Chapter 23 Oxytocin and Other Drugs Acting on Uterus

Drugs acting on uterus can primarily affect the endometrium or the myometrium. The most important drugs affecting endometrium are estrogens, progestins and their antagonists. Myometrium receives both sympathetic and parasympathetic innervation. As such, autonomic drugs can affect its motility. However, the directly acting drugs are more important and have more selective action. The responsiveness of myometrium to drugs is markedly affected by the hormonal and gestational status.

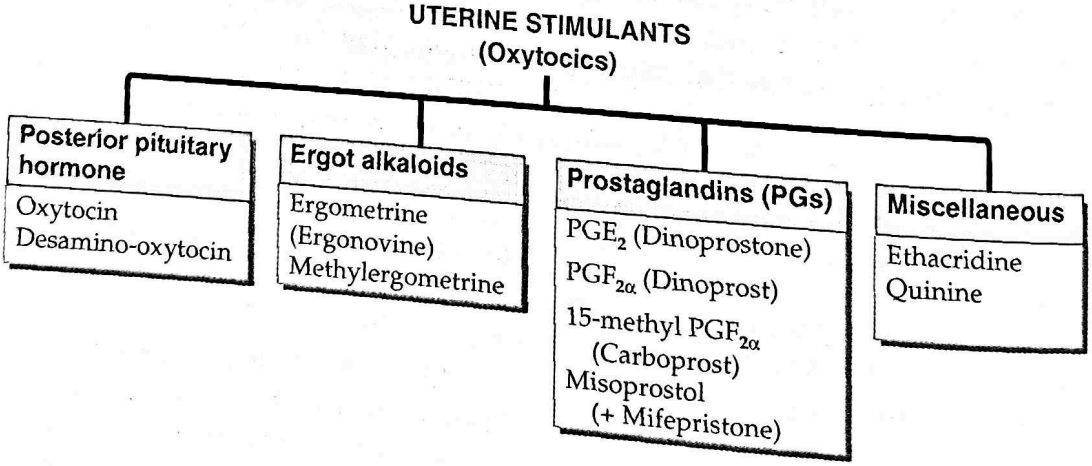
UTERINE STIMULANTS (Oxytocics, Abortifacients)

These drugs increase uterine motility, especially at term.

OXYTOCIN

Oxytocin is a nonapeptide secreted by the posterior pituitary along with argenine vasopressin (AVP or ADH). Pituitary extract was first used in labour in 1909. Controversy as to whether the antidiuretic and uterine stimulating activities were due to one substance or two separate substances was finally resolved by du Vigneaud in 1953 when he separated *Oxytocin* and *Vasopressin*, determined their chemical structure and synthesized them. Both have 9 amino acids, and differ at positions 3 and 8.

Both oxytocin and AVP are synthesized within the nerve cell bodies in supraoptic and paraventricular nuclei of hypothalamus; are transported down the axon and stored in



the nerve endings within the neurohypophysis. They are stored in separate neurones as complexes with their specific binding proteins (neurophysins) to form granules. Both are released by stimuli appropriate for oxytocin, i.e. coitus, parturition, suckling; or for ADH, i.e. hypertonic saline infusion, water deprivation, haemorrhage, etc., or nonspecific, i.e. pain and apprehension. However, the proportion of oxytocin to ADH can vary depending upon the nature of the stimulus.

ACTIONS

1. Uterus Oxytocin increases the force and frequency of uterine contractions. With low doses, full relaxation occurs inbetween contractions; basal tone increases only with high doses. Estrogens sensitize the uterus to oxytocin. They increase oxytocin receptors. Nonpregnant uterus and that during early pregnancy is rather resistant to oxytocin; sensitivity increases progressively in the third trimester, and there is a sharp increase near term. A quick fall in sensitivity occurs during puerperium. Progestins decrease the sensitivity, but this effect is not marked *in vivo*.

At term the enhancement of contractility is restricted to the fundus and body; lower segment is not contracted; may even be relaxed.

