Uterotonic and Tocolytic drugs
What should the anaesthesiologist know?

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Many drugs are administered with the specific purpose of influencing uterine tone. The two main classes and indications are uterotonic agents for the prevention and treatment of postpartum haemorrhage (PPH), and tocolytic drugs for preterm labour. These agents have a narrow therapeutic range in terms of maternal and fetal morbidity. The exact dose, route and rate of administration are therefore important, as well as a detailed knowledge of the pharmacology.[1]

A: Uterotonic agents

Introduction

Every year 166,000 women die of obstetric haemorrhage, and more than 50% of these deaths occur in sub-Saharan Africa. Uterine atony is the commonest cause of severe PPH. Uterotonic drugs are thus an essential pharmacological intervention by anaesthetists during caesarean section (CS), in order to diminish the risk of PPH and improve maternal safety.

Oxytocin

The nonapeptide oxytocin was discovered by Sir Henry Dale and was the first polypeptide hormone synthesised, by Du Vigneaud, in 1953. The peptide binds to a G-protein on the surface of the uterine myocyte, resulting in the generation of diacylglycerol (DAG) and inositol tri-phosphate (IP3) via the action of phospholipase C on phosphatidyl inositol bisphosphate (Figure 1). DAG stimulates prostaglandin synthesis, and IP3 stimulates the release of calcium from the sarcoplasmic reticulum. The resulting Ca^{2+}-Calmodulin complex activates myosin light chain kinase and results in phosphorylation of myosin and further initiation of the actin-myosin ATPase, and hence contraction. Oxytocin also activates COX-2 via a further G-protein interaction, and in so doing stimulates prostaglandin synthesis.

