

## Should cisapride have been “blacklisted”?

The recent decision by the Committee on the Safety of Medicine effectively to “blacklist” cisapride for use in neonates has led to considerable debate. The following is intended as a contribution to that debate.

### Indications for the use of cisapride

In mild gastro-oesophageal reflux disease (GORD) parental reassurance and dietary manipulation is the most appropriate course of action. In moderate or severe GORD, when medication is thought to be necessary, cisapride is considered to be the most appropriate drug.<sup>1</sup> Although it is recognised that cisapride does not consistently show an improvement in all the parameters measured, it consistently shows improvement in at least some of them, most of the time.<sup>2</sup> Lack of similar data for the efficacy of domperidone, metoclopramide, and erythromycin precludes their use as first line agents for GORD.<sup>3</sup> Published findings on the efficacy of cisapride in the treatment of motility related gastrointestinal disorders in premature infants is not entirely clear.<sup>2,3</sup> The impending studies of cisapride in the USA should clarify the issue. Cisapride is useful in several other conditions, such as chronic respiratory disease caused by GORD, oesophagitis, functional dyspepsia and postoperative ileus.<sup>2,3</sup>

### Risks associated with cisapride

Cisapride is known to prolong the QTc interval.<sup>3,5</sup> At therapeutic doses in children, however, there is no direct association between serum concentrations and QTc prolongation. Even in overdose situations the drug has a remarkable safety profile.<sup>3,6</sup>

Events which also predispose towards prolongation of the QTc interval must be avoided—that is, concurrent administration of macrolide antibiotics and azole antifungals, as well as hypokalaemia and hypomagnesaemia. In these situations there is a real risk that QTc prolongation may have an adverse clinical outcome such as torsade de pointes or a clinically significant degree of heart block.<sup>3</sup>

### Safety data

Cisapride has been used in 140 million patient treatments of which 18% (25.2 million) were in the age group 0–1 years<sup>7</sup> and 9% (12.6 million) in the age group 1–20 years. There was not a single report of a death in a previously healthy child taking an appropriate dose of cisapride.<sup>3</sup> The single most worrying feature of cisapride is its potential to prolong the QT interval. However, the fact that there is no agreed method for measuring the normal QTc interval, nor is there an agreed normal range in neonates and premature infants, makes any comment on QTc prolongation rather suspect. Although normal ranges in infants have been published,<sup>8</sup> those in premature infants are unknown. A review of published findings suggests that a QTc beyond 0.5 seconds is prolonged,<sup>3</sup> implying that cisapride should be withheld in these cases. All reported cases of the arrhythmia torsade de pointes were associated either with concomitant administration of a macrolide antibiotic, or a cisapride overdose, or both.<sup>3,5</sup>

From post-marketing experience it can be concluded that cisapride can be used safely at a maximal dose of 0.8 mg/kg/day. It is this dose that we feel should be recommended.

Safety data for fundoplication for intractable GORD showed the “accepted” risk of death was 0.07% in the group of “normal” children and 0.8% in the group of chil-

dren who were neurologically impaired.<sup>9</sup> The equivalent figures of risk of death from the use of cisapride in the normal population are significantly lower than that—1 in 250 000 being a conservative estimate.

### Pharmacokinetic data

In adults a dose of 10 mg four times a day gives a plasma concentration of 48–76 ng/ml.<sup>10</sup> (According to company data on a larger cohort of patients, plasma concentrations range from 14.1–192 ng/ml). In 66 premature infants a similar profile (7.1–170 ng/ml) was achieved with a dose of 0.2 mg/kg three to four times a day (unpublished observations). In spite of the immaturity of the drug metabolising capacity and the renal function, the plasma concentrations of cisapride in premature infants appeared very similar to those in term infants, children, and adults.<sup>11</sup>

In 41 infants ranging from 3–51 weeks a similar dose produced plasma concentrations not dissimilar to those of the premature infants, albeit with a lower mean: 42.6 (36.6) ng/ml (range 0–155 ng/ml).<sup>12</sup> Thus at the appropriate dose, plasma cisapride concentrations in premature and term infants, as well as in children, were within the therapeutic and safe range observed in adults. (Company data suggest that plasma concentrations in older children follow a similar pattern.)

### Precautions

All premature infants (36 weeks of gestation or less) should have an ECG before starting treatment with cisapride; this should be repeated three days later. This recommendation is based on the fact that premature infants treated with cisapride are thought to be specifically at risk of QTc prolongation. Furthermore, it is very important to ensure that electrolyte status is normal.

For term infants we do not feel it necessary to check an ECG before starting treatment with cisapride unless there are indications of congenital problems (prolonged QT).

Concomitant administration of macrolide antibiotics such as erythromycin, clarithromycin, and troleandomycin, as well as azole antifungal agents are contraindicated.

### Conclusions

Cisapride is safe, but can potentially be associated with serious side effects if used inappropriately. We suggest that the Committee on the Safety of Medicine re-evaluate their guidance on cisapride use in infants and children, as has already been suggested.<sup>12</sup> Trials shortly to begin in the USA should be used to finalise data on the drug’s efficacy and safety. An appropriate license for use in children should be obtained in the UK as soon as possible.

Cisapride should not be used in the dose range >0.8 mg/kg/day except under strict specialist guidance. Safety monitoring with an ECG 2 to 3 days after starting treatment should be mandatory. Cisapride should not be used in conjunction with macrolide antibiotics and azole antifungals. Hypokalaemia and hypomagnesaemia must be corrected before treatment is started and electrolytes should be checked during treatment. Further information is required about the excretion in breast milk of other pro-arrhythmic drugs such as antihistamines and antidepressants in case drugs given to breast feeding mothers may affect their infants. Premature infants should also have an ECG checked routinely before treatment with cisapride as well as three days after starting treatment.

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M MARKIEWICZ

Imperial College School of Medicine at Chelsea & Westminster Hospital,  
369 Falham Road,  
London SW10 9NH

Y VANDEN PLAS

AZ-VUB  
Department of Paediatrics,  
Laarbeeklaan 101,  
1090 Brussels,  
Belgium

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