Mechanism of action Action of oxytocin on myometrium is independent of innervation. There are specific G-protein coupled oxytocin receptors on the myometrium which mediate the response mainly by depolarization of muscle fibres and influx of Ca^{2+} *ions* as well as through phosphoinositide hydrolysis and IP_3 mediated intracellular release of Ca^{2+} ions. The number of oxytocin receptors increases markedly during later part of pregnancy. Oxytocin also increases PG synthesis and release by the endometrium which may contribute to the contractile response. Distinct subtypes of oxytocin receptors have been shown on the myometrium and the endometrium.

2. Breast Oxytocin contracts the myoepithelium of mammary alveoli and forces milk into the bigger milk sinusoids. Oxytocin mediates the 'milk ejection reflex' (milk letdown in cattle) which is initiated by suckling, so that milk may be easily sucked by the infant. Oxytocin has been used in milch cattle to facilitate milking.

3. CVS Conventional doses of oxytocin used in obstetrics have no effect on BP, but higher doses cause vasodilatation producing brief fall in BP, reflex tachycardia and flushing. This action is most marked in chicken and is used for bioassay of oxytocin. The umbilical vessels are markedly constricted; oxytocin may help in their closure at birth.

4. Kidney Oxytocin in high doses exerts ADH-like action—urine output is decreased: pulmonary edema can occur if large amounts of i.v. fluids and oxytocin are infused together. Conventional doses are without any effect.

Physiological role

1. ***Labour*** Oxytocin is released during labour and the uterus is highly sensitive to it at this time. However, it does not appear to be obligatory for initiating parturition. Delivery occurs even in hypophysectomized animals and humans, though labour may be prolonged in its absence. A facilitatory role is more plausible. PGs and PAF are complementary to oxytocin.

2. ***Milk ejection reflex*** Suckling reflexly induces oxytocin release from pituitary and it contracts the myoepithelial cells. These cells in breast are more sensitive than the myometrium to oxytocin. Milk ejection reflex is absent in the hypophysectomized animal.

3. ***Neurotransmission*** Oxytocin appears to function as a peptide neurotransmitter of oxytocinergic neurones in the hypothalamus and brainstem which serves to regulate autonomic outflow.

PHARMACOKINETICS

Being a peptide, oxytocin is inactive orally and is generally administered by i.m. or i.v.

routes, rarely by intranasal spray. It is rapidly degraded in liver and kidney; plasma t½ 6–12 min. This is further shortened at term. Pregnant uterus and placenta elaborate a specific aminopeptidase called *oxytocinase*. This enzyme can be detected in maternal plasma.

Unitage and preparations 1 IU of oxytocin = 2 µg of pure hormone. Commercially available oxytocin is produced synthetically.

OXYTOCIN, SYNTOCINON 2 IU/2 ml and 5 IU/ml inj., PITOCIN 5 IU/0.5 ml inj.

USE

1. *Induction of labour* Labour needs to be induced in case of postmaturity or even prematurely in toxaemia of pregnancy, diabetic mother, erythroblastosis, ruptured membranes or placental insufficiency. For this purpose oxytocin is given by slow i.v. infusion: 5 IU is diluted in 500 ml of glucose or saline solution (10 milli IU/ml)—infusion is started at a low rate and progressively accelerated according to response (0.2–2.0 ml/min). Before starting the infusion, it should be made certain that:

- presentation is correct
- foetal lungs are adequately mature
- there is no cephalopelvic disproportion
- no placenta previa
- no foetal distress and
- no uterine scar (due to previous surgery).

Uterine contractions are then closely monitored: the drug is discontinued when they are strong enough. Usually a total of 2–4 IU is needed.

2. *Uterine inertia* When uterine contractions are feeble and labour is not progressing satisfactorily—oxytocin can be infused i.v. (as described above) to augment the contractions. It should not be used to hasten normally progressing labour. Before deciding to use an oxytocic for strengthening uterine contractions, all the conditions as setout above (for induction of labour) must be fulfilled. Too strong contraction can be catestrophic: use should only be made in selected cases and by experienced people.

