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Cover picture

THEOPHRASTUS, FATHER OF BOTANY (350 B.C.)

The Greek teacher and botanist, Theophrastus, systematized knowledge of herbs and plants, describing their medicinal qualities, preparations, and uses. His students learned of nature by observing her treasures at firsthand.

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

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

How to minimise the pain associated with insulin injections

Case report: the patient who would not take insulin

A 55-year old patient with type 2 diabetes and secondary oral hypoglycaemic failure was on a twice daily premixed biphasic insulin mixture (soluble insulin and isophane insulin 30/70) 40 units mane and 20 units nocte. However, her glycaemic control continued to be poor with the fasting blood glucose values repeatedly above 250 mg/dl. To achieve glycaemic control the insulin doses were progressively increased by her doctor, but, the glycaemic control remained poor.

On being asked whether she took the insulin as directed by the doctor, the patient replied in the affirmative. On further questioning she disclosed that she missed out on several doses of insulin every week, sometimes a few days at a stretch! The reason given was the severe pain with the insulin injections. The insulin was injected to her by her husband and on *Poya* days her son pleaded with his father not to give insulin to his mother since he felt that his mother should be spared the agony of painful injections at least on *Poya* days.

It was later found that the needle used by the patient to inject insulin was not meant for that purpose and had an unacceptably large needle (gauge 25). The syringe was just a 1 ml syringe and did not have insulin units marked on it. Several inaccuracies were noted in the insulin injection procedure as well as the technique used by her husband. The insulin was injected immediately after taking the vial out of the refrigerator while still cold. He never checked whether there were air bubbles in the insulin drawn into the syringe.

This story shows the importance of educating patients and caregivers regarding correct insulin injection technique and the correct devices used for injecting insulin. It also shows the importance of repeatedly checking on the patient's compliance to treatment by detailed but specific questions.

Methods of minimising the pain associated with insulin injections.

1. Select the correct insulin needle and syringe with the correct needle size. There is a special needle and syringe for the subcutaneous injection of insulin. It has a very fine needle of 29 gauge. The needle is permanently fixed to the syringe and cannot be removed. The 1 ml syringe is marked in units up to 100 to enable accurate drawing up of insulin into the syringe.

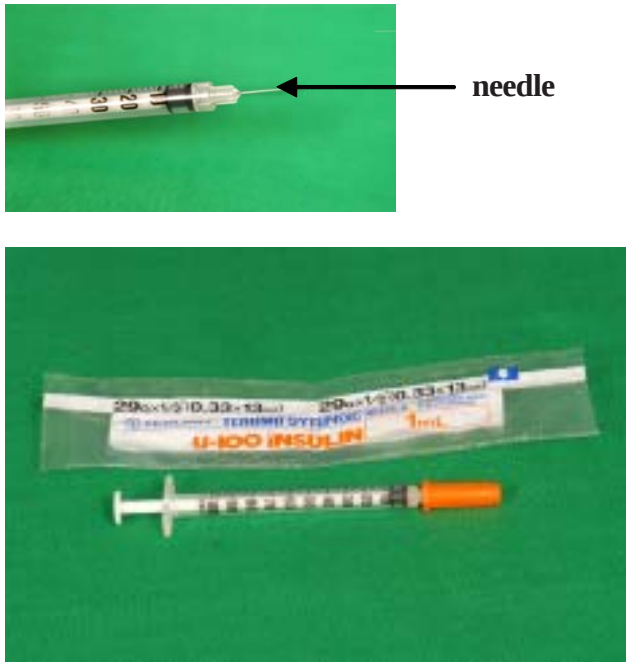

Figure 1. Insulin needle and syringe.

2. Only if this needle size is not available, a larger sized needle may be used, such as 27 or 28 gauge. Needle gauges below 27 gauge should not be used to inject insulin subcutaneously since they can cause pain during injection.

3. It is preferable to use an insulin pen device if the patient can afford it, since it has a very fine needle of 31 gauge. The patient would experience minimal pain when using such a needle.