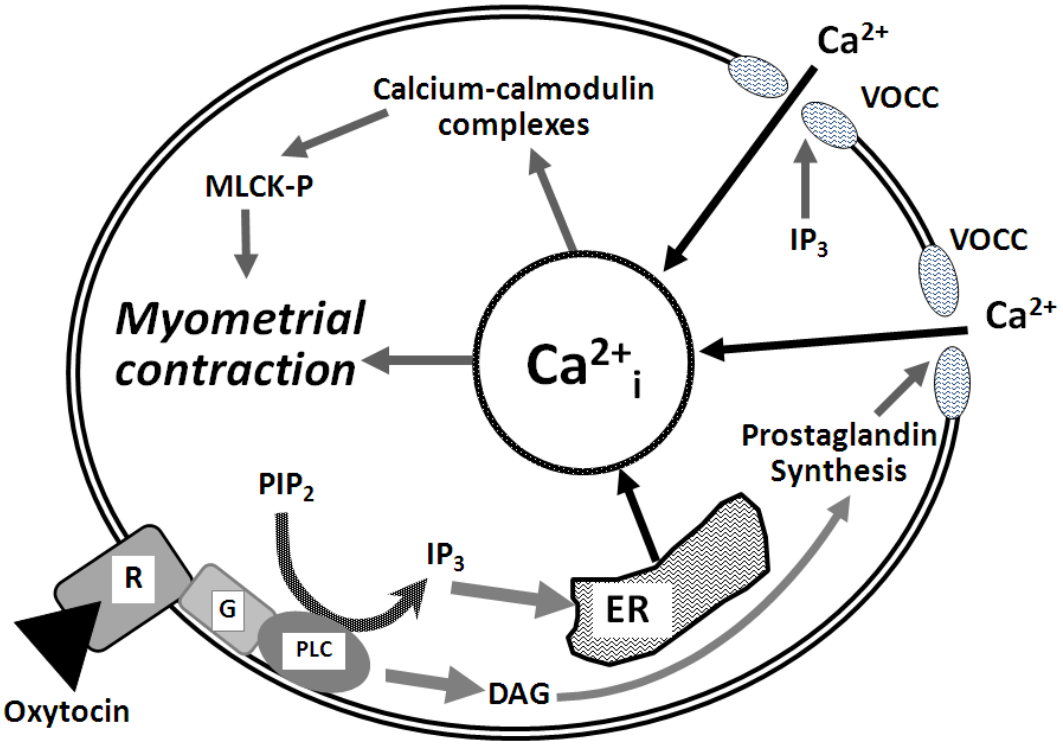

Figure 1: Mechanism of action of oxytocin

The concentration of myometrial receptors as well as myometrial gap junctions increase as gestation advances, thus increasing sensitivity to oxytocin. Oxytocin has numerous physiological effects. Most importantly, it causes contraction, followed by relaxation of the uterus, and at pharmacological doses can cause an increased frequency and incomplete relaxation of the uterine musculature. It also has a role in cardiovascular regulation, in sexual and maternal behaviour, and in memory and the regulation of food and drink intake. This agent remains the first line uterotonic during CS.

Major maternal adverse effects are cardiovascular (hypotension, myocardial ischaemia and arrhythmias), nausea, vomiting, headache and flushing. The cardiovascular effects are complex. Hypotension is predominantly caused by transient relaxation of vascular smooth muscle cells, probably via calcium dependent stimulation of the nitric oxide pathway. Oxytocin also causes the release of atrial and brain natriuretic peptide. In animal studies, oxytocin may have negative inotropic effects, but in human tissue, this effect appears to be restricted to the influence of its commercial preservative chlorbutanol on atrial myocytes in vitro. Due to structural similarities with vasopressin, overdose of oxytocin may cause water retention, hyponatraemia, seizures and coma.

Recently, studies using beat by beat pulse wave form monitors transthoracic bioimpedance, have elucidated a clinical picture of peripheral vasodilatation, hypotension, and increased cardiac output mediated by an increase in heart rate and stroke volume. Pulmonary artery pressures are markedly increased and sustained for at least 10 minutes after a bolus of 10 IU during general anaesthesia. One observational study has demonstrated similar effects of 2.5 IU on the systemic vasculature in patients with severe preeclampsia. These effects could be poorly tolerated if ventricular function were abnormal, and in the presence of mitral or aortic stenosis, or hypovolaemia. A fatality was recorded in the Confidential Enquiry into Maternal Deaths of the United Kingdom in the triennium 1997-1999, when oxytocin 10IU was administered during the resuscitation of a hypovolaemic patient with probable high spinal anaesthesia (SA) for CS. In the Report on Confidential Enquiries into Maternal Deaths in South Africa for the triennium 2005-2007, there were 2 deaths in which oxytocin was contributory. In one case a high dose compounded spinal hypotension. In the other, a poorly resuscitated patient undergoing emergency CS received 10 IU of oxytocin and a fatal cardiac arrest ensued.

In contrast to the effects on the systemic vasculature, oxytocin has been shown to cause coronary vasoconstriction in an isolated dog heart model. There may also be considerable ST segment changes following 10 IU oxytocin during SA for CS and in volunteers. A Holter investigation has demonstrated more ST segment depression in healthy women during elective CS under SA, who received a 10 IU- rather than 5 IU bolus of oxytocin. These complications and research findings indicate that a rapid bolus of 10 IU is no longer advised after delivery at CS.

How can the cardiovascular effects of oxytocin be obtunded? A comparison of 2 IU with 5 IU as a bolus showed more minor heart rate and blood pressure changes after 2 IU. The administration of 5 IU of oxytocin by slow infusion has been shown to produce less cardiovascular instability than a bolus of 5 IU. In an observational study, oxytocin was used in incremental doses of 0.1-0.5 IU during CS in parturients with advanced cardiac disease, including cardiomyopathy, congenital and valvular heart disease, with acceptable haemodynamic stability. Co-administration of phenylephrine with oxytocin may obtund the peripheral vascular effects, with some overshoot of the effects of phenylephrine. A recent study showed that administration of phenylephrine prior to bolus oxytocin is relatively ineffective in obtunding hypotension. An interesting animal study has shown that that the effects of phenylephrine on cardiac output are dependent on the position on the Frank-Starling curve.