Oxytocin is the drug of choice and is preferred over ergometrine/PGs for the above two purposes:

(a) Because of its short t½ and slow i.v. infusion, intensity of action can be controlled and action can be quickly terminated.

(b) Low concentrations allow normal relaxation inbetween contractions—foetal oxygenation does not suffer.

(c) Lower segment is not contracted: foetal descent is not compromised.

(d) Uterine contractions are consistently augmented.

3. *Postpartum haemorrhage, Caesarean section* Oxytocin 5 IU may be injected i.m. or given by i.v. infusion for an immediate response, especially in hypertensive women in whom ergometrine is contraindicated. It acts by forcefully contracting the uterine muscle which compresses the blood vessels passing through its mesh work to arrest haemorrhage from the inner surface exposed by placental separation.

4. *Breast engorgement* It may occur due to inefficient milk ejection reflex. Oxytocin is effective only in such cases but not when milk secretion is deficient. An intranasal spray may be given few minutes before suckling. Oxytocin does not increase milk production.

5. *Oxytocin challenge test* It is performed to determine uteroplacental adequacy in high risk pregnancies. Oxytocin is infused i.v. at very low concentrations till uterine contractions are elicited every 3–4 mins. A marked increase in foetal heart rate indicates uteroplacental inadequacy. The test is risky and is rarely performed.

Adverse effects

- Injudicious use of oxytocin during labour can produce too strong uterine contractions forcing the presenting part through incompletely dilated birth canal, causing maternal and foetal soft tissue injury, rupture of uterus, foetal asphyxia and death.
- Water intoxication: This occurs due to ADH like action of large doses given along with i.v. fluids, especially in toxaemia of pregnancy and renal insufficiency. It is a serious (may be fatal) complication.

Desamino-oxytocin It has been developed as a buccal formulation. The action is similar to injected oxytocin, but less consistent. Its indications are:

Induction of labour: 50 IU buccal tablet repeated every 30 min, max 10 tabs.
Uterine inertia: 25 IU every 30 min.
Promotion of uterine involution 25–50 IU 5 times daily for 7 days.
Breast engorgement 25–50 IU just before breast feeding.
BUCTOCIN 50 IU tab.

Carbetocin It is a long-acting analogue of oxytocin that has been introduced recently for prevention of uterine atony after caesarean section and to control PPH.

ERGOMETRINE, METHYLERGOMETRINE

The pharmacology of ergot alkaloids is described in Ch. 12. Only the amine ergot alkaloid ergometrine (ergonovine) and its derivative methylergometrine are used in obstetrics. Both have similar pharmacological property.

1. *Uterus* These alkaloids increase force, frequency and duration of uterine contractions. At low doses, contractions are phasic with normal relaxation in between, but only moderate increase in dose raises the basal tone, contracture occurs with high doses. Gravid uterus is more sensitive. Marked increase in sensitivity occurs at term and in early puerperium. Their stimulant action involves the lower segment of uterus as well. The uterotonic action is believed to result from partial agonistic action on 5-HT_2 and α adrenergic receptors.

2. *CVS* Ergometrine and methylergometrine are much weaker vasoconstrictors than ergotamine and have low propensity to cause endothelial damage. Though they can raise BP, this is not significant at doses used in obstetrics.

3. *CNS* No overt effects occur at usual doses. However, high doses produce complex actions—partial agonistic/antagonistic interaction with adrenergic, serotonergic and dopaminergic receptors in the brain have been shown.

4. *GIT* High doses can increase peristalsis.

Methylergometrine is 1½ times more potent than ergometrine on the uterus, but other actions are less marked. It has thus replaced ergometrine at many obstetric units.

Pharmacokinetics In contrast to the amino acid ergot alkaloids, ergometrine and methyl ergometrine are rapidly and nearly completely absorbed from the oral route. The onset of uterine action is: Oral—15 min; i.m.—5 min; i.v.—almost immediate.

They are partly metabolized in liver and excreted in urine. Plasma t½ is 1–2 hours. Effects of a single dose last 3–4 hours.

