Misoprostol on its own is only a weak abortifacient, particularly when given orally, and congenital malformations have been reported after failed abortion attempts using misoprostol alone (see Effects on the Fetus, above). However, there is interest in finding a regimen that is effective, particularly in countries where mifepristone is unavailable. A dose of 800 micrograms vaginally, repeated after 24 hours, has been suggested for pregnancy of up to 63 days.[16,17] A large study[18] has also reported that 800 micrograms given every 12 hours for 3 doses was less effective when given sublingually than vaginally; the routes were equally effective when misoprostol was given every 3 hours, but sublingual administration caused more adverse effects such as fever, chills, shivering, and diarrhoea.

Misoprostol has also been studied for termination of pregnancy during the *second trimester*. It has been used in various regimens to induce medical termination, given either alone[19,20] or after oral mifepristone,[21,22] and reported to be effective when given vaginally, sublingually, or orally. The time to complete abortion may depend on the dose, dosage interval, and route of administration. Compared with other prostaglandins, intravaginal misoprostol alone (generally as a single dose of 200 micrograms or repeated after 12 hours if necessary) has been reported to be as effective as dinoprostone for medical termination.[23] Another study[24] found 400 micrograms intravaginally every 3 hours, up to 5 doses, to be at least as effective as intra-amniotic carboprost. The use of buccal misoprostol to prepare the cervix before surgical termination has also been described.[25]

In the management of first trimester *pregnancy failure*, intravaginal misoprostol has been proposed as an alternative to surgery for evacuation of the uterus.[26] Doses have ranged from 400 to 800 micrograms, but the lower doses tend to be less effective.[27] Misoprostol has also been used with mifepristone for uterine evacuation after pregnancy failure (see Termination of Pregnancy, p.2012) and to induce labour where late *intra-uterine fetal death* has occurred (see Labour Induction, p.2012).

1. Ngai SW, *et al.* The use of misoprostol for pre-operative cervical dilatation prior to vacuum aspiration: a randomized trial. *Hum Reprod* 1999; **14:** 2139–42.
2. Saxena P, *et al.* Comparison between the sublingual and oral route of misoprostol for pre-abortion cervical priming in first trimester abortions. *Hum Reprod* 2004; **19:** 77–80.
3. Vimala N, *et al.* Cervical priming with sublingual misoprostol vs. 15-methyl-prostaglandin F2α prior to surgical abortion. *Int J Gynecol Obstet* 2005; **88:** 134–7.
4. Carbonell Esteve JL, *et al.* Sublingual versus vaginal misoprostol (400 µg) for cervical priming in first-trimester abortion: a randomized trial. *Contraception* 2006; **74:** 328–33.
5. Peyron R, *et al.* Early termination of pregnancy with mifepristone (RU 486) and the orally active prostaglandin misoprostol. *N Engl J Med* 1993; **328:** 1509–13.
6. Spitz IM, *et al.* Early pregnancy termination with mifepristone and misoprostol in the United States. *N Engl J Med* 1998; **338:** 1241–7.
7. El-Refaey H, *et al.* Induction of abortion with mifepristone (RU 486) and oral or vaginal misoprostol. *N Engl J Med* 1995; **332:** 983–7.
8. Ashok PW, *et al.* Termination of pregnancy at 9-13 weeks' amenorrhoea with mifepristone and misoprostol. *Lancet* 1998; **52:** 542–3.
9. Schaff EA, *et al.* Vaginal misoprostol administered 1, 2, or 3 days after mifepristone for early medical abortion: a randomized trial. *JAMA* 2000; **284:** 1948–53.
10. Shannon C, *et al.* Regimens of misoprostol with mifepristone for early medical abortion: a randomised trial. *BJOG* 2006; **113:** 621–8.
11. Hamoda H, *et al.* A randomised controlled trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion up to 13 weeks of gestation. *BJOG* 2005; **112:** 1102–8.
12. Creinin MD, *et al.* Medical abortion with oral methotrexate and vaginal misoprostol. *Obstet Gynecol* 1997; **90:** 611–16.
13. Carbonell JLL, *et al.* Oral methotrexate and vaginal misoprostol for early abortion. *Contraception* 1998; **57:** 83–8.
14. Borgatta L, *et al.* Early medical abortion with methotrexate and misoprostol. *Obstet Gynecol* 2001; **97:** 11–16.
15. Aldrich T, Winikoff B. Does methotrexate confer a significant advantage over misoprostol alone for early medical abortion? A retrospective analysis of 8678 abortions. *BJOG* 2007; **114:** 555–62.
16. Philip NM, *et al.* A consensus regimen for early abortion with misoprostol. *Int J Gynecol Obstet* 2004; **87:** 281–3.
17. Blanchard K, *et al.* Misoprostol alone for early abortion: an evaluation of seven potential regimens. *Contraception* 2005; **72:** 91–7.
18. von Hertzen H, *et al.* WHO Research Group on Postovulatory Methods of Fertility Regulation. Efficacy of two intervals and two routes of administration of misoprostol for termination of early pregnancy: a randomised controlled equivalence trial. *Lancet* 2007; **369:** 1938–46.
19. Tang OS, *et al.* A prospective randomised comparison of sublingual and vaginal misoprostol in second trimester termination of pregnancy. *BJOG* 2004; **111:** 1001–5.
20. Caliskan E, *et al.* Randomized comparison of 3 misoprostol protocols for abortion induction at 13–20 weeks of gestation. *J Reprod Med* 2005; **50:** 173–80. Correction. *ibid.*; 732. [dose]
21. Hamoda H, *et al.* A randomized trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion at 13–20 weeks gestation. *Hum Reprod* 2005; **20:** 2348–54.
22. Tang OS, *et al.* A prospective randomized comparison of sublingual and oral misoprostol when combined with mifepristone for medical abortion at 12–20 weeks gestation. *Hum Reprod* 2005; **20:** 3062–6.
23. Jain JK, Mishell DR. A comparison of intravaginal misoprostol with prostaglandin E for termination of second-trimester pregnancy. *N Engl J Med* 1994; **331:** 290–3.
24. Su L-L, *et al.* A prospective, randomized comparison of vaginal misoprostol versus intra-amniotic prostaglandins for midtrimester termination of pregnancy. *Am J Obstet Gynecol* 2005; **193:** 1410–14.
25. Patel A, *et al.* Planned Parenthood Federation of America Buccal Misoprostol Waiver Group. Adequacy and safety of buccal misoprostol for cervical preparation prior to termination of second-trimester pregnancy. *Contraception* 2006; **73:** 420–30.
26. Zhang J, *et al.* A comparison of medical management with misoprostol and surgical management for early pregnancy failure. *N Engl J Med* 2005; **353:** 761–9.
27. Neilson JP, *et al.* Medical treatment for early fetal death (less than 24 weeks). Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 30/06/08).