In view of the multiple side effects of oxytocin, it is desirable to administer the lowest possible effective dose in the most stable manner. The dose and rate of intravenous infusion of oxytocin after delivery during CS remain controversial. There have been only three dose-finding studies. The first study in healthy uncomplicated pregnancies at low risk for uterine atony, showed that the ED90 is 0.35 IU. In a case series of patients with labour arrest, the ED90 was found to be 3.0 IU. A pragmatic recent editorial advocates the "rule of threes". Up to 3 times 3 IU oxytocin are administered at 3 minute intervals no faster than 15 seconds, followed by slow infusion and second line pharmacological options as necessary.[3]

An early investigation showed that when compared with vasopressin, oxytocin is much less active as an antidiuretic when the infusion rate is less than 45 milliunits/minute. This suggests that the rate of infusion for prophylaxis of PPH should be restricted to a lower infusion rate than this, particularly in patients with preeclampsia, who are at higher risk of pulmonary oedema. The current recommended infusion rate for PPH prophylaxis in South Africa is 20 IU/L at 100-150 mL/h. If this cannot be reliably administered, it may be better to give either oxytocin 10 IU IM, repeated at 4 h, or syntometrine IM.[4] For treatment of PPH, the Royal College of Obstetricians and Gynaecologists (RCOG) recommend a

rapid infusion oxytocin 40 IU/500 mL crystalloid at 125 mL/hour, until haemorrhage is controlled. Great care should be exercised in the hypovolaemic patient, and effective resuscitation and vasopressor therapy should accompany oxytocin administration.

In keeping with the mechanism of action of oxytocin, involving G-protein receptor interactions, the phenomenon of receptor desensitisation may influence the effectiveness of the dose given by the anaesthetist at delivery. Definitive laboratory work has shown that there is loss of oxytocin receptors during oxytocin-induced and oxytocin-augmented labour. The concentration of oxytocin receptors decreased more than 3-fold, and oxytocin receptor mRNA concentrations decreased 60- and 300-fold during oxytocin-augmented and oxytocin-induced labour respectively. In view of the fact that repeated doses of oxytocin may become increasingly ineffective, second-line uterotonic agents are still required.

The in vivo half-life of oxytocin is only 5-10 minutes. The newly developed synthetic analogue of oxytocin, **carbetocin**[5], an octapeptide (1-desamino-1-monocarbo-[2-O-methyltyrosine]-oxytocin), has a half-life of 42 minutes. Carbetocin produces contractions of sustained higher frequency and amplitude. The advantage is thus that carbetocin may be used as a single bolus dose. IV carbetocin 8-30 µg causes a tetanic contraction within 2 minutes and lasting 6 minutes, followed by rhythmic contractions for 60 minutes. IM injection 10-70 µg causes tetanic contraction for 11 minutes, followed by rhythmic contractions for 2 hours. Clinical dose-finding studies have used 20-120 µg. The incidence of hypotension and other side effects is similar to that associated with oxytocin, and carbetocin also exhibits receptor desensitisation. The ED90 has been found to be 14.8 µg at elective CS, <20% of the current recommended dose of 100 µg. In cases of labour arrest this increases to 121 µg. Carbetocin is associated with lower risk of PPH than oxytocin, as well as a reduced requirement for additional uterotonics after CS. After vaginal delivery, the mean fall in Hb is lower than when oxytocin/ergometrine is administered. There is no evidence that carbetocin reduces the incidence of severe PPH. A new room temperature stable formulation of carbetocin is under investigation. This could have important application in limited resource environments.