Figure 2. Insulin pen device.

4. If the insulin vial is stored in a refrigerator it should be taken out at least 15 to 30 minutes before the injection time since injection of cold insulin causes more pain compared to insulin at room temperature.

5. Check for any air bubbles in the insulin drawn into the syringe. Remove air bubbles by tapping gently on the syringe while the needle is still inside the insulin vial which has been turned upside down to draw insulin.

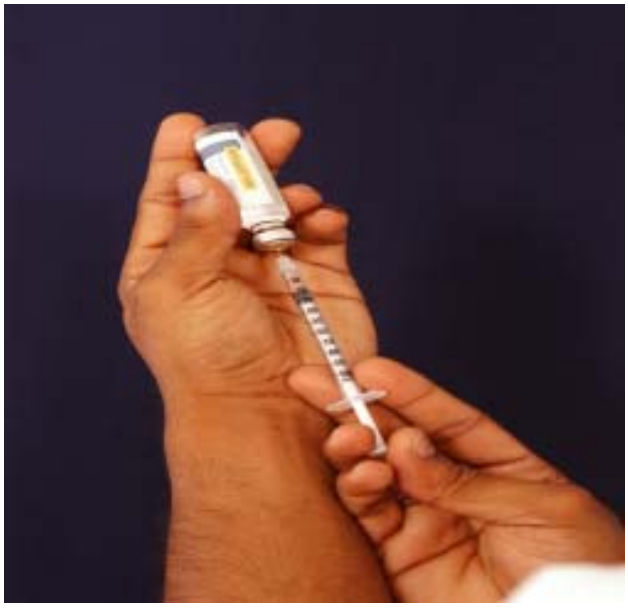

Figure 3. Check for air bubbles.

6. Daily application of surgical spirit may cause roughening of the skin and difficulty in piercing the skin leading to pain. Therefore, surgical spirit should not be applied routinely to clean the skin before injection at home. The recommended method of cleaning the injection site at home is with soap and water. However, cleaning of the injection site should be done with surgical spirit in hospitals or clinics to prevent possible infection of the injection site.

7. During subcutaneous injections select an injection site with sufficient subcutaneous fat and raise a skin fold up. This is important especially if the patient is thin or wasted.

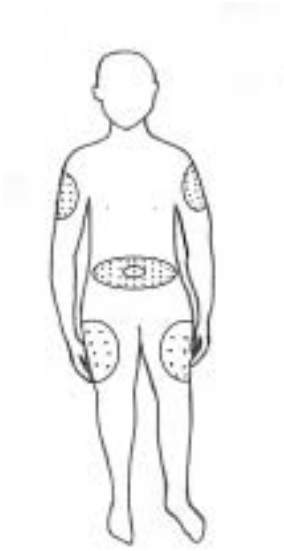

Figure 4. Sites for subcutaneous injection of insulin.

- Deltoid region (upper arm)
- Abdomen
- Upper thighs

8. Insert the injection needle at 90 degrees to the skin rather than at an angle.

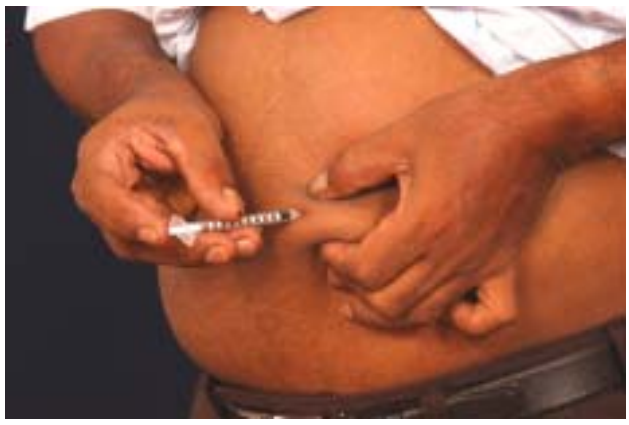

Figure 5. Needle is vertical.

