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Chapter 27.

DRUGS IN PREGNANCY AND LABOUR

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27.1 Introduction.

It is a condition of use of many drugs that extra care and attention should be used when administered to pregnant women. It is well established that some drugs can have temporary or permanent effects on the developing foetus. Drugs that have such an effect are known as teratogens, the most notorious being **thalidomide** which was prescribed to pregnant women as a treatment for morning sickness and resulted in a variety of serious birth defects for many thousands of babies. However, this chapter is concerned with drugs that are used to treat medical complaints arising from problems occurring in pregnancy and labour and not with adverse effects on mother or foetus as a result of drug administration.

27.2 Common complaints in pregnancy and labour and their treatments

27.2.1 Pre-eclampsia and eclampsia.

Pre-eclampsia is defined as a hypertensive state of unknown cause occurring in pregnancy. Pre-eclampsia is diagnosed when consistent systolic pressures over 140mm Hg and/or diastolic pressures over 90 mm Hg are observed. These changes are accompanied by elevated protein levels in the urine (hyperproteinuria). Pre-eclampsia can progress to eclampsia, a condition characterised by tonic clonic convulsive seizures. Treatment involves reduction of blood pressure with antihypertensives and control of seizures with anticonvulsives. If these treatments are unsuccessful, abortion or delivery of the foetus is the only effective alternative.

Most antihypertensives exert their effects by dilating blood vessels, easing constricted blood flow and reducing intravessel pressure. These drugs are used to treat a number of disease

states including angina, congestive heart failure and acute myocardial infarction in which lowering of blood pressure is crucial in alleviating symptoms. Antihypertensives used in the treatment of pre-eclampsia include **nifedipine**, **hydralazine**, **labetalol** and **methyldopa**.

Nifedipine is a selective blocker of L-type voltage-sensitive calcium channels in arterial smooth muscle. Inhibition of these channels results in reduced calcium entry into these cells causing vasodilation. Adverse effects of **nifedipine** include headache, flushing, nausea, vomiting and peripheral oedema.

A second antihypertensive used in the treatment of pre-eclampsia is **hydralazine**. Although its exact mechanism of action is unclear, **hydralazine** degrades to **nitric oxide** which is a direct acting vasodilator. **Hydralazine** has similar adverse effects to **nifedipine**.

Labetalol is a mixed α/β adrenoceptor antagonist ($\alpha 1$, $\beta 1$, $\beta 2$) which produces peripheral vasodilation by blocking the effects of sympathetic nervous system thereby reducing blood pressure. **Labetalol** has a number of adverse effects including postural hypotension and bronchoconstriction and as such should not be used in patients with asthma, bradycardia and second or third degree atrioventricular block.

Methyldopa is converted to its active metabolite **α-methylnoradrenaline** in sympathetic neurons and stored in the secretory vesicles of these cells. When released, **α-methylnoradrenaline** acts as an agonist of presynaptic central nervous system $\alpha 2$-adrenergic receptors. Activation of these receptors in the brainstem appears to inhibit sympathetic nervous system output and lower blood pressure. However, it is contraindicated in patients with active liver disease and phaeochromocytoma (tumour of the adrenal gland) and use of **methyldopa** may exacerbate depression in sufferers. Adverse effects are those associated with sympathetic disruption and include sedation, orthostatic hypotension, dry mouth and rash.

Progression of pre-eclampsia to eclampsia is characterised by the appearance of tonic clonic seizures. **Magnesium sulphate** is the drug of choice to prevent these convulsions. The resultant elevated blood magnesium levels (hypermagnesaemia) depresses neuronal activity, reducing excitation and calming the uncontrolled nerve firing that can result in seizures. The magnesium competes with excitatory calcium decreasing neurotransmitter release at the synapse. This treatment is contraindicated with patients with existing elevated blood magnesium levels and those with kidney problems. Concomitant use of **magnesium sulphate** and **nifedipine** can result in hypotension and use of these drugs in combination should be monitored. Adverse effects include myasthenia gravis, muscle weakness, respiratory depression, bradycardia and thirst.

When pharmacological treatment for pre-eclampsia and eclampsia fails, there is real concern for the safety of the mother. Abortion or delivery by caesarean section or labour induction is the treatment of choice. Myometrial stimulants (also known as **oxytocics**) are used for induction and augmentation of labour, prevention and treatment of post-partum haemorrhage, control of bleeding due to incomplete abortion, active management of the third stage of labour. The oxytocics most commonly used are **oxytocin**, **prostaglandin E** and **ergometrine**.

Oxytocin is a 9 amino acid produced in the posterior pituitary gland. Exogenous **oxytocin**, administered by means of continuous infusion by pump, stimulates the frequency and force of uterine contractions, initiating labour and parturition. Prolonged use can result in water

intoxication, uterine rupture and hypotension in the mother and bradycardia, brain damage, seizures and death in the infant.

Prostaglandin E2 (**dinoprostone**) and **prostaglandin E1** (**misoprostol**) are first line drugs of choice as labour inductor. These form part of the eicosanoids, a family of lipid derived hormones which have a multiplicity of different cellular functions including smooth muscle contraction.

