Obstetrics drugs

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Introduction

The drugs that are used daily in obstetric anaesthesia can have a huge impact on the outcome of both mother and child. Therefore, obstetric anaesthetic providers need to have a very clear understanding of the mechanism of action, doses and side-effects of the most commonly used drugs. This presentation will not address local anaesthetics and opioids, but will mainly focus on drugs used by obstetricians that have an impact on anaesthetic outcome.

Drugs to be discussed include:

- *Uterotonics:* Oxytocin, carbetocin, prostaglandins, and ergometrine/syntometrine.
- *Tocolytics:* β2-adrenergic receptor agonists, calcium-channel blockers, magnesium sulphate, prostaglandin synthetase inhibitors (indomethacin and ketorolac), and oxytocin antagonist (atisoban).

Uterotonics

Oxytocin

Oxytocin is routinely used in obstetrics practice. It is mainly given for the prophylaxis and treatment of postpartum haemorrhage and also for the induction and augmentation of labour. Postpartum haemorrhage is still a major cause of maternal mortality in sub-Saharan Africa. The problem is that optimal doses need to be used to avoid side-effects. This is why this long-standing drug is so controversial.

Mechanism of action

Polypeptide hormone is synthesised together with antidiuretic hormone in the hypothalamus and stored in the posterior pituitary. Oxytocin acts on the oxytocin receptors that are G protein-coupled. The receptors are found in the uterus, breast, heart and central nervous system, which may explain some of the actions and side-effects of the drug.

Receptor stimulation causes an increase in prostaglandin synthesis and the release of calcium from the sarcoplasmic reticulum.

The physiological actions of oxytocin include:

- Uterine contraction, followed by relaxation.
- Contraction of the myoepithelial cells in the breast, causing milk ejection.
- Memory regulation.
- Maternal behaviour, including bonding of mothers with their babies (it has been referred to as the cuddling hormone).
- Regulation of food intake.
- Used in the treatment of autism.

Dosage

The parenteral route is the most commonly used, but oxytocin can be absorbed from buccal and nasal mucosa.

Oxytocin has been shown to be the drug of choice, rather than misoprostol, for postpartum haemorrhage following vaginal delivery.

Few national and international standardised protocols govern the dosage of oxytocin. Therefore, there are varying practices and consensus is very difficult.

There has been a growing concern about nonstandardised doses with regard to induction of labour and in the prevention and treatment of postpartum haemorrhage. As a result, the Institute of Safe Medication Practices has classified oxytocin as a high-alert medicine (a drug that can cause risk if used erroneously). It has been noted that prior exposure to oxytocin during labour may put the patient at risk of postpartum haemorrhage because of receptor desensitisation. There is a higher requirement or need for a second-line agent.

For prophylaxis dosing in elective Caesarean section, 1- 3 iu should be administered slowly via intravenous infusion. This should be followed-up by 3 iu in 1 000 ml of Ringer's lactate.

An initial dose of 3 iu is suggested as an infusion in healthy, uncomplicated patients who are at low risk of uterine atony. If the initial response is not adequate, the dose can be repeated after 3-5 minutes.

Varying doses are recommended in established postpartum haemorrhage. An initial dose of 3-5 iu infusion is suggested in combination with phenylephrine.

The Royal College of Obstetricians and Gynaecologists recommends an infusion of 40 iu in 500 ml Ringer's lactate at 125 ml/hour. The American Congress of Obstetricians and Gynaecologists recommends 20 iu in 500 ml Ringer's lactate at 125 ml/hour. There should be a low threshold to using second-line agents to avoid side-effects.

Carvalho reported that the effective dose (ED90) for oxytocin was 0.35 iu to order to achieve successful uterine contraction in elective Caesarian section. Butwick et al conducted a double-blinded, randomised control study to examine the effects of four different doses and placebo. Seventy-three per cent of patients had adequate contraction with placebo or low oxytocin doses. The authors concluded that an oxytocin dose of 0.5-3 iu was adequate to achieve uterine contraction. Balki carried out an emergency Caesarean section for labour arrest. The ED90 was reported to be 2.99 iu, the highest dose needed to achieve adequate uterine contraction in non-elective cases.