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Cytotec; ***Austria:*** Cyprostol; ***Belg.:*** Cytotec; ***Braz.:*** Cytotec; ***Canad.:*** Cytotec†; ***Chile:*** Misotrol; ***Cz.:*** Cytotec†; ***Denm.:*** Cytotec; ***Fin.:*** Cytotec; ***Fr.:*** Cytotec; Gymiso; ***Ger.:*** Cytotec†; ***Gr.:*** Cytotec; ***Hong Kong:*** Cytotec; ***India:*** Cytolog; Misoprost; ***Indon.:*** Cytotec; Gastrul; Noprostol; ***Irl.:*** Cytotec; ***Israel:*** Cytotec; ***Ital.:*** Cytotec; Misodex; ***Malaysia:*** Cytotec; ***Mex.:*** Cytotec; ***Neth.:*** Cytotec; ***Norw.:*** Cytotec; ***NZ:*** Cytotec; ***Pol.:*** Cytotec; ***Port.:*** Cytotec; ***Rus.:*** Cytotec (Сайтотек)†; ***S.Afr.:*** Cytotec; ***Singapore:*** Cytotec; ***Spain:*** Cytotec; Glefos†; ***Swed.:*** Cytotec; ***Switz.:*** Cytotec; ***Thai.:*** Cytotec; ***Turk.:*** Cytotec; ***UK:*** Cytotec; ***USA:*** Cytotec; ***Venez.:*** Cytotec.

Used as an adjunct in: ***Arg.:*** Oxaprost; ***Austral.:*** Arthrotec; ***Austria:*** Arthrotec; ***Belg.:*** Arthrotec; ***Canad.:*** Arthrotec; ***Cz.:*** Arthrotec†; ***Denm.:*** Arthrotec; ***Fin.:*** Arthrotec; ***Fr.:*** Artotec; ***Ger.:*** Arthotec; ***Gr.:*** Arthrotec; ***Hong Kong:*** Arthrotec; ***Irl.:*** Arthrotec; ***Israel:*** Arthrotec; ***Ital.:*** Artrotec; Misofenac; ***Mex.:*** Artrenac Pro; Artrene; Artrotec; ***Neth.:*** Arthrotec; Artrotec; Misofenac; Normulen; ***Norw.:*** Arthrotec; ***Pol.:*** Arthrotec; ***Port.:*** Arthrotec; Diclotec; ***Rus.:*** Arthrotec (Артротек)†; ***S.Afr.:*** Arthrotec; ***Spain:*** Artrotec; Normulen; ***Swed.:*** Arthrotec; ***Switz.:*** Arthrotec; ***Thai.:*** Arthrotec†; ***UK:*** Arthrotec; Napratec; ***USA:*** Arthrotec; ***Venez.:*** Arthrotec.

Oxytocin *(BAN, rINN)*

Alpha-hypophamine; Hipofamina; Ocitocina; Oksitocinas; Oksitosiini; Oksitosin; Oxitocin; Oxitocina; Oxytocine; Oxytocinum. Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2 cyclic (1→6) disulphide; [2-Leucine,7-isoleucine]vasopressin.

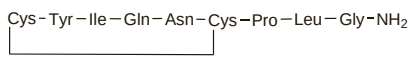
Окситоцин

$C_{43}H_{66}N_{12}O_{12}S_2$ = 1007.2.

CAS — 50-56-6.

ATC — H01BB02.

ATC Vet — QH01BB02.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Oxytocin). A cyclic nonapeptide having the structure of the hormone produced by the posterior lobe of the pituitary that stimulates contraction of the uterus and milk ejection in receptive mammals. It is obtained by chemical synthesis and is available in the freeze-dried form as an acetate. A white or almost white, hygroscopic powder. Very soluble in water and in dilute solutions of dehydrated alcohol and of acetic acid. A 2% solution in water has a pH of 3.0 to 6.0. Store at 2° to 8° in airtight containers. Protect from light.

Ph. Eur. 6.2 (Oxytocin Concentrated Solution). A solution of oxytocin with a concentration of not less than 250 micrograms of oxytocin per mL. It may contain a suitable antimicrobial preservative. A clear colourless liquid with a pH of 3.0 to 5.0. Store at 2° to 8°. Protect from light.