9. Do not rotate the needle while the needle is inside the skin.

10. Insert the needle smartly through the skin.

11. Inject the insulin smoothly and rapidly into the subcutaneous tissue. The needle should not be withdrawn until 5 seconds after injection with a 29 G needle and until 10 seconds after injecting with a 31G needle of a pen or doses >25 units of insulin by syringe and needle. This is to allow dispersion of insulin into the tissues and to prevent insulin leaking from the site of injection.

12. Withdraw the needle rapidly.
    Slow insertion of the needle, slow injection and slow withdrawal of the needle cause more pain.

13. Even though the same needle and syringe can be reused several times in the same patient stop reuse if the needle is blunt or bent. The needle should not be reused if it is contaminated with blood or if it touches a surface other than the injecting site.

Comments and recommendations

Doctors, nurses and pharmacists should be conversant with the correct technique of insulin injection and suitable devices for injecting insulin. This would enable them to advise and educate their patients and caregivers on simple measures to reduce the pain of insulin injections.

The injection techniques and the devices should be demonstrated carefully to the patients. The patients should be asked to take an injection while being observed by the health care professional/s involved to make sure they understand and apply what has been learnt. The patient should be interviewed, doubts cleared and the technique reinforced at follow up visits to ensure compliance to treatment.

It is common practice among doctors to request patients verbally to buy the insulin syringe and needle from a pharmacy without giving a prescription. It is important to give a prescription for the insulin needle and the syringe stating the correct specifications to ensure that the patients get the correct device. This will not only help minimise pain of injection but also prevent other errors such as injecting the incorrect dose of insulin.

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Medical nutrition therapy and type 2 diabetes mellitus

With the increasing prevalence of obesity and an ageing population, type 2 diabetes mellitus (type 2 DM) is one of the most common chronic diseases in Sri Lanka. Type 2 DM is a metabolic disease characterised by insulin resistance and relative insulin deficiency which is strongly associated with obesity in genetically susceptible individuals [1]. Medical nutrition therapy (MNT) has an important role complementary to the pharmaceutical treatment in type 2 DM, and is a key component of any diabetes management plan, along with recommendations for physical activity.

Ideally, patients with diabetes require comprehensive dietary advice at diagnosis, with a follow up visit 3 months after initial dietary intervention, and a yearly review of dietary therapy thereafter. The term "diabetic diet" is a misconception. The diet that a patient with diabetes follows to manage the blood glucose concentration, is based on the same nutrition principles that should govern the eating habits of any healthy person. Most foods eaten by a non- diabetic individual can be consumed by a diabetic, but since both quality and quantity of foods can affect blood glucose concentrations, dietary management is vital.

Goals of MNT in type 2 DM

The main goals of dietary intervention in diabetes mellitus are to consume the correct amounts of nutrients and calories to maintain an ideal body weight, achieve and maintain blood glucose at normal or near normal levels that would minimise complications of diabetes mellitus, and attain an optimal lipid profile. Maintaining the pleasures of eating through evidence based food choices rather than rigid restriction should be a key consideration.

The principles of dietary management in type 2 DM

Weight loss

In overweight [body mass index (BMI) >23.0 kg/m^2] or obese (BMI >27.5 kg/m^2) individuals, modest weight loss reduces insulin resistance [2]. The primary objective is to achieve a weight loss of 5-10% of initial body weight at diagnosis if the patient is overweight or obese. Weight loss can be achieved through a diet in which energy intake is balanced by regular physical activity, the intake of complex carbohydrates, a reduced intake of fat, and an increased fibre intake.

The optimal macronutrient distribution of weight loss diets has not been fully established [3]. Although low fat diets have traditionally been promoted for weight loss, many newer studies report success with low carbohydrate diets as well, with more favourable changes in serum triglycerides and HDL cholesterol. However, since other effects of low carbohydrate diets have not been studied in detail caution is necessary, and in patients following such a diet, regular monitoring of lipid profile and renal function is mandatory. Either low carbohydrate or low fat calorie-restricted diets are effective when combined with physical activity. Very low calorie diets appear to have limited value in the treatment of type 2 DM, and should not be a regular treatment option [3].