Side-effects

The side-effects of oxytocin are:

- *Cardiovascular*: Hypotension (vasodilation and the release of brain and atrial natriuretic peptide), tachycardia and arrhythmias, and ST-segment changes on electrocardiogram.
- *Genitourinary*: Uterine hypertonicity.
- *Central nervous system:* Seizures which may relate to water intoxication and hyponatraemia. Neonatal seizures have been reported.
- *Gastrointestinal tract*: Nausea and vomiting.

Carbetocin

Mechanism of action

Carbetocin is a newly-developed non-US Food and Drug Administration (FDA)-approved synthetic analogue of oxytocin which has a 4-10 times longer duration of action than oxytocin.

Dosage

There are no clear-cut recommended doses for carbetocin. A suggested dose of 100 µg intramuscularly was based on a limited trial which had a duration of action of 120 minutes.

Side-effects

Carbetocin has the same side-effect profile as oxytocin and is also contraindicated in patients with pre- eclampsia for reasons which are still unclear.

Ergometrine/syntometrine

Mechanism of action

Ergometrine/syntometrine is a naturally occurring alkaloid which has been in use since 1932. It remains as a second-line intervention for uterine atony that persists after oxytocin administration, provided that there is no contraindication to its use.

Little is known about its exact mechanism of action. It is thought to act via Ca^{2+} channels, is a partial agonist at the α adrenergic receptor and has possible action on the dopamine receptors. The end result is tonic contraction of the uterine contraction, making it unsuitable for use during labour.

Dosage

The recommended dosage for ergometrine/syntometrine is 0.2-0.5 mg intramuscularly or intravenously. If given intravenously, it must be given slowly and titrated to effect.

Side-effects

Side-effects that pertain to ergometrine/syntometrine include nausea and vomiting, pulmonary artery spasm, and vasoconstriction causing hypertension (increase mean arterial pressure by 11%). Therefore, it is contraindicated in patients with hypertension and cardiovascular disease.

Prostaglandins

Mechanism of action

Prostaglandins increase intramyometrial calcium concentration and enhance uterine contraction. They act on the G protein-coupled receptors and activate the calcium channels.

Clinical uses include:

- Inducing labour.
- Terminating pregnancy.
- As a second-line agent in treating postpartum haemorrhage.
- Treating peptic ulcers.
- Preventing closure of the patent ductus arteriosus.