Ergot alkaloids

Ergot, derived from the fungus *Claviceps purpurea*, was the first effective oxytocic drug. The fungus was known as “the noxious pustule in the ear of grain” since 600 BC, owing to epidemics of ergotism, characterised by either central nervous complications or peripheral gangrene. These agents have been used in obstetrics from 1582-1822, when the view on their role changed from “pulvis ad partum” (the powder of birth), to “pulvis ad mortem” (the powder of death), due to the associated tetanic uterine contractions, leading to fetal asphyxia, stillbirth and uterine rupture. Ergometrine is a naturally occurring alkaloid, first isolated in 1932 by Dudley and Chassar Moir. Currently this agent, although appropriately banned from intrapartum use, remains the second line intervention in the absence of contraindications, if uterine atony persists after oxytocin administration during caesarean delivery.

Ergometrine maleate or methylergometrine cause a rapid and sustained contraction of the pregnant and non-pregnant uterus. The half-life of ergometrine is 120 minutes. Little is known about the mechanism of action, which may be via a calcium channel, or an α-receptor in the inner myometrial layer. Ergometrine is also a partial agonist at α-adrenergic, 5HT-1, and dopamine receptors.

Although ergometrine and methylergometrine have the least vasoconstrictor effects of all the ergot alkaloids, the use of ergometrine has been associated with a mean arterial pressure increase of 11% after 0.2 mg IV, and pulmonary wedge pressure and pulmonary artery pressure increases of 30%. There are also reported cases of renal and coronary artery spasm, and there are several cases of myocardial infarction in the literature associated with their use. In some of these cases the use of ergot alkaloids was inappropriate. One patient had familial hypercholesterolaemia and ergometrine precipitated the requirement for stenting of the left anterior descending coronary artery. In another case a fatal myocardial infarction followed the administration of ergometrine to a hypertensive patient with preeclampsia. Despite these rare complications, ergot alkaloids still have an important role as a second line agent at CS when administered with due care, but are contraindicated in preeclampsia.

The RCOG guideline recommends 0.5 mg IV *slowly* for the management of uterine atony, while the World Health Organisation (WHO) stipulates 0.2 mg IV or IM, to be repeated as necessary every 15 minutes to a maximum of 1 mg. The high incidence of nausea and vomiting after the recommended 0.5 mg dose has discouraged its use as a first line agent at CS. **Syntometrine** is a combination preparation seldom used during CS, containing 5 IU oxytocin and 0.5 mg ergometrine. Following IM administration, the time to onset of the uterine response is considerably shorter than after ergometrine alone, and the duration of action is several hours.

Prostaglandins

Like oxytocin, prostaglandins increase intramyometrial calcium concentrations and enhance uterine contraction. Their effects are mediated via G-proteins and the activation of a calcium channel. Side effects after pharmacological administration include fever, diarrhoea, nausea, vomiting and pyrexia. The use of intramyometrial prostaglandin F2α (dinoprost) for atonic PPH was first described by Takagi in 1976. Subsequently, 15-methyl prostaglandin F2α (carboprost) was shown to have an extended half-life, fewer gastrointestinal and vasopressor side-effects, and good uterotonic activity. Since 15-methyl prostaglandin F2α may be associated with bronchospasm, ventilation perfusion mismatch and hypoxaemia, this agent is best used as a last resort therapy and not as prophylaxis. There is very limited experience with intravenous administration. Infusion at 100 μg/minute during early pregnancy has been shown to cause systemic and pulmonary hypertension, in contrast with prostaglandin E2, which is associated with a marked decrease in systemic vascular resistance and hypotension. The recommended dose is 250 μg IM, repeated every 15 minutes to a maximum of 8 doses. Carboprost 500 μg may be administered intramyometrially, but this remains the responsibility of the clinician.