Carbohydrates

The amount and type of carbohydrate taken is usually the main determinant of postprandial response. The daily energy intake should consist of 55-60% in the form of carbohydrates with a preferential intake of complex carbohydrates rich in fibre and low in glycaemic load such as whole grains, legumes and vegetables. Of the daily caloric intake, a small quantity (2-5 %) could be simple carbohydrates consumed in the context of a varied meal, and a moderate quantity of fructose (from fruits) is recommended. The carbohydrate intake should be spread out evenly over the day to smoothen blood glucose management. Matching the doses of insulin and insulin secretagogues to the carbohydrate content of meals is important.

The glycaemic index (GI) of foods compares their postprandial responses to constant amounts of different carbohydrate containing foods. The GI is the increase above fasting in the blood glucose area

over 2 hours after ingestion of a 50 g carbohydrate portion divided by the response to a reference food (usually glucose or bread). In patients consuming a diet with high GI, change to low GI foods can produce modest benefits in controlling postprandial hyperglycaemia [4].

The glycaemic load is a better index of postprandial blood glucose response to foods or meals and is calculated by multiplying the GI of the constituent foods by the amounts of carbohydrate in each food and then totaling the values for all foods [3].

Proteins

The consumption of proteins should be about 10-15% of the daily caloric intake and about 0.8-1 g of good quality protein /kg of body weight is required for diabetic patients without renal complications. High protein diets are not recommended as a method for weight loss since the long term effects on type 2 DM and its complications are unknown, although such diets may produce short term weight loss and improved glycaemia.

Fats

The principal goal with regard to dietary fat in individuals with diabetes is to limit the total intake of fats to 20- 30% of energy intake, of which saturated fats should be less than 8-10% (further restricted to 7-8% for individuals with LDL cholesterol of ≥100mg/dl and other cardiovascular risk factors). Polyunsaturated fatty acids should be <10%, and the monounsaturated fatty acids should consist of 10% of the total caloric intake [2]. Saturated and trans fatty acids are the principal dietary determinants of plasma LDL cholesterol, and their avoidance, in addition to assisting with weight reduction, will be of value in management of hyperlipidaemia and in reducing overall cardiovascular disease risk. Avoidance of saturated and trans fats do not adversely affect the ratio of LDL cholesterol to HDL cholesterol. The intake of cholesterol through the diet should be <200 mg/d or less for individuals with high levels of LDL cholesterol [2]. Omega-3 polyunsaturated fatty acid supplements reduce plasma triglyceride levels in individuals with type 2 DM who are hypertriglyceridaemic. Although there maybe a small rise in plasma LDL cholesterol, an increase in HDL cholesterol may offset this. [5]

Fibre

A regular intake of the recommended amount of fibre (>25 g/day) by choosing a variety of fibre containing foods such as legumes, fibre rich cereals, grains, fruits, and vegetables reduces blood glucose, hyper-insulinaemia, and lipaemia in subjects with type 2 DM.

Micronutrients

The importance of acquiring daily vitamin and mineral requirements from the diet is essential as poorly controlled diabetes is often associated with micronutrient deficiencies. No clear evidence of benefit from vitamin or mineral supplementation is available for patients with type 2 DM without underlying micronutrient deficiencies [3].

Alcohol in diabetes management

Alcohol intake should be limited to a moderate quantity [3] . Moderate alcohol consumption (when ingested alone) has no acute effect on blood glucose and insulin concentrations, but carbohydrate taken with alcohol (as in a mixed drink or snacks) may raise blood glucose [6].

Safe conduct of exercise

Patients treated with insulin or insulin secretagogues, should be advised regarding safe conduct of exercise, including the prevention and treatment of hypoglycaemia.

Facts and fallacies in dietary management of type 2 DM

- Fad diets/crash diets and so-called miracle dietary cures that are not backed by sound scientific evidence should be avoided.