Dosage

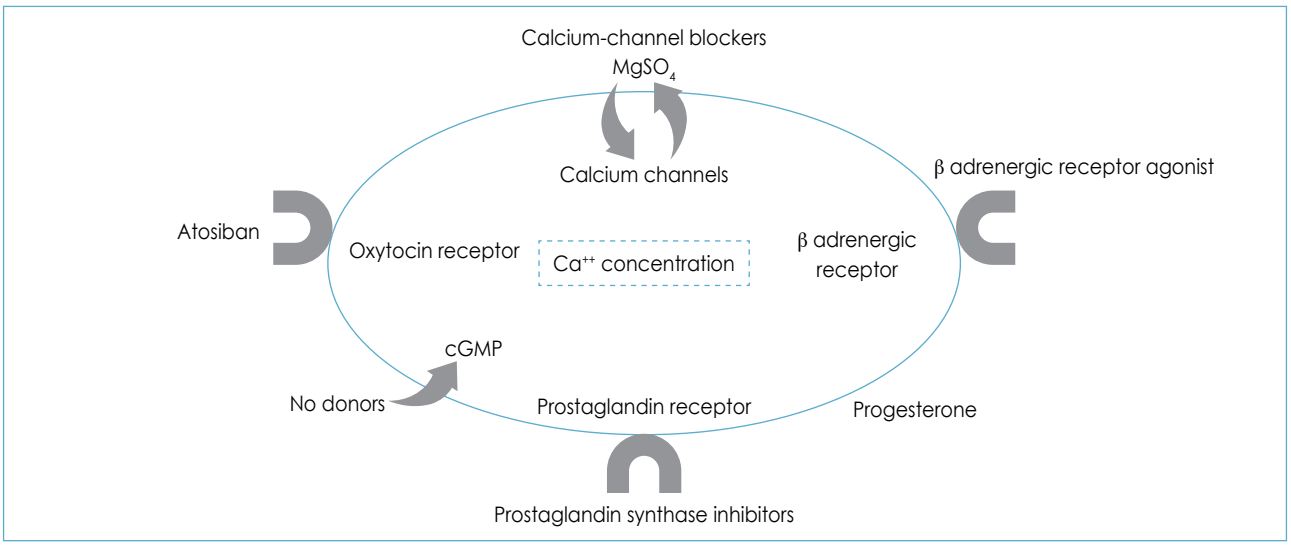
Misoprostol (PGE1) is cheap and easy to store. It is widely used during termination of pregnancy. It has also been used off label for the management of postpartum haemorrhage as a second-line agent. The most reliable route is sublingual, but it can also be used rectally or through the intravaginal route. One study concluded that following vaginal delivery and prophylactic oxytocin doses, misoprostol 800 µg was as effective as oxytocin 40 iu in managing postpartum haemorrhage.

Further research is still needed, and until then, the recommended dosage for postpartum haemorrhage is 400-800 µg. However, higher doses are associated with side-effects.

Prostaglandin F2α (PGF2α) produces contraction of the uterine muscles, bronchial smooth muscles and vasoconstriction. The recommended dose is 250 µg intramuscularly or 500 µg intramyometrially.

Side-effects

The side-effects of prostaglandins include fever, diarrhoea, nausea and vomiting, and an increase in pulmonary and systemic pressure.



cGMP: cyclic guanosine monophosphate, $MgSO_4$: magnesium sulphate

Figure 1: Site of action of tocolytic drugs

Recommendations

In general, no more than 3 iu of an intravenous infusion, over 3- 5 minutes, with no boluses, is the recommendation for uterotonic drugs. Doses can be repeated twice. If there is inadequate uterine contraction, a drug with a different mechanism of action should be utilised. Doses should be given as discussed above for uterine atony.

Figure 1 shows the action of tocolytic drugs.

Tocolytics

Mechanism of action

Tocolytics are used for the prevention of preterm labour. They can delay labour by 48-72 hours, giving clinicians time to administer steroids, treat underlying infections and transfer the patient to a centre with good neonatal facilities.

Contraindications to tocolysis include:

- Pregnancy greater than 34 weeks' gestation.
- Cervical dilatation more than 4 cm.
- Chorioamnionitis or intrauterine infection.
- Foetal congenital or chromosomal abnormalities.
- Severe pre-eclampsia or eclampsia.

Frequently used drugs include the β_2-adrenergic receptor agonists, calcium-channel blockers, magnesium sulphate, prostaglandin synthetase inhibitors, and antagonist (atisoban).

β_2-adrenergic receptor agonists

Mechanism of action

β_2-adrenergic receptor agonists include sulbutamol, ritodrine and fenetrol. They can postpone labour by 24-48 hours.

β_2-adrenergic receptor agonists cause an increase in cyclic guanosine monophosphate (cGMP) which inhibits myosin light-chain kinase, and thus inhibits uterine contraction. Problems with these drugs relate to the maternal and foetal side-effects.

Side-effects

Maternal side-effects include tachycardia, cardiac arrhythmias, nervousness, hyperglycaemia and hypotension. The effects may last up to 90 minutes following cessation of the drug and may contribute to hypotension under anaesthesia.