Adverse effects Ergometrine and methylergometrine are less toxic than ergotamine. When correctly used in obstetrics—hardly any complications arise. Nausea, vomiting and rise in BP occur occasionally. They can decrease milk secretion if higher doses are used for many days postpartum. This is due to inhibition of prolactin release (dopaminergic action). Ergometrine should be avoided in—

- patients with vascular disease, hypertension, toxaemia.
- presence of sepsis—they may cause gangrene.
- liver and kidney disease.

They are contraindicated during pregnancy and before 3rd stage of labour.

Use

1. The primary indication for ergometrine/methylergometrine is to control and prevent postpartum haemorrhage (PPH): 0.2–0.3 mg i.m. at delivery of anterior shoulder reduces blood loss attending delivery and prevents PPH. However, routine use in all cases is not justified. They should be employed only in patients prone to bleed more, e.g. grand multipara, uterine inertia. Multiple pregnancy should be excluded before injecting.

If PPH is occurring—0.5 mg i.v. is recommended. A combination of 0.5 mg ergometrine with oxytocin 5 IU i.m./i.v. may be used in severe bleeding.

These drugs produce sustained tonic uterine contraction: perforating uterine arteries are compressed by the myometrial meshwork—bleeding stops.

2. After caesarean section/instrumental delivery these alkaloids serve to prevent uterine atony.

3. To ensure normal involution: A firm and active uterus involutes rapidly. To ensure this:

0.125 mg of ergometrine or methylergometrine has been given TDS orally for 7 days. However, routine use in all cases is not justified because normal involution is not hastened. Multipara and others in whom slow involution is apprehended, these drugs may be given prophylactically.

4. Diagnosis of variant angina: A small dose of ergometrine injected i.v. during coronary angiography causes prompt constriction of reactive segments of coronary artery that are responsible for variant angina.

ERGOMETRINE 0.25, 0.5 mg tab, 0.5 mg/ml inj.
Methylergometrine: METHERGIN, METHERONE, ERGOMET 0.125 mg tab, 0.2 mg/ml inj.

PROSTAGLANDINS

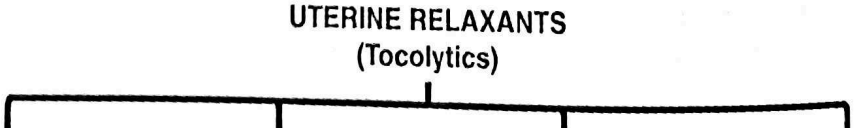
PGE_2, $PGF_{2\alpha}$ and 15-methyl $PGF_{2\alpha}$ are potent uterine stimulants, especially in the later part of pregnancy. They also promote ripening of cervix. Their actions and use in obstetrics is described in Ch. 13. Since misoprostol (a PG analogue) produces less side effects, it is being used for obstetric indications as well.

Ethacridine Available as 50 mg/50 ml solution (EMCREDIL, VECREDIL) for extra-amniotic infusion: 150 ml (containing 150 mg) is injected slowly for medical termination of pregnancy in the 2nd trimester. This is an alternative method used occasionally.

UTERINE RELAXANTS (Tocolytics)

These are drugs which decrease uterine motility. They have been used to delay or postpone labour, arrest threatened abortion and in dysmenorrhoea. Prevention of premature labour in those at higher risk due to past history or short cervix has been attempted by administration of high dose *progesterone* in the later half of pregnancy, with some success demonstrated in prospective controlled trials. Suppression of premature labour may be needed to allow the foetus to mature, to allow time for initiating glucocorticoid therapy for foetal lung maturation (*see* p. 316) or to transfer the mother in labour to a centre with proper facilities. However, no clearly satisfactory drug is available since none of them has been shown to improve foetal outcome. An attempt to delay premature labour is likely to succeed only if cervical dilatation is < 4 cm and 'taking up' of lower segment is minimal. Measures to delay labour should not be undertaken if membranes have ruptured, antepartum haemorrhage is occurring, in severe toxaemia of pregnancy, intrauterine infection or foetal death.

