

Use

Cisapride was once widely used to treat babies with gastro-oesophageal reflux, but withdrawn from sale in America and the UK in 2000 when it became clear that drug accumulation could cause serious arrhythmia.

Pharmacology

Cisapride is a substituted benzamide first patented in 1983 that increases gut motility without stimulating gastric secretion, probably by increasing the release of acetylcholine within the nerve plexus of the gut wall.

It is readily absorbed when taken by mouth, and undergoes rapid first pass metabolism in the liver and gut wall. The metabolites are then excreted in the urine and faeces (the adult plasma elimination half life being 7–10 hours). Bioavailability is approximately halved when the drug is given rectally. The commonest sign of an overdose in adults is abdominal cramp and intestinal hurry, but headache, dizziness, tachycardia and convulsions have also been reported. More seriously, drug accumulation can prolong the QT interval and cause a potentially dangerous arrhythmia (especially if there is hypokalaemia or hypomagnesaemia). Little is known about use in pregnancy, and high doses might be fetotoxic, but the baby is exposed to less than 1% of the maternal dose on a weight for weight basis during lactation.

Cisapride can increase the tone of the gastro-oesophageal sphincter, accelerate gastric emptying and mitigate some of the symptoms of gastro-oesophageal reflux but, despite widespread use, there is no controlled trial evidence that it is of any value in the management of neonatal reflux, and little evidence that it is of very much use in older children either. The drug came to be widely used in neonates in the mid 1990s before any pharmacokinetic studies were done in young children even though the manufacturer never sought a license to recommend use in children less than 12 years old. Indeed cisapride was being used in 80% of all UK neonatal units by 1998, and some units were giving it to 40% of their preterm babies. Use in the USA was equally widespread. Use then declined, almost as abruptly as it had risen, once controlled trials were done and an overview of those trials was published by the Cochrane Collaboration.

Cisapride, and erythromycin (q.v.), both normally cause a decrease in small and large bowel transit time, but neither seems to reduce the time it usually takes for most preterm babies to achieve full enteral feeding. That is not, however, to deny that further study might have shown that the cisapride could be useful in the management of babies with stubborn ileus, especially after surgery, had serious misuse not led to the product's abrupt withdrawal.

Drug interactions

Patients taking amiodarone, doxapram, erythromycin, spiramycin, or any of the systemic imidazole or triazole antifungal agents (such as fluconazole) should **never** be given cisapride: these all interfere with the metabolic inactivation of cisapride and can prolong the QT interval, causing ventricular arrhythmia.

Treatment

By mouth: Try 200 micrograms/kg once every 8–12 hours. Do not exceed 800 micrograms/kg a day.

Rectally: 1 mg/kg, given once every 12 hours, has been shown to be of benefit in the treatment of severe postoperative ileus, especially in babies with gastroschisis or malrotation.

Monitoring for toxicity

ECG measurement of the QT and RR intervals should be used to watch for potential overtreatment, especially in the preterm baby. Use lead II for consistency. The *corrected* QT interval ($QT_c = QT/\sqrt{RR}$) averaged over 5–10 beats should not exceed 0.45, or rise by more than 10% on treatment.

Supply

Cisapride monohydrate suspension contains the equivalent of 1 mg/ml of anhydrous cisapride, plus sucrose and parabens (100 ml costs £3.70). It can be given rectally when necessary. A more dilute suspension is stable for 7 days. The drug is no longer on general sale in the US, or in the UK.

References

See also the relevant Cochrane reviews ©

Lander A, Redkar R, Nicholls G, *et al.* Cisapride reduces neonatal postoperative ileus: a randomised placebo controlled trial. *Arch Dis Child* 1997;**77**:F119–22. [RCT]

Vandenplas Y, Belli DC, Benatar A, *et al.* The role of cisapride in the treatment of pediatric gastroesophageal reflux. *J Pediatr Gastroenterol Nutr* 1999;**28**:518–28. (A European Society of Pediatric Gastroenterology, Hepatology and Nutrition statement)

Lander A, Desai A. The risks and benefits of cisapride in premature neonates, infants and children. *Arch Dis Child* 1998;**79**:469–70.

Tréluyer J-M, Rey M, Sonnier M, *et al.* Evidence of impaired cisapride metabolism in neonates. *Br J Clin Pharmacol* 2001;**52**:419–25.

Semama DS, Bernardini S, Louf S, *et al.* Effects of cisapride on QTc interval in term neonates. *Arch Dis Child* 2001;**84**:F44-6

Bourke B, Drumm B. Cochrane's epitaph for cisapride in childhood gastro-oesophageal reflux. *Arch Dis Child* 2002;**86**:71-2.

Cools F, Benatar A, Bruneel E, *et al.* A comparison of the pharmacokinetics of two dosing regimens of cisapride and their effects on corrected QT interval in premature infants. *Eur J Clin Pharmacol* 2003;**59**:17-22.

Kophl M, Wuerdemann I, Clemen J, *et al.* Cisapride may improve feeding tolerance of preterm infants: a randomized placebo-controlled trial. *Biol Neonate* 2005;**88**:270–5. [RCT] (See also Commentary 276–7.)