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.

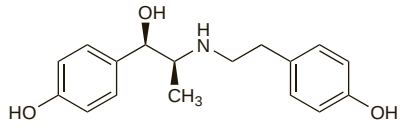
Ритодрина Гидрохлорид

$C_{17}H_{21}NO_3$,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;

Indon.: Yutopar; ***Israel:*** Ritopar; ***Ital.:*** Miolene; ***Port.:*** Pre-Par†; ***Spain:*** Pre-Par; ***Turk.:*** Pre-Par; ***UK:*** Yutopar.

Sulprostone *(USAN, rINN)*

CP-34089; 16-Phenoxy-ω-17,18,19,20-tetranor-prostaglandin E_2-methylsulfonylamide; SHB-286; Sulproston; Sulprostona; Sulprostoni; Sulprostonum; ZK-57671. (*Z*)-7-{(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*R*)-3-hydroxy-4-phenoxybut-1-enyl]-5-oxocyclopentyl}-*N*-(methylsulphonyl)hept-5-enamide.

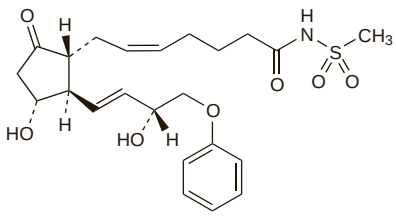
Сульпростон

$C_{23}H_{31}NO_7S$ = 465.6.

CAS — 60325-46-4.

ATC — G02AD05.

ATC Vet — QG02AD05.



Adverse Effects and Precautions

As for Dinoprostone, p.2007. In some countries, such as France, the licensed product information for sulprostone contra-indicates its use in smokers or those who have smoked in the last 2 years, and in women over 35 years of age.

Once a prostaglandin has been given to terminate pregnancy it is essential that termination take place; if the prostaglandin is unsuccessful other measures should be used.

Effects on the cardiovascular system. A 31-year-old woman died from cardiovascular shock during an abortion induced by mifepristone followed by sulprostone. She had 12 children, one previous abortion, and was a heavy cigarette smoker.[1] Four other deaths with sulprostone had not been associated with abortion. Other reported cases that did not result in death have included myocardial infarction in a 32-year-old woman given sulprostone for intra-uterine fetal death,[2] and cardiac arrest in a 38-year-old woman, with no history of smoking, after sulprostone was given by both intramyometrial and intravenous bolus injection for postpartum haemorrhage;[3] in both cases the authors suggested that sulprostone had caused coronary artery spasm.

Inadvertent subcutaneous infusion of sulprostone was thought to have caused arterial spasm with pain and oedema in the arm of a woman being treated for postpartum haemorrhage; she recovered after treatment with iloprost infusion.[4]

1. Anonymous. A death associated with mifepristone/sulprostone. *Lancet* 1991; **337:** 969–70.
2. Fliers E, *et al.* A prostaglandin analogue as a probable cause of myocardial infarction in a young woman. *BMJ* 1991; **302:** 416.
3. Chen FG, *et al.* Cardiac arrest associated with sulprostone use during caesarean section. *Anaesth Intensive Care* 1998; **26:** 298–301.
4. de Koning YWCM, *et al.* Critical limb ischemia after accidental subcutaneous infusion of sulprostone. *Eur J Obstet Gynecol Reprod Biol* 1995; **61:** 171–3.

Effects on the nervous system. For a report of convulsions in epileptic patients given sulprostone, see under Dinoprostone, p.2007.

Effects on the uterus. For reference to hyperstimulation and uterine rupture after use of prostaglandins, including sulprostone, for termination of pregnancy or induction of labour, see under Dinoprostone, p.2007.

Interactions

As for Dinoprostone, p.2008.

Uses and Administration

Sulprostone is a synthetic derivative of dinoprostone (prostaglandin E_2; p.2007) that has uterine stimulant effects. It is used for dilatation of the cervix before surgical termination of pregnancy in the first trimester, for medical termination of pregnancy in the second trimester (p.2004), and to empty the uterus in missed abortion, hydatidiform mole, and intra-uterine fetal death. It is also used to control postpartum haemorrhage (p.2003).

Sulprostone is given by intravenous infusion. A dose of 500 micrograms over 3 to 6 hours is used for cervical dilatation in the first trimester. For termination of pregnancy in the second trimester, or to empty the uterus, sulprostone is infused at a rate of 100 micrograms/hour for up to 10 hours; if necessary the infusion rate may be increased to up to 500 micrograms/hour, to a maximum total dose of 1.5 mg in 24 hours. If termination is unsuccessful the course may be repeated once, 12 to 24 hours after the end of the first infusion.

To control postpartum haemorrhage, an initial infusion of 100 micrograms/hour is given. This may be increased to 500 micrograms/hour if necessary to control bleeding, then reduced to a maintenance dose of 100 micrograms/hour. A total dose of 1.5 mg in 24 hours should not be exceeded.

Sulprostone has also been given extra-amniotically and locally into the cervix. It has also been given by the intramuscular route, but this is no longer recommended.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Nalador; ***Fin.:*** Nalador†; ***Fr.:*** Nalador; ***Ger.:*** Nalador; ***Hong Kong:*** Nalador; ***Hung.:*** Nalador†; ***Ital.:*** Nalador; ***Neth.:*** Nalador; ***Port.:*** Nalador; ***Switz.:*** Nalador; ***Thai.:*** Nalador.