- Non-nutritive sweeteners: acesulfame potassium, aspartame, neotame, saccharin, and sucralose have been rigorously tested for safety before being allowed on the market, and shown to be safe for people, including those with diabetes [3].

- Reduced calorie sweeteners: use of sugar alcohols (polyols) such as isomalt, maltitol, mannitol, sorbitol, xylitol and hydrogenated starch hydrolysates produce a lower postprandial glucose response than sucrose or glucose, and have lower available energy.

- Antioxidants and trace metals: routine supplementation with antioxidants, such as vitamins E and C and carotene, or trace metals such as chromium and magnesium is not advised for of lack of evidence of efficacy, and concerns related to long term safety [3].

- Herbal therapy: there is insufficient evidence to demonstrate efficacy of herbs and supplements in diabetes management. Further, available products are often not standardised, vary in the content of active ingredients and have the potential to interact with other medications. Hence, it is important that health professionals be aware when patients with diabetes are using these products [7].

Control of blood glucose to achieve normal or near-normal levels is the key objective of diabetes management. Food and nutrition interventions that reduce postprandial blood glucose excursions are the basis of medical nutrition therapy in diabetes mellitus.

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Analgesics and pain relief in pregnancy and breastfeeding

Summary

Women should be reassured that pain can be treated during pregnancy and lactation and that they need not suffer unnecessarily. Overall, appropriate therapeutic doses of the commonly used analgesics including paracetamol, aspirin and opioids have not been associated with an increased incidence of birth defects. The use of non-steroidal anti-inflammatory drugs in the third trimester is not recommended. Untreated persistent pain can have adverse effects for the mother and her pregnancy and women with persistent pain should ideally have optimisation of their pain management before pregnancy.

Key words: codeine, non-steroidal anti-inflammatory drugs, opioids, paracetamol.

(Aust Prescr 2011;34:8-10)

Introduction

Pain during pregnancy may be due to acute conditions such as injury or infection, or secondary to underlying medical disorders such as rheumatoid arthritis. Pain related to pregnancy can also occur.

Inadequately managed persistent pain can result in depression and anxiety. These may impact on a woman's physical and psychological wellbeing and can potentially have an adverse effect on her pregnancy.

Women should not suffer unnecessarily from pain during pregnancy and lactation. If used appropriately, common analgesics such as paracetamol, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are relatively safe.

In counselling women about taking medicines during pregnancy it is always important to emphasise that all couples have a background risk of around 3% of having a baby with a major birth defect and that approximately 15% of all recognised pregnancies end in miscarriage, regardless of any drug exposures. Over 85% of women use some medication during pregnancy and analgesics are the most common preparations used, after vitamins, in all trimesters of pregnancy, with over 50% of women using analgesics during their pregnancy.[1]

The risks or otherwise of drug exposures need to be put into the context of this background risk. Women and their health professionals can then make informed decisions and weigh up the potential risks of treating versus not treating pain during pregnancy and breastfeeding.

Paracetamol

Paracetamol is the analgesic and antipyretic drug most widely used in Australia, particularly by pregnant women. Although it readily crosses the placenta in its unconjugated form, in therapeutic doses it does not appear to increase the risk of birth defects or other adverse pregnancy outcomes. Despite paracetamol's widespread use there are, somewhat surprisingly, no prospective controlled studies about its use in pregnancy.

The drug is not considered to be teratogenic although some retrospective studies including the US Collaborative Perinatal Project found an increased risk of any congenital abnormality and specifically an increase in congenital dislocation of the hip in exposed infants. A registry-based study from Denmark of 26 424 children who were exposed to paracetamol *in utero* during the first trimester found no increase in either the specific or the overall rate of birth defects compared with unexposed controls.[2]

Aspirin

Aspirin is used to treat mild pain and fever, and low-dose aspirin is also prescribed by some obstetricians (often with heparin) to reduce the risk of adverse outcomes in pregnant women with antiphospholipid

syndrome and recurrent miscarriages.[3] Overall, aspirin is not associated with an increased risk of congenital malformations, although one meta-analysis suggested an association between first trimester aspirin use and increased risk of gastroschisis*.[4]