USP 31 (Oxytocin). A nonapeptide hormone having the property of causing the contraction of uterine smooth muscle and of the myoepithelial cells within the mammary glands. It is prepared by synthesis or obtained from the posterior lobe of the pituitary of healthy domestic animals used for food by man. Its oxytocic activity is not less than 400 units/mg. Store in airtight containers at 2° to 8°.

Units

12.5 units of oxytocin for bioassay are contained in about 21.4 micrograms of synthetic peptide (with human albumin 5 mg and citric acid) in one ampoule of the fourth International Standard (1978).

Adverse Effects

Oxytocin given in high doses, or to women who are hypersensitive to it, may cause uterine hyperstimulation with hypertonic or tetanic contractions, leading to uterine rupture and soft tissue damage. Effects in the fetus include bradycardia, arrhythmias, asphyxiation, and perhaps death.

Maternal deaths from severe hypertension and subarachnoid haemorrhage have occurred. Rapid intravenous injection of oxytocin has produced acute transient hypotension with flushing and reflex tachycardia. Postpartum haemorrhage, fatal afibrinogenaemia, and disseminated intravascular coagulation have been reported, but may be due to complications of labour induction rather than oxytocin itself.

High doses of oxytocin infused over prolonged periods can also cause water retention leading to hyponatraemia and intoxication, which may progress to convulsions, coma, and even death. Vasopressin-like activity (see p.2412) is more likely with oxytocin of natural origin but may occur even with the synthetic peptide.

Other adverse effects include headache, nausea and vomiting, skin rashes, cardiac arrhythmias, pelvic haematoma, and anaphylactic and other hypersensitivity reactions.

There are reports of neonatal jaundice and retinal haemorrhage associated with the use of oxytocin in the management of labour.

Adverse effects after intranasal use of oxytocin have included nasal irritation, rhinorrhoea, lachrymation, uterine bleeding, and violent uterine contractions.

Inappropriate use. In a 1988 comment on the misuse of oxytocin in labour,[1] it was noted that statements on the management of labour were often misinterpreted as meaning that all women who failed to make adequate progress in terms of cervical dilatation should be given oxytocin. This was only true if poor progress was due to poor uterine action, and would be dangerous where there was disproportion; the decision to use oxytocin required careful assessment by an experienced obstetrician. In the previous 2 years the authors had seen one case of fractured pelvis, 2 of ruptured uterus, and 7 of cerebral palsy from fetal hypoxia, all of which were thought to be due to the ill-advised use of oxytocin to augment labour. More than a decade later the injudicious use of oxytocin during labour, with adverse outcomes including neonatal brain damage and death, continues to be reported. A review[2] of obstetric malpractice claims in Sweden found that the incorrect use of oxytocin was obvious in 37 of 54 cases; often, the oxytocin infusion had been increased despite a non-reassuring fetal heart-rate pattern with or without overly frequent uterine contractions, or fetal monitoring was inadequate and hence fetal distress not recognised.

For reference to haemorrhage and to neonatal hyperbilirubinaemia occurring after an oxytocin challenge test, see under Uses and Administration, below.

1. Taylor RW, Taylor M. Misuse of oxytocin in labour. *Lancet* 1988; **i:** 352.
2. Jonsson M, *et al.* Analysis of malpractice claims with a focus on oxytocin use in labour. *Acta Obstet Gynecol Scand* 2007; **86:** 315–19.

Neonatal jaundice. Analysis of neonatal jaundice in 12 461 single births confirmed a higher incidence of jaundice in offspring of mothers given oxytocin, independent of gestational age at birth, sex, race, epidural analgesia, method of delivery, and birth-weight, which were also associated with jaundice.[1] A later review[2] of 12 023 single births also found some of these factors to be associated with neonatal hyperbilirubinaemia, but not epidural analgesia or the use of oxytocin. Another smaller population study[3] also concluded that oxytocin was not significantly related to neonatal jaundice. In a total of 90 infants born to mothers after oxytocin-induced labour in 2 studies,[4,5] haematological disturbances were noted. These included erythrocyte fragility or reduction in erythrocyte deformability, hyponatraemia, hypoosmolality, and an increase in serum-bilirubin concentration. Glucose injection, used as a vehicle for oxytocin may have further aggravated these changes.[5] A comparison[6] of women who received oxytocin infusion in either glucose 5% or sodium chloride 0.9% found the use of glucose to be associated with more cases of hyponatraemia in cord plasma, and neonatal hyperbilirubinaemia. In contrast, another study[7] found no difference between these diluents, but did report that neonatal bilirubin concentrations were higher when oxytocin had been used for augmentation of labour, compared with labour induction.

See also under Oxytocin Challenge Test in Uses and Administration, below.

1. Friedman L, *et al.* Factors influencing the incidence of neonatal jaundice. *BMJ* 1978; **1:** 1235–7.
2. Linn S, *et al.* Epidemiology of neonatal hyperbilirubinemia. *Pediatrics* 1985; **75:** 770–4.
3. Seidman DS, *et al.* Predicting the risk of jaundice in fullterm healthy newborns: a prospective population-based study. *J Perinatol* 1999; **19:** 564–7.
4. Buchan PC. Pathogenesis of neonatal hyperbilirubinaemia after induction of labour with oxytocin. *BMJ* 1979; **2:** 1255–7.
5. Singhi S, Singh M. Pathogenesis of oxytocin-induced neonatal hyperbilirubinaemia. *Arch Dis Child* 1979; **54:** 400–2.
6. Omigbodun AO, *et al.* Effect of saline and glucose infusions of oxytocin on neonatal bilirubin levels. *Int J Gynecol Obstet* 1993; **40:** 235–9.
7. Oral E, *et al.* Oxytocin infusion in labor: the effect different indications and the use of different diluents on neonatal bilirubin levels. *Arch Gynecol Obstet* 2003; **267:** 117–20.