Prostaglandin E1 (misoprostol) is a cheap and widely available oxytocic, which is less effective than oxytocin and ergometrine for the prevention of PPH, and confers no benefit in the management of PPH in women who have received conventional uterotonics, but does however have a role as a first line agent where the former are unavailable (www.misoprostol.org). The sublingual route is probably the most reliable, since misoprostol is a methyl ester and undergoes first pass elimination. Misoprostol is frequently used off-label via the sublingual or rectal route for the management of uterine atony. There have been a limited number of studies of its use during CS. One study concluded that buccal misoprostol may reduce the need for additional uterotonic agents at CS. In a further small randomised comparison, oral misoprostol was concluded be as effective as intravenous oxytocin in reduction of intra-operative blood loss during elective CS under regional anesthesia. Importantly, 600 μg misoprostol via the vaginal route in the midtrimester did not alter maternal haemodynamics as assessed by transthoracic bioimpedance measurements. A recent editorial points out that side effects, in particular shivering and hyperpyrexia, are dose dependent, and cautions that the administration of a therapeutic dose of misoprostol after an initial prophylactic dose may be harmful. A recent systematic review reports 11 maternal deaths during five trials. Eight of these women received 600 μg or more of misoprostol and 3 were controls. Further research will elucidate whether a dose of 400 μg is safer than 600 μg as prophylaxis, and whether doses as high as 800 μg are required for treatment of PPH.

Nausea and vomiting

Nausea and vomiting can make caesarean delivery under SA unpleasant. Contributing factors have been reviewed,[6] and uterotonic drugs are frequently causative. The incidence of nausea has been reported as 29%, and vomiting 9% after a bolus of 5 IU of oxytocin, and 10% after 250 μg of intramyometrial 15-methyl prostaglandin F2α during elective caesarean delivery under SA. A high incidence of 46% of nausea or vomiting has been reported after 0.5 mg ergometrine IV. A recent Cochrane review of the obstetric literature suggested that for the prevention of PPH > 1000 mL, syntometrine had a similar efficacy to oxytocin, but was associated with a 5-fold increase in nausea, vomiting and hypertension.

Summary: A plan of action
Uterotonic drugs remain an important intervention in the prevention of uterine atony. In addition, these agents are essential adjuncts to aggressive resuscitation and surgical management of PPH during CS.[7,8] Current evidence is that oxytocin remains the uterotonic of first choice. There are few definitive studies upon which to base a protocol for recommendations for dosing of oxytocin or second-line uterotonics. Recommendations vary considerably from country to country. The following is a reasonable protocol, based upon current literature:

A Prophylaxis of uterine atony

- In healthy parturients at low risk for uterine atony, a bolus dose of 3 IU IV over 30 seconds, repeated twice at three minute intervals, is reasonable. This may be followed by a continuous infusion containing 20 IU oxytocin at 100-150 mL/hour.
- In resource constrained environments where oxytocin infusion cannot be guaranteed, consider intramuscular syntometrine (0.5 mg ergometrine plus 5 IU oxytocin).
- In patients with preeclampsia, oxytocin infusion should be at the lowest required rate, to avoid fluid retention. Administration of oxytocin in advanced cardiac disease requires further investigation. Slow infusion of small doses would seem prudent, with special care in patients with pulmonary hypertension.
- Carbetocin is a useful long-acting oxytocin analogue, commonly administered in a dose of 100 μg IV or IM.

B Management of established uterine atony / postpartum haemorrhage

- In view of down-regulation of oxytocin receptors following prior exposure to oxytocin, there should be a low threshold for the use of uterotonics with a different mechanism of action, such as ergometrine, and prostaglandins F2α and E1, in cases of established uterine atony.
- Ergometrine 0.1-0.5 mg IV slowly or 0.5 mg IM, in the absence of contraindications, is the currently recommended second line therapy, but many practitioners use doses as low as 0.05 mg IV at CS.
- 15-methyl prostaglandin F2α, 250 μg – 500 μg is used intramyometrially as a last resort, but this agent is not licensed for administration via this route. Current guidelines stipulate that 250 μg should be given IM, repeated every 15 minutes to a maximum of 8 doses, as the last resort.
- In preeclampsia, the best second line agent is misoprostol, since ergot alkaloids are contraindicated, and prostaglandin F2α may be hazardous. The optimal dose and route of administration of misoprostol for the prophylaxis and management of PPH, remain to be established. Currently, expert opinion advises regimens such as 200 μg sublingually, together with 400 μg rectally.
- During established PPH, the infusion of oxytocin 40 IU/500 mL at 125 mL/hour has been recommended, accompanied by effective resuscitation and the co-administration of second line agents as described.
- Extreme care is required in the use of oxytocin in haemodynamically unstable patients.