NSAIDs

NSAIDs including ibuprofen, naproxen, indomethacin and diclofenac are widely used to treat mild to moderate pain and fever. They are inhibitors of cyclo-oxygenase. In the fetus and newborn, cyclo-oxygenase is a potent dilator of the ductus arteriosus and pulmonary resistance vessels. Its inhibition could potentially cause premature closure of these vessels. These drugs have not been shown to increase the risk of structural birth defects or other adverse outcomes such as preterm delivery or low birth weight. However, a case-control and population-based observational cohort study from Scandinavia demonstrated an increased risk of spontaneous abortion with first trimester use of NSAIDs but with no evidence of other adverse pregnancy outcomes. Major flaws in this study, however, were that it was prescription-based and retrospective and did not control for the indications of use of NSAIDs (such as underlying fever or viral illness).[5]

A Californian study also showed an 80% increase in the risk of miscarriage associated with first trimester use of both aspirin and NSAIDs. This association was not seen with paracetamol.[6]

A suggested mechanism to explain the increased risk of miscarriage is interference with implantation as a result of effects on the prostaglandin pathway. Women who have used NSAIDs inadvertently during the first trimester should be reassured about the use, but other analgesics such as paracetamol should be recommended as preferable options for subsequent use.

Use of NSAIDs after 30 weeks gestation is contraindicated because of their potential to cause premature closure of the fetal ductus arteriosus and persistent pulmonary hypertension. High doses of NSAIDs in the third trimester may also reduce perfusion of the fetal kidneys and decrease fetal urine output. This is why NSAIDs are occasionally used as an intervention to try and reduce liquor volume and the chances of cord entanglement in cases of mono-amniotic twin pregnancy. Most of the cases of reduced output are reversible, but there have been reports of only partial resolution and even of death due to anuric renal failure.[7,8]

As with the older NSAIDs, the main concerns with the COX-2 inhibitors are effects on the ductus arteriosus as well as perfusion of the fetal/neonatal kidney and intestine. Topical NSAIDs generally result in negligible blood levels and would be considered to be relatively safe in pregnancy although absorption is increased by use over a large surface area or the application of heat.

Opioids

Opioids such as codeine, oxycodone, hydromorphone, hydrocodone and morphine, as well as drugs such as pethidine and tramadol, are used to treat moderate to severe pain. Codeine is also widely used in various over-the-counter preparations. Overall, opioid analgesics have not been associated with an increase in birth defects or other adverse outcomes such as miscarriage. There are also reassuring data on longer-term neurodevelopmental follow up in exposed infants. The main concern about these drugs is that persistent use may lead to dependence and tolerance in the mother with resultant withdrawal (neonatal abstinence syndrome) in the neonate.

Women with persistent pain who may require high doses of opioids during pregnancy should seek advice about optimising their pain management before pregnancy. Sometimes alternative drugs including tricyclic antidepressants may help to control persistent pain and reduce opioid exposure. Tricyclic antidepressants have not been associated with an increased rate of birth defects or long term neurodevelopmental effects.[9]

* an abdominal wall defect resulting from rupture of the amniotic membrane during gut-loop herniation or, later, due to delayed umbilical ring closure

Breastfeeding

Paracetamol is considered to be safe for use during lactation. The estimated dose received via breast milk is 6% of the maternal dose. It should be remembered that paracetamol is widely used at doses far greater than this for children.

NSAIDs, such as ibuprofen and diclofenac, are considered to be compatible with breastfeeding. The infant doses relative to the maternal doses are 0.65% and 1% respectively, even in women taking high doses - for example diclofenac suppositories 75 mg.[10] The advantage of using these drugs, especially in the immediate postpartum period, is a reduced need for opioids and the potential risks associated with them.