Water intoxication. Oxytocin-induced water intoxication is most likely to arise as a result of prolonged attempts to empty the uterus in missed abortion or mid-trimester termination of pregnancy, but it has also been described after oxytocin infusion in other conditions including induction of labour.[1] Irrespective of the oxytocin concentration, patients in virtually all the reported cases have received more than 3.5 litres of infused fluid. Convulsions and somnolence associated with hyponatraemia have also been reported in a patient who was drinking more than 5 litres of herbal tea daily while using intranasal oxytocin 8 times or more daily.[2]

Another factor contributing to hyponatraemia is the antidiuretic effect of the pethidine and morphine commonly used for analgesia with oxytocin infusions. Water intoxication usually presents with fits and loss of consciousness but in some cases there may be preceding signs such as raised venous pressure, bounding pulse, and tachycardia. Diagnosis is confirmed by profound hyponatraemia; the mechanism appears to be more complex than simply haemodilution by the infused water. Treatment consists of controlling convulsions and maintaining an airway; oxytocin infusion must be stopped and isotonic, or even hypertonic, saline may be infused. Diuresis may then be assisted with furosemide. The prime objective, however, should be prevention; no patient should receive more than 3 litres of fluid containing oxytocin, and a careful fluid balance record is essential.

1. Feeney JG. Water intoxication and oxytocin. *BMJ* 1982; **285:** 243.
2. Mayer-Hubner B. Pseudotumour cerebri from intranasal oxytocin and excessive fluid intake. *Lancet* 1996; **347:** 623.

Precautions

Oxytocin should not be given where spontaneous labour or vaginal delivery are liable to harm either the mother or the fetus. This includes significant cephalopelvic disproportion or unfavourable presentation of the fetus, placenta praevia or vasa praevia, placental abruption, cord presentation or prolapse, mechanical obstruction to delivery, fetal distress or hypertonic uterine contractions. It should not be used where there is a predisposition to uterine rupture, as in multiple pregnancy or high parity, polyhydramnios, or the presence of a uterine scar from previous caesarean section. Oxytocin should not be used for prolonged periods in resistant uterine inertia, severe pre-eclampsia, or severe cardiovascular disorders.

When given for induction or enhancement of labour particular care is needed in borderline cephalopelvic disproportion, less severe degrees of cardiovascular disease, and in patients over 35 years of age or with other risk factors. Careful monitoring of fetal heart rate and uterine motility is essential so that dosage of oxytocin can be adjusted to individual response; the drug should be given by intravenous infusion, preferably by means of an infusion pump. Infusion should be stopped immediately if fetal distress or uterine hyperactivity occur.

Over-vigorous labour should be avoided in cases of intra-uterine fetal death, or where there is meconium-stained amniotic fluid, because there is a risk of amniotic fluid embolism.

The risk of water intoxication should be borne in mind, particularly when high doses of oxytocin are given over a long time. Infusion volumes should be kept low, and in such circumstances an electrolyte-based infusion fluid should be used rather than glucose solution. Fluid intake by mouth should be restricted and a fluid balance chart maintained; serum electrolytes should be measured if electrolyte imbalance is suspected.

Oxytocin challenge test. For the suggestion that oxytocin challenge testing should be used with caution in women whose offspring might be at risk of hyperbilirubinaemia, see under Uses and Administration, below.

Interactions

Oxytocin may enhance the vasopressor effects of sympathomimetics. Some inhalational anaesthetics, such as cyclopropane or halothane, may enhance the hypotensive effect of oxytocin and reduce its oxytocic effect; cardiac arrhythmias may occur. Prostaglandins and oxytocin may potentiate the effects of each other on the uterus; the UK licensed product information for oxytocin states that it should not be started for 6 hours after use of vaginal prostaglandins.

Pharmacokinetics

Oxytocin undergoes enzymatic destruction in the gastrointestinal tract but it is rapidly absorbed from the mucous membranes when given intranasally. It is metabolised by the liver and kidneys with a plasma half-life of only a few minutes. Only small amounts are excreted unchanged in the urine.

◊ References.

1. Seitchik J, *et al*. Oxytocin augmentation of dysfunctional labor IV: oxytocin pharmacokinetics. *Am J Obstet Gynecol* 1984; **150:** 225–8.
2. Perry RL, *et al*. The pharmacokinetics of oxytocin as they apply to labor induction. *Am J Obstet Gynecol* 1996; **174:** 1590–3.

Uses and Administration

Oxytocin is a cyclic nonapeptide secreted by the hypothalamus and stored in the posterior lobe of the pituitary gland. It may be prepared from the gland of mammals or by synthesis.

Oxytocin causes contraction of the uterus, the effect increasing with the duration of pregnancy due to proliferation of oxytocin receptors. Small doses increase the tone and amplitude of the uterine contractions; large or repeated doses result in tetany. Oxytocin also stimulates the smooth muscle associated with the secretory epithelium of the lactating breast causing the ejection of milk but having no direct effect on milk secretion. It has a weak antidiuretic action.