B: Tocolytic drugs

Preterm delivery, defined as delivery before 37 weeks' gestation, occurs in 5-13% of pregnancies. Tocolysis per se does not prevent preterm delivery or improve neonatal outcomes, but allows for the initiation of other treatments or interventions that can improve outcomes. Short term tocolysis, typically <48 hours, in patients with a viable fetus of gestational age <34 weeks, allows for the administration of corticosteroids to for fetal lung maturity, and/or for urgent transfer to the referral unit or operating theatre. Tocolysis may also be given, for example, before external cephalic version, in the event of tachysystole with fetal heart changes, or to allow for magnesium sulphate administration in preterm infants, for neuroprotection. There are obstetric contraindications to tocolysis, including preeclampsia, and haemorrhage with haemodynamic instability.
Analyses comparing the use of available agents, calcium channel blockers, B agonists, cyclo-oxygenase inhibitors, atosiban, nitric oxide donors, progesterone, and magnesium sulphate with placebo as primary tocolysis, show that all of these agents have shown effect in prolonging pregnancy for up to 48 hours, but there is no beneficial effect on neonatal morbidity or mortality. Magnesium is not efficacious as a tocolytic agent, but may be administered for fetal neuroprotection before 32 weeks' gestation, or commonly for seizure prophylaxis in preeclampsia. Maintenance tocolysis is of no benefit, and may be harmful.[9,10]

Calcium channel blockers (CCB)

Lowering of intracellular calcium reduces MLCK activity. In many units, CCB, typically nifedipine 20 mg orally 6 hourly, are the most commonly used agents for preterm labour, because of the low incidence of side effects, which include hypotension, nausea, flushing, and occasionally pulmonary oedema.

β Agonists

Increased β 2 receptor activity increases intracellular cAMP and lowers intracellular calcium levels, reducing MLCK activity. These agents, ritodrine, terbutaline and salbutamol, have become less popular, due to maternal side effects, which include hypotension, tachycardia, arrhythmias, hypokalaemia and hyperglycaemia; however the overall incidence is low. In our unit, salbutamol 250 µg is typically administered IV as part of intrauterine fetal resuscitation, to inhibit labour contractions in a patient in labour and at risk of uterine rupture, for external cephalic version, or if there is cord prolapse in the presence of active labour.

Cyclo-oxygenase inhibitors

These agents, of which indomethacin is most commonly used, are inhibitors of prostaglandin synthesis. This is the only class of tocolytics which decreases the preterm birth rate at <37 weeks' gestation. During such short term use, only minor complications such as nausea and heartburn are noted. Transient ductal constriction has been noted in 50% of fetuses between 26- and 31 weeks' gestation. Used in short courses in very pre-term infants, closure of the ductus arteriosus is relatively uncommon (5-10% until 32 weeks, rising to 50% thereafter). It is usually reversible with early recognition and discontinuation of the agent. Oligohydramnios may also occur due to decreased fetal urine output, possible due to an enhanced anti-diuretic hormone effect. There may be an increased risk of necrotising enterocolitis and intraventricular haemorrhage.

Oxytocin receptor antagonist

The oxytocin receptor antagonist atosiban is not yet FDA approved in the US, but widely used in many countries. There are no apparent advantages over the established agents.

Nitric oxide donors

Once again, no advantages have been shown for the use of transdermal nitroglycerin.

Progesterone

There is insufficient evidence for the benefits of the use of progesterone in acute tocolysis, but some evidence that progesterone may have a role in maintenance tocolysis.

Conclusion

Overall, the anaesthesiologist should have a good understanding of the pharmacology and therapeutic range of drugs administered to alter uterine tone, since uterotonic agents have a crucial role to play in obstetric haemorrhage, and the use of tocolytic drugs impacts significantly on anaesthesia practice.

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