Finally, **ergometrine**, an alkaloid structurally similar to LSD can also be used to facilitate delivery of the placenta and to prevent bleeding after childbirth by reducing blood flow through constriction of smooth muscle in the blood vessel walls causing vessel narrowing. It is usually combined with **oxytocin** as **syntometrine**.

27.2.2 Suppression of early labour.

A number of drugs are used as uterine relaxants. These drugs, known as **tocolytics**, are particularly useful in the suppression of early or premature labour affording time for further foetal development and prolonging foetal survival. Several drug classes have been shown to possess tocolytic properties. These include β2 adrenergic receptor agonists, oxytocin antagonists and calcium channel blockers.

Included in the β2 adrenoceptor agonist class are **terbutaline**, **ritodrine**, **salbutamol**, **fenoterol** and **adrenaline**. These drugs work by directly activating adrenergic receptors that mediate smooth muscle relaxation terminating uterine contractions. However, these drugs can have a number of adverse effects on both the mother and the foetus due to their ability to act on the respiratory and cardiovascular systems. Common maternal adverse effects include cardiac arrhythmias, altered thyroid function and tachycardia whilst tachycardia, hypoglycaemia, hypotension and myocardial ischaemia have been noted in the foetus and neonate.

Atosiban is a peptide analogue of **oxytocin** which antagonises the uterine contracting properties of the hormone at its receptor resulting in cessation of preterm labour. It is preferred over the β2 adrenergic agonists due to its lower incidence of adverse effects although reactions to the drug such as nausea, vomiting and hyperglycaemia have been noted.

Calcium channel blockers such as **nifedipine**, which has previously been discussed for its use as an antihypertensive in pre-eclampsia is also has tocolytic properties.

27.2.3 Neonatal respiratory distress syndrome.

One consequence of premature birth is impairment of lung development in the neonate. This manifests itself as neonatal respiratory distress syndrome and is characterised by a deficiency in lung surfactant which causes the integrity of the lung structure to collapse resulting in severe breathing difficulties. Intraventricular haemorrhage and death may follow. Corticosteroids such as **dexamethasone** and **bexamethasone** are used in conjunction with tocolytics as therapies to treat this syndrome. The tocolytics prevent premature birth giving the lungs extra time to develop whilst the steroids act via cell surface receptors to directly activate survival genes. Adverse reactions to these steroids include fluid and electrolyte imbalances, muscle weakness, GI disturbances and hypertension.

27.2.4 Postpartum haemorrhage.

Postpartum haemorrhage is the leading cause of maternal mortality causing approximately 140000 deaths each year. Oxytocics, particularly **oxytocin**, are the preferred treatment. Problems associated with the use of **oxytocin** are outlined above.

27.2.5 Prolactin excess.

Prolactin is a peptide hormone secreted by lactotrophic cells in the anterior pituitary. Increases in prolactin secretion, during pregnancy, results in maturation of milk secreting duct in the mammary gland. Although not restricted to pregnant women, excess production of **prolactin** (hyperprolactinaemia) will result in overactive, secreting mammary tissue. **Prolactin** secretion is under the control of D2 **dopamine** receptors in the lactotrophic cells.

Dopamine, secreted from the hypothalamus, acts on these receptors to inhibit the **prolactin** production. Hyperprolactinaemia results when circulating levels of **dopamine** drop and the inhibitory processes compromised resulting in large levels of circulating **prolactin** in the blood. Treatment is with **bromocriptine**, a **dopamine** receptor agonist, which decreases excessive **prolactin** secretion. Adverse effects include nausea and vomiting, dizziness and constipation.

27.2.6 Nausea.

Nausea and vomiting during pregnancy (also known as morning sickness) is common during the early stages of pregnancy. These are multiple causes ranging from changes in circulating steroid hormones such as oestrogen and progesterone to hypoglycaemia resulting from placental transfer of glucose from the mother to the foetus. In most cases no treatment is required as the condition will normally disappear after the first trimester of pregnancy. However, severe morning sickness known as hyperemesis gravidarum (HG) affecting around one in 1,000 pregnant women can occur. The symptoms of hyperemesis gravidarum include repeated vomiting, weight loss and dehydration. Treatment usually involves hospitalisation, and the administering of intravenous liquids and nutrition. The possible complications associated with untreated hyperemesis gravidarum include electrolyte imbalances, extreme depression and anxiety and malnourishment of the foetus.

In extreme cases of morning sickness, antiemetics may be prescribed. These drugs work by blocking neurotransmitter inputs to the chemoreceptor trigger zone (CTZ), the principal vomiting control centre, of the medulla. First choice is **ondansetron**, a blocker of 5HT-3 receptors found in the CTZ, given orally or by injection. This drug, which is also used as an antiemetic during cancer chemotherapy, has a number of unwanted effects such as headache and GI upset. Other drugs used include **promethazine** (histamine H1 receptor blocker) and **metoclopramide** and **chlorpromazine** (dopamine D2 receptor blockers).