Oxytocin is used for the induction and augmentation of labour, to control postpartum bleeding and uterine hypotonicity in the third stage of labour, and to promote lactation in cases of faulty milk ejection. It is also used in missed abortions, but other measures may be preferred.

For the **induction** or **augmentation of labour** (below) oxytocin may be given by slow intravenous infusion preferably by means of an infusion pump. A solution containing 5 units in 500 mL of a physiological electrolyte solution such as sodium chloride 0.9% has been recommended but more concentrated solutions may be given via infusion pump, and current UK guidelines suggest 10 or 30 units in 500 mL of diluent. Infusion is begun at a recommended initial rate of 1 to 2 milliunits/minute and then gradually increased at intervals of at least 30 minutes, until a maximum of 3 or 4 contractions are occurring every 10 minutes. A rate of up to 6 milliunits/minute is reported to produce plasma oxytocin concentrations comparable to those in natural labour, and 12 milliunits/minute is usually the most that is needed but doses of up to 20 milliunits/minute or more may be required. UK guidelines suggest that 32 milliunits/minute should not be exceeded, and no more than a total of 5 units should be given in 1 day. Oxytocin should not be started for 6 hours after vaginal prostaglandins have been given. Fetal heart rate and uterine contractions should be monitored continuously. Once labour is progressing, oxytocin infusion may be gradually withdrawn.

For the treatment and prevention of **postpartum haemorrhage** (below) oxytocin may be given by slow intravenous injection in a dose of 5 units; this may be followed in severe cases by intravenous infusion of 5 to 20 units in 500 mL of a suitable non-hydrating diluent. The *BNF* suggests that in the treatment of uterine bleeding, higher doses may also be considered: a single dose of 10 units by slow intravenous injection may be used, followed if necessary by an infusion containing up to 30 units in 500 mL. A single dose of 5 units by slow intravenous injection has also been given during caesarean section, immediately after delivery of the child. An alternative for the prophylaxis of postpartum haemorrhage in the routine management of the third stage of labour is the intramuscular injection of oxytocin 5 units with ergometrine maleate 500 micrograms after delivery of the anterior shoulder, or, at the latest, immediately after delivery of the infant; the *BNF* suggests a single intramuscular dose of oxytocin 10 units used alone if ergometrine is contra-indicated. In the USA a dose of 10 units of oxytocin, by intravenous infusion at a rate of 20 to 40 milliunits/minute, or as an intramuscular injection, has been recommended for treatment of postpartum haemorrhage.

In **missed abortion** a suggested dose in the UK is 5 units by slow intravenous injection, followed if necessary by intravenous infusion at a rate of 20 to 40 milliunits/minute or higher.

Oxytocin nasal spray is used to facilitate **lactation**; a dose of one spray, delivering 4 units, into one nostril 5 minutes before suckling has been used. However, evidence for its efficacy is limited and there is a danger that the mother may become dependent upon its action; such usage is not generally recommended (see p.2003).

An **oxytocin challenge test** (below) has been used to evaluate fetal distress in pregnant patients at high risk.

Synthetic derivatives of oxytocin such as demoxytocin (p.2006) have been used similarly.

Labour induction and augmentation. Oxytocin infusions have proved to be one of the most successful agents for induction and augmentation of labour, as discussed on p.2002. There have been numerous studies on the dosage of oxytocin required to induce or augment labour. Various dosage regimens have been tried, and studies have reported using initial doses ranging from 0.5 to 6 milliunits/minute, dose increases of 1 to 6 milliunits/minute, and intervals between increases of 15 to 40 minutes.[1] Higher doses and shorter intervals between increases can shorten labour and reduce rates of intra-amniotic infection and caesarean delivery, but result in more uterine hyperstimulation and emergency caesarean deliveries for fetal distress.[1] Low-dose regimens are now generally advocated; for example, UK guidelines[2] favour a starting dose of 1 to 2 milliunits/minute, increased at intervals of 30 minutes, and titrated against contractions to a maximum of 32 milliunits/minute. WHO[3] suggests a starting dose of 2.5 milliunits/minute, increased at intervals of 30 minutes, and titrated against contractions to a maximum of 60 milliunits/minute. However, it has been pointed out that no one regimen has been clearly proved superior.[1,4,5]

1. Stubbs TM. Oxytocin for labor induction. *Clin Obstet Gynecol* 2000; **43:** 489–94.
2. Royal College of Obstetricians and Gynaecologists. Induction of labour: evidence-based clinical guideline number 9 (issued June 2001). Available at: http://www.nice.org.uk/nicemedia/pdf/inductionoflabourrcogrep.pdf (accessed 30/06/08)
3. Department of Reproductive Health and Research. Induction and augmentation of labour. In: WHO. *Managing complications in pregnancy and childbirth: a guide for midwives and doctors.* Geneva: WHO, 2003: P17–P26. Also available at: http://www.who.int/reproductive-health/impac/Procedures/Induction_P17_P25.html (accessed 30/06/08)
4. Patka JH, *et al.* High- versus low-dose oxytocin for augmentation or induction of labor. *Ann Pharmacother* 2005; **39:** 95–101.
5. Smith JG, Merrill DC. Oxytocin for induction of labor. *Clin Obstet Gynecol* 2006; **49:** 594–608.

