are more sophisticated.

Mechanism of action

In all methods of NIV a positive pressure is applied to the nasal or the face mask. This facilitates inspiration because it widens the pressure gradient for gas flow; the pressure gradient of atmospheric to intrapleural becomes mask pressure to intrapleural. During expiration the patient has to exhale against the mask pressure. This generates a positive end-expiratory pressure (PEEP) which prevents the alveolar collapse at end expiration and improves the V/Q mismatch. With NIV there is resting of respiratory musculature without muscle paralysis, and the patient generates a less negative pressure for inspiration, which decreases the work of breathing.

In patients with COPD, the ventilatory response to raised $PaCO_2$ is decreased, specially during sleep. By maintaining lower nocturnal $PaCO_2$ during sleep by NIV, it is possible to make the respiratory centre more responsive to increased $PaCO_2$. These patients are then able to maintain a more normal $PaCO_2$ throughout the daytime without the need of ventilatory support. The major mechanism causing acute respiratory failure in COPD is dynamic hyperinflation as a result of increased airway resistance, which prevents complete exhalation before the next inspiration. This greatly increased intrinsic PEEP (physiological PEEP in the respiratory system) increases the work of breathing, resulting in early respiratory muscle fatigue. NIV acts by using externally applied PEEP to offset the intrinsic PEEP, and to reduce dynamic hyperinflation and the work of breathing. The panels 1-6 give details of NIV.

Panel 1. Advantages of NIV

1. Avoidance of intubation
2. Enhanced patient comfort : the patient can eat, drink and communicate
3. Ease of application and removal to allow ventilator free periods
4. Can be used in the ward and reduce the need for ICU
5. Reduces sedation requirement
6. Preservation of airway defense mechanisms
7. Decreases incidence of nosocomial pneumonia
8. Partial unloading of respiratory muscles
9. Reduced cost
10. Reduces mortality and ICU stay

Panel 2. Disadvantages of NIV

1. Mask uncomfortable
2. Time consuming for medical and nursing staff
3. Airway is not protected
4. No direct access to bronchial tree for suction

Panel 3. Indications for NIV

1. Acute respiratory failure
2. Acute exacerbation of COPD
3. Post-extubation difficulty
4. Weaning difficulties
5. Thoracic wall deformities
6. Patients who are not for intubation

Panel 4. Contraindications

1. Respiratory arrest
2. Unstable cardiovascular status
3. Uncooperative or extremely anxious patient
4. Impaired mental status
5. Inability to protect the airway – impaired cough
6. Facial, oesophageal or gastric surgery
7. Craniofacial trauma or burns
8. Anatomic lesions of the upper airway
9. Morbid obesity
10. Copious secretions
11. Need for continuous ventilatory assistance
12. Life-threatening refractory hypoxemia (PaO_2 < 60 mm Hg on 100% O_2)

Panel 5. Factors predictive of success

1. Younger age
2. Patients ability to cooperate and coordinate breathing with the ventilator
3. Moderate hypercapnia ($PaCO_2$ 70 to 80 mm Hg)
4. Moderate acidaemia (pH 7.1 to 7.3)
5. Improvement of gas exchange within the first 2 hours

Panel 6. Complications

Most complications are minor and are mask-related. They include:

1. Nasal bridge ulceration
2. Facial erythema
3. Nasal congestion
4. Eye irritation

Aerophagia occurs in up to 25% of patients, and all patients receiving NIV should have a nasogastric tube in situ.

Modes of non-invasive ventilation

NIV can be delivered by all modes of ventilation. A volume or pressure controlled ventilator, a bi-level positive airway pressure (BIPAP) device, or a continuous positive airway pressure (CPAP) device can be used. The indications for use are listed in panel 4.

CPAP

Continuous positive airway pressure by application of a face mask provides a pneumatic splint which holds the upper airway open. It provides positive airway pressure throughout respiration. It increases the functional residual capacity and opens collapsed alveoli. CPAP is an effective treatment for pulmonary oedema. Pressures are usually limited to 5-12 cm of H_2O. Though a higher CPAP may aid inspiration, it may result in CO_2 accumulation because the patient has to exhale against the high pressure.

BIPAP

Bi-level positive airway pressure by application of a face mask with the BIPAP device provides two levels of positive pressure. A higher level during inspiration and a lower level during expiration. Airflow in the circuit is sensed by a transducer in the BIPAP device and upon detection of inspiration a higher pressure is delivered. Cycling between inspiratory and expiratory mode is triggered by the patient's breaths. As the expiratory pressure is low it does not impede exhalation.

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Self-assessment questions

(And clinical physiology in small doses)

*Select the **best** response to each question*

1. When imipramine hydrochloride is used in the management of childhood enuresis, the drug is known to

   a. increase the depth of sleep
   b. cause daytime urgency of urination
   c. induce sleep apnoea
   d. control enuresis in 70 – 80% of affected children
   e. have a relapse rate of over 80% on stopping the drugs

2. In the management of primary hypothyroidism with thyroxine in an adult patient with no other disease

   a. treatment should start with a dose of 100 microgram daily
   b. TSH should be measured at 2 weeks after starting treatment
   c. TSH should be maintained at about 4 milliunits per litre (normal range 0.4 – 5.0)
   d. once the dose is stabilized, assessment of TSH every 6 – 12 months is usually sufficient to maintain euthyroidism
   e. measurement of FT3 (tri-iodothyronine) annually is advisable for ideal management

3. Which statement regarding synthesis, secretion and function of thyroid hormones is true?

   a. Most of the reverse triiodothyronine (RT3) in blood is produced by the thyroid gland
   b. Thyroglobulin in the blood transports T3 and T4
   c. Thyroid cells synthesise thyroglobulin
   d. The minimum daily iodine intake required to maintain thyroid function in the healthy adult is about 350 microgram
   e. Small amounts of mono- and diiodotryrosine are secreted by thyroid cells into the blood

Answers to self-assessment questions

Question 1. Correct response, e. The relapse rate on stopping imipramine is about 90%. It reduces depth of sleep, has an anticholinergic effect on bladder function, and does not induce sleep apnoea. It may cause dry mouth and constipation. See article by Dr Hemamali Perera in this issue of *SLP*.

Question 2. Correct response, d. Thyroxine treatment should start at a dose of 25 or 50 micrograms/day. The initial TSH measurement should be at 4 – 6 weeks. TSH values should be maintained close to the minimum of the reference range in the absence of any contraindications. Measurement of FT3 is rarely or never useful. See article by Dr Peter Davoren in this issue of *SLP*.

Question 3. Correct response, c. Most of the T3 and RT3 in blood (over 80%) is derived from conversion in peripheral tissues including liver, kidney and muscle. The function of thyroglobulin in blood is unknown. It does not transport hormones. The daily minimum recommended iodine intake for adults is about 150 microgram. MIT and DIT are not secreted into the blood. RT3 has no significant hormonal action on tissues.

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