Aspirin is generally not recommended for treatment of pain during breastfeeding mainly because there may be significant adverse effects in infants (the relative infant dose may be as high as 10%) and safer alternatives are available. There is also the theoretical concern that aspirin can cause Reye's syndrome in infants.[10]

Genetic polymorphisms and opioids

Cytochrome P450 2D6 catalyses the O-demethylation of codeine to morphine and genetic polymorphisms in the CYP2D6 gene can affect the metabolism of codeine. One of the polymorphisms may result in reduced efficacy of codeine which can be a potential clinical problem.

The case report of a breastfed neonate, who died following maternal codeine use postpartum, highlights the risks of opioid toxicity in patients with another polymorphism – duplication of the CYP2D6 gene.[11] This results in ultra-rapid metabolism of codeine and significantly increases the production of morphine. In adults this can lead to significant opioid toxicity despite small doses of drug, and thus breastfed infants of such patients are also at risk of serious toxicity. The incidence of this gene duplication varies in different populations, from approximately 1% in Denmark and Finland to 10% in Greece and Portugal and up to 30% in Ethiopia.

There are also other genetic polymorphisms involved in morphine metabolism that theoretically could reduce its clearance.

Caution needs to be exercised in terms of breastfeeding and minimising the risk of opioid toxicity in both mothers and babies. Short term use is unlikely to pose a significant risk but longer term or chronic use can be potentially dangerous, particularly in those people who are ultra-rapid metabolisers due to the CYP2D6 duplication. Mothers and babies should be carefully observed and monitored for signs of opioid toxicity. In most cases the occurrence of central nervous system depression with opioids is consistent between mother and baby (although babies appear to be more sensitive to the effects of opioids) and so if a mother appears to have adverse effects of opioids there should be a low threshold for examining the baby and excluding toxicity.[12] If longer term pain relief is required, then other drugs such as NSAIDs should be considered as first-line treatment.

Conclusion and recommendations

At MotherSafe we reassure women regarding inadvertent NSAID use, but recommend paracetamol as first-line treatment of fever and pain during pregnancy. Codeine or another opioid analgesic can be added to treat more severe pain. NSAID use is contraindicated in the third trimester and alternative analgesics should also be considered in the first trimester.

Women and their doctors should however be reassured that there are safe options to treat pain, both acute and chronic, during pregnancy and breastfeeding.

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Self-assessment questions

(Select the *best* response in each question)

1. In the long term management of dose stabilised primary hypothyroidism the following measures are clinically important.
   a) Storing thyroxine tablets on the middle shelf of a refrigerator.
   b) Measuring serum free T_3 at six-monthly intervals.
   c) Measuring serum free T_4 at six-monthly intervals.
   d) Measuring serum TSH at 6- to 12- month intervals.
   e) Maintaining serum TSH at the upper end of the reference range (0.4 – 5.0 mIU/l).

2. Which statement is true regarding the metabolism of thyroxine?
   a) It has a half-life of 3 – 4 days.
   b) The metabolically active hormone is T_4, not T_3.
   c) Thyroid hormone protein binding in plasma varies between 75 and 80% of the total amount.
   d) In severe non-thyroidal illness more T_4 may be converted to reverse T_3 (rT_3), which is metabolically inactive, than to active T_3.
   e) The thyroid gland secretes more T_3 than T_4.

3. The absorption of thyroxine is **not** reduced by
   a) losartan potassium
   b) ferrous sulfate
   c) aluminium hydroxide
   d) colestipol
   e) cholestyramine

Answers to self-assessment questions

1. The correct response is **d**. Thyroxine tablets are best stored in a cool dry environment, not in a refrigerator. For optimum therapeutic response serum TSH should be maintained close to the lower end of the reference range, by testing at 6 – 12 month intervals.

2. The correct response is **d**. The half-life of thyroxine is 7 – 10 days, and protein-binding of thyroid hormones is greater than 99%. In severe illnesses more reverse T_3 is produced from T_4 in tissues, than T_3.

3. The correct response is **a**. The other four medications are known to decrease the absorption of thyroxine if they are given less than 2 hours before or after thyroxine.

References

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