Oxytocin challenge test. The oxytocin challenge test (OCT) is designed to detect placental insufficiency, and identify fetuses at risk of still-birth or complications during labour. In a study, it was performed on 399 occasions in 305 women with pregnancies at risk and a gestational age of 36 weeks or more.[1] Oxytocin 1 milliunit/minute was given by infusion pump and increased every 5 to 10 minutes until a contraction rate of 3 per 10 minutes was achieved. Less than 10% of late or variable decelerations of fetal heart rate (FHR) was judged negative; 10 to 29% was judged equivocal; and 30% or more was judged positive. The finding of a positive or equivocal response to the OCT was considered a prediction of decelerations of the FHR during parturition, though the type of risk might vary. After 100 OCTs in 90 pregnant women considered at risk[2] it was concluded that a negative result is a reliable test of fetal well-being which should encourage obstetricians to await spontaneous onset of labour in preference to intervention. However, there have been reports of fetal death occurring despite a negative response to the OCT.[3-5] Another study[6] found that in 239 women with an unequivocal OCT result, a negative response was a reliable test for a good outcome, but that a positive result was not a reliable predictor of poor outcome.

Adverse effects associated with the OCT have included haemorrhage occurring in a patient after the second of two tests (the patient was found to have a major placenta praevia)[7] and neonatal hyperbilirubinaemia.[8] The latter effect led to the suggestion that the OCT should be used with caution in women whose babies might be at risk from hyperbilirubinaemia.

1. Schulman H, *et al.* Quantitative analysis in the oxytocin challenge test. *Am J Obstet Gynecol* 1977; **129:** 239–44.
2. Sellappah S, Wagman H. Oxytocin challenge test as an out patient procedure. *Br J Clin Pract* 1984; **38:** 255–8.
3. Marcum RG. False negative oxytocin challenge test. *Am J Obstet Gynecol* 1977; **127:** 894.
4. Lorenz RP, Pagano JS. A case of intrauterine fetal death after a negative oxytocin challenge test. *Am J Obstet Gynecol* 1978; **130:** 232.
5. Dittman R, Belcher J. False-negative oxytocin challenge test. *N Engl J Med* 1978; **298:** 56.

6. Ocak V, *et al*. The predictive value of fetal heart rate monitoring: a retrospective analysis of 2165 high-risk pregnancies. *Eur J Obstet Gynecol Reprod Biol* 1992; **44:** 53–8.
7. Ng KH, Wong WP. Risk of haemorrhage in oxytocin stress test. *BMJ* 1976; **2:** 698–9.
8. Peleg D, Goldman JA. Oxytocin challenge test and neonatal hyperbilirubinaemia. *Lancet* 1976; **ii:** 1026.

Postpartum haemorrhage. Oxytocin is used for the prophylaxis and treatment of postpartum haemorrhage (p.2003). In the active management of the third stage of labour, the combination of oxytocin and ergometrine may be associated with a small reduction in the risk of postpartum haemorrhage compared with oxytocin alone, but a higher incidence of nausea, vomiting, and hypertension.

Retained placenta. Oxytocin injected into the vein of the umbilical cord has been used to assist the removal of retained placenta. A meta-analysis[1] of 12 studies found evidence that oxytocin reduced the incidence of manual removal of the retained placenta, although there was no apparent benefit in terms of other measures including blood loss, curettage, and infection. The removal of the placenta is important to allow contraction of the myometrium and prevention of excessive blood loss, and is one reason for the use of oxytocin in the active management of the third stage of labour, as discussed under Postpartum Haemorrhage—see above and on p.2003.

1. Carroli G, Bergel E. Umbilical vein injection for management of retained placenta. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 30/06/08).

Preparations

BP 2008: Ergometrine and Oxytocin Injection; Oxytocin Injection; ***USP 31:*** Oxytocin Injection; Oxytocin Nasal Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Hipofisina; Syntocinon; Veracuril; ***Austral.:*** Syntocinon; ***Austria:*** Syntocinon; ***Belg.:*** Syntocinon; ***Braz.:*** Naox; Orastina; Oxiton; Syntocinon; ***Chile:*** Syntocinon; ***Denm.:*** Syntocinon; ***Fin.:*** Syntocinon; ***Fr.:*** Syntocinon; ***Ger.:*** Orasthin†; Syntocinon; ***Hong Kong:*** Syntocinon; ***India:*** Gynotocin; Pitocin; Syntocinon; ***Indon.:*** Induxin; Pitogin; Piton-S; Syntocinon; ***Irl.:*** Syntocinon; ***Ital.:*** Syntocinon; ***Malaysia:*** Syntocinon; ***Mex.:*** Oxitopisa; Syntocinon; Xitocin; ***Neth.:*** Piton-S†; Syntocinon; ***Norw.:*** Syntocinon; ***NZ:*** Syntocinon; ***Philipp.:*** Estima; Fetusin; NeOxyn; Obcin; Oxitone; Oxtimon; Solvoxine; Syntocinon; Tranoxy; ***Port.:*** Syntocinon; ***S.Afr.:*** Syntocinon; ***Singapore:*** Syntocinon; ***Spain:*** Syntocinon; ***Swed.:*** Syntocinon; ***Switz.:*** Syntocinon; ***Turk.:*** Postuitrin; Synpitan; ***UK:*** Syntocinon; ***USA:*** Pitocin; ***Venez.:*** Pitocin†; Syntocinon.

Multi-ingredient: ***Austral.:*** Syntometrine; ***Ger.:*** Syntometrin†; ***Hong Kong:*** Syntometrine†; ***Irl.:*** Syntometrine; ***Malaysia:*** Syntometrine; ***NZ:*** Syntometrine; ***S.Afr.:*** Syntometrine; ***UK:*** Syntometrine.