Foetal side-effects include neonatal tachycardia, hypoglycaemia, intraventricular haemorrhage and myocardial ischaemia.

Calcium-channel blockers

Mechanism of action

Nifedipine is the most commonly used agent. These drugs have proved to be superior to β_2-receptor agonists in reducing preterm labour and improving neonatal outcome.

They should be considered as first-line agents in the management of preterm labour as they also have less side-effects.

They act by blocking calcium entry into the cells and also block release of calcium from the endoplasmic reticulum.

Dosage

The recommended dosage for calcium-channel blockers is 10-20 mg four-hourly.

Side-effects

Side-effects include hypotension (which may reduce placental perfusion), headaches and flushing, conduction abnormalities (which may be more profound with a volatile anaesthetic), and difficulties in managing postpartum haemorrhage using oxytocin and prostaglandins as they all work in the calcium receptor.

An important anaesthetic consideration is hypotension and difficulty in managing postpartum haemorrhage.

Magnesium sulphate

Mechanism of action

Magnesium sulphate uses include seizure prophylaxis in patients with imminent eclampsia and prevention of preterm labour, but meta-analyses have failed to support its use as a tocolytic agent.

Magnesium competes for the binding site with calcium on the sarcoplasmic reticulum and for reducing intracellular calcium. Magnesium also increases cGMP, causing muscle relaxation.

Dosage

The recommended dose for magnesium sulphate is a 4-6 g infusion over 20 minutes and continued using 1g per hour. This drug has multiple side-effects that were demonstrated in the Magnesium Sulphate for Prevention of Eclampsia (MAGPIE) trial. It should only be used in selected patients, e.g. those with imminent eclampsia.

Side-effects

The side-effects of magnesium sulphate include flushing and lethargy, generalised muscle weakness, pulmonary oedema, cardiac arrest and death, toxicity relating to the plasma magnesium level, and the need to monitor tendon reflexes and urine output to avoid side-effects, as well as sensitivity to muscle relaxants. The side-effects relate to plasma magnesium levels (Table I).

Table I: Magnesium toxic levels

Normal	0.8-1 mmol/l
Therapeutic levels	1.7-3.5 mmol/l
Prolonged PR interval and wide QRS	2.5-5 mmol/l
Loss of tendon reflexes	5-7.49 mmol/l
Respiratory paralysis	7.5-11.9 mmol/l
Cardiac arrest	≥ 12 mmol/l

Prostaglandin synthetase inhibitors (indomethacin and ketorolac)

Mechanism of action

A meta-analysis that compared different tocolytic agents found these drugs to be effective in prolonging pregnancy by 2-7 days. Side-effects on the foetus limit their use to 48-72 hours, and they need to be given before 32 weeks' gestation. They work best when administered before the contractions start.

Prostaglandin synthetase inhibitors' mechanism of action is reversible inhibition of cyclo-oxygenase 1 and 2, preventing prostaglandin synthesis and uterine relaxation.

Dosage

The dosage for prostaglandin synthetase inhibitors is indocid starting at 50 mg, followed by 25 mg four- to six-hourly.

Side-effects

Side-effects include nausea and heartburn, platelet dysfunction and a decrease in renal blood flow. Foetal side-effects include premature closure of the ductus arteriosus, oligohydramnios, intraventricular haemorrhage, necrotising enterocolitis and pulmonary oedema.

Oxytocin antagonist (atisoban)

Mechanism of action

Atisoban, an oxytocin antagonist, is a competitive inhibitor at the oxytocin receptor. Its mechanism of action is to bind on both myometrial and decidua. It has the same effect on preterm labour as β_2 agonists, with fewer side-effects.

Dosage

Atisoban is administered as an intravenous infusion at 300 µg per minute.

Side-effects

Atisoban has not been approved for tocolysis by the FDA, but is widely used in Europe because of its less severe side-effect profile with regard to both mother and foetus. It is considered to be a second-line agent after the calcium-channel blockers.

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