1. Adrenergic agonists (*see* Ch. 9) *Ritodrine*, the β_2 selective agonist having more prominent uterine relaxant action is approved to suppress premature labour and to delay delivery in case of some exigency or acute foetal distress. For dependable action it is started as 50 µg/min i.v. infusion, the rate is increased every 10 min till uterine contractions cease or maternal HR rises to 120/min. Contractions are kept suppressed by continuing i.v. infusion or by 10 mg i.m. 4–6 hourly followed by 10 mg oral 4–6 hourly. However, treatment beyond 48 hours is not recommended, since risk to mother increases and benefit is uncertain. Delivery can be postponed in about 70% cases by few hours to few weeks. However, cardiovascular (hypotension, tachycardia, arrhythmia, pulmonary edema) and metabolic (hyperglycaemia, hyperinsulinaemia, hypokalaemia) complications and anxiety, restlessness, headache occur frequently. Use of ritodrine to arrest labour has been found to increase maternal morbidity.



Foetal pulmonary edema can develop; volume of i.v. infusion should be kept to a minimum to avoid fluid overload. The neonate may develop hypoglycaemia and ileus. It should not be used if mother is diabetic, having heart disease, or receiving β blockers or steroids.

Ritodrine has been discontinued in the USA, but is still available in UK and India.
YUTOPAR. RITROD 10 mg/ml inj (5 ml amp), 10 mg tab. RITODINE 10 mg tab, 10 mg in 1 ml inj.

Salbutamol and terbutaline can be used as alternatives to ritodrine. *Isoxsuprine* oral/i.m. has been used to stop threatened abortion, but efficacy is uncertain.

2. Calcium channel blockers Because influx of Ca^{2+} ions plays an important role in uterine contractions, Ca^{2+} channel blockers (*see* Ch. 40) reduce the tone of myometrium and oppose contractions. These drugs, especially nifedipine, which has prominent smooth muscle relaxant action, can postpone labour if used early enough. Efficacy comparable to β_2 adrenergic agonists has been demonstrated and side effects are fewer. Oral *nifedipine* 10 mg repeated once or twice after 20–30 min, followed by 10 mg 6 hourly has been used. Tachycardia and hypotension are prominent at doses which suppress uterine contractions. Reduced placental perfusion causing foetal hypoxia is apprehended. However, fewer babies delivered after nifedipine needed intensive care.

3. Oxytocin antagonist *Atosiban* is a peptide analogue of oxytocin that acts as antagonist at the oxytocin receptors. In clinical trials, i.v. infusion of atosiban has been found to suppress premature uterine contractions and postpone preterm delivery with fewer cardiovascular and metabolic complications than β_2 adrenergic agonists. In Europe and UK it is available for inhibition of labour between 24–33 weeks of gestation, and may offer better benefit: risk ratio than other tocolytics. However, it is not approved in USA and India.

4. Magnesium sulfate Infused i.v. it is a first line drug for prevention and treatment of seizures in preeclampsia and eclampsia. It also acts as a tocolytic by competing with Ca^{2+} ions for entry into myometrium through both voltage sensitive as well as ligand gated Ca^{2+} channels. However, its use to delay premature labour is risky, may increase perinatal mortality and is not recommended now.

5. Miscellaneous drugs Ethyl alcohol, nitrates, progesterone, general anaesthetics and indomethacin (PG synthesis inhibitors) are the other drugs, which can depress uterine contractions. However, their effect is not dependable and they are not used clinically as tocolytics.

Halothane is an efficacious uterine relaxant that has been used as the anaesthetic when external or internal version is attempted.

PROBLEM DIRECTED STUDY

23.1 A full term primigravida aged 26 years is brought to the hospital with the complaint of having labour pains for the past 24 hours without making much progress. Two hours ago she had passed meconium stained liquor. The lady is in distress, mildly dehydrated and looks exhausted. The presentation is vertex and head is engaged, but cervix is incompletely dilated and uterine contractions are relatively weak. Foetal tachycardia is noted with irregularity during contractions.

(a) What course of action is appropriate?

(b) Can she be administered a uterine stimulant to strengthen the contractions? If yes, which drug should be given and how? If no, then why?

(see Appendix-1 for solution)