Prolactin

Galactin; Galactina; Hormona lactogénica; Hormona luteotrópica; Lactoestimulina; Lactogen; Lactogenic Hormone; Lactógeno; Lactotropin; LMTH; LTH; Luteomammotropic Hormone; Luteotrophic Hormone; Luteotropin; Luteotropina; Mammotropin; Mamotropina; Prolactina.

Пролактин

CAS — 9002-62-4; 12585-34-1 (sheep); 56832-36-1 (ox); 9046-05-3 (pig).

Profile

Prolactin is a water-soluble protein from the anterior pituitary; it is structurally related to growth hormone (p.1799). In *animals*, prolactin has many actions and is involved in reproduction, parental care, feeding of the young, electrolyte balance, and growth and development. In humans it has a definite role in inducing milk production; oxytocin (p.2016) stimulates milk ejection. Relatively high concentrations of prolactin have been found in amniotic fluid. Placental lactogen has been shown to have prolactin-like activity. Prolactin secretion is stimulated by suckling and, for a few months after delivery, it has an inhibitory effect on the ovaries, acting as a natural contraceptive.

The hypothalamus can both stimulate and inhibit prolactin secretion by the anterior pituitary; the inhibitory influence is predominant and is mediated through a dopaminergic system. Dopamine binds to the lactotrope D_2 receptor to inhibit prolactin synthesis and release. Noradrenaline and gamma-aminobutyric acid are also inhibitory as are dopaminergic drugs such as bromocriptine. Although protirelin (p.2176) has prolactin-releasing activity, there is evidence for the existence of a separate hypothalamic releasing factor (PRF). Prolactin secretion may also be stimulated by methyldopa, metoclopramide, reserpine, opioid analgesics, and phenothiazine or butyrophenone antipsychotics.

Hyperprolactinaemia, which is associated with a variety of other endocrine disorders, is discussed on p.2079.

Prolactin has been given by intramuscular injection in the management of lactation disorders and some forms of menstrual disturbance.

Ritodrine Hydrochloride

(BANM, USAN, rINNM) ⊗

DU-21220 (ritodrine); Hidrocloruro de ritodrina; Ritodrin Hidroklorür; Ritodrine, Chlorhydrate de; Ritodrini Hydrochloridum. *erythro*-2-(4-Hydroxyphenethylamino)-1-(4-hydroxyphenyl)propan-1-ol hydrochloride.

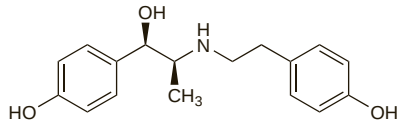
Ритодрина Гидрохлорид

$C_{17}H_{21}NO_3$,HCl = 323.8.

CAS — 26652-09-5 (ritodrine); 23239-51-2 (ritodrine hydrochloride).

ATC — G02CA01.

ATC Vet — QG02CA01.



(ritodrine)

Pharmacopoeias. In *Br.*, *Jpn*, and *US*.

BP 2008 (Ritodrine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; soluble in dehydrated alcohol; practically insoluble in acetone and in ether. A 2% solution in water has a pH of 4.5 to 6.0. Store in airtight containers.

USP 31 (Ritodrine Hydrochloride). A white to nearly white, odourless or practically odourless, crystalline powder. Freely soluble in water and in alcohol; practically insoluble in ether; soluble in propyl alcohol. pH of a 2% solution in water is between 4.5 and 6.0. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects and Precautions

As for Salbutamol Sulfate, p.1131. Leucopenia or agranulocytosis has been reported occasionally with prolonged intravenous use.

In women given ritodrine for premature labour, the risk of pulmonary oedema means that extreme caution is required and the precautions and risk factors discussed under Salbutamol Sulfate, p.1132, apply.

Effects on the eyes. Ritodrine and to a lesser extent salbutamol have been implicated in retinopathy in the premature infant when used for premature labour.[1]

1. Michie CA, *et al*. Do maternal β-sympathomimetics influence the development of retinopathy in the premature infant? *Arch Dis Child* 1994; **71:** F149.

Effects on the heart. Myocardial ischaemia or signs of myocardial ischaemia have been reported in patients given ritodrine.[1-3] Sinus tachycardia and ST-segment depression commonly occur in patients given ritodrine, but the relationship between these changes and ischaemia remains unclear.[3]

1. Brosset P, *et al*. Cardiac complications of ritodrine in mother and baby. *Lancet* 1982; **i:** 1468.
2. Ben-Shlomo I, *et al*. Myocardial ischaemia during intravenous ritodrine treatment: is it so rare? *Lancet* 1986; **ii:** 917–18.
3. Verhaert D, Van Acker R. Acute myocardial infarction during pregnancy. *Acta Cardiol* 2004; **59:** 331–9.

Effects on skeletal muscle. Elevated serum-creatine kinase concentrations have been found in women given ritodrine tocolysis,[1] and there have been rare reports of rhabdomyolysis.[1,2]

1. Matsuda Y, *et al*. Evaluation of creatine kinase level during long-term tocolysis. *J Perinat Med* 2002; **30:** 476–9.
2. Nasu K, *et al*. Rhabdomyolysis caused by tocolysis with oral ritodrine hydrochloride in a pregnant patient with myotonic dystrophy. *Gynecol Obstet Invest* 2006; **61:** 53–5.

Pulmonary oedema. Several cases of pulmonary oedema have been reported in patients given a $beta_2$ agonist, including ritodrine, for premature labour.[1-4] In 1995 the UK CSM[4] commented that it had received 10 reports of pulmonary oedema, fatal in 2 patients. The CSM considered that fluid overload was the most important predisposing factor. Other risk factors included multiple pregnancies, a history of cardiac disease, and maternal infection. For further discussion of the precautions necessary in the use of $beta_2$ agonists to treat premature labour, and the risk factors involved, see Salbutamol, p.1132.

1. Hawker F. Pulmonary oedema associated with β -sympathomimetic treatment of premature labour. *Anaesth Intensive Care* 1984; **12:** 143–51.
2. Pisani RJ, Rosenow EC. Pulmonary edema associated with tocolytic therapy. *Ann Intern Med* 1989; **110:** 714–18.
3. Clesham GJ, *et al*. β Adrenergic agonists and pulmonary oedema in preterm labour. *BMJ* 1994; **308:** 260–2.
4. Committee on Safety of Medicines/Medicines Control Agency. Reminder: ritodrine and pulmonary oedema. *Current Problems* 1995; **21:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 30/06/08)

Interactions

As for Salbutamol Sulfate, p.1132.

Pharmacokinetics

Ritodrine is rapidly absorbed from the gastrointestinal tract but is subject to fairly extensive first-pass metabolism; about 30% of an oral dose is bioavailable. It is metabolised in the liver primarily by conjugation with glucuronic acid or sulfate and excreted in urine as unchanged drug and metabolites. About 70 to 90% of a dose is reported to be excreted in the urine within 10 to 12 hours. It crosses the placenta.

◊ References.

1. Gandar R, *et al*. Serum level of ritodrine in man. *Eur J Clin Pharmacol* 1980; **17:** 117–22.
2. Gross AS, Brown KF. Plasma protein binding of ritodrine at parturition and in nonpregnant women. *Eur J Clin Pharmacol* 1985; **28:** 479–81.
3. Kuhnert BR, *et al*. Ritodrine pharmacokinetics. *Clin Pharmacol Ther* 1986; **40:** 656–64.
4. Caritis SN, *et al*. Pharmacokinetics of orally administered ritodrine. *Am J Obstet Gynecol* 1989; **161:** 32–5.
5. Caritis SN, *et al*. Pharmacokinetics of ritodrine administered intravenously: recommendations for changes in the current regimen. *Am J Obstet Gynecol* 1990; **162:** 429–37.
6. Caritis SN, *et al*. Pharmacokinetics and pharmacodynamics of ritodrine after intramuscular administration to pregnant women. *Am J Obstet Gynecol* 1990; **162:** 1215–19.
7. Pacifici GM, *et al*. Sulphation and glucuronidation of ritodrine in human foetal and adult tissues. *Eur J Clin Pharmacol* 1993; **44:** 259–64.
8. Pacifici GM, *et al*. Ritodrine sulphation in the human liver and duodenal mucosa: interindividual variability. *Eur J Drug Metab Pharmacokinet* 1998; **23:** 67–74.

Uses and Administration

Ritodrine hydrochloride is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist). It has general properties similar to those of salbutamol (see p.1133). It decreases uterine contractility and is used to arrest premature labour (p.2003).

Ritodrine hydrochloride is usually given by intravenous infusion. Where possible this should be with the aid of a **syringe pump**, when the concentration should be 3 mg/mL, using glucose 5% as the diluent. A recommended initial rate of infusion is 50 micrograms/minute increased at intervals of 10 minutes by increments of 50 micrograms/minute until there is evidence of patient response, which is usually at a rate of 150 to 350 micrograms/minute, the latter figure being the maximum recommended rate. If no syringe pump is available then the infusion may be made using a **controlled infusion device** to deliver a more dilute solution of 300 micrograms/mL, with glucose 5% being used once again as the diluent. The same dose is used as with the syringe pump.

The maternal pulse should be monitored throughout the infusion and the rate adjusted to avoid a maternal heart rate of more than 140 beats/minute. A close watch should also be kept on the patient's state of hydration since fluid overload is considered to be a key risk factor for pulmonary oedema. The infusion should be continued for 12 to 48 hours after the contractions have stopped. Ritodrine hydrochloride may subsequently be given **by mouth** in an initial dose of 10 mg every 2 hours for 24 hours, starting 30 minutes before the end of the intravenous infusion. Thereafter, 10 to 20 mg may be given every 4 to 6 hours according to the patient's response. The total daily oral dose should not exceed 120 mg.

If intravenous infusion is inappropriate, 10 mg may be given **intramuscularly** every 3 to 8 hours and continued for 12 to 48 hours after the contractions have stopped.

◊ Reviews.

1. Yaju Y, Nakayama T. Effectiveness and safety of ritodrine hydrochloride for the treatment of preterm labour: a systematic review. *Pharmacoepidemiol Drug Safety* 2006; **15:** 813–22.

Preparations

BP 2008: Ritodrine Injection; Ritodrine Tablets; ***USP 31:*** Ritodrine Hydrochloride Injection; Ritodrine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Ritopar; ***Belg.:*** Pre-Par; ***Braz.:*** Miodrina; ***Chile:*** Materlac†; ***Cz.:*** Pre-Par†; ***Gr.:*** Pre-Par†; Yutopar; ***Hong Kong:*** Yutopar†; ***India:*** Yutopar;