Cisapride

Cochrane's epitaph for cisapride in childhood gastro-oesophageal reflux

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Cisapride in childhood gastro-oesophageal reflux

The coincidental appearance of the Cochrane Review Group's systematic appraisal of the utility of cisapride for gastro-oesophageal reflux (GOR) in children,[1] and the withdrawal of this drug in many countries[2] could not have been more appropriate. However, there exists a possibility that this serendipitous occurrence will undermine the impact of the Cochrane Review findings. Essentially, the outcome of the study was negative, with no benefits being shown for cisapride in improving the symptoms of GOR in children. In addition, the authors of the report were critical of the quality of data available, noting in particular evidence for substantial publication bias in favour of studies with a positive outcome. Both the immediate and wider implications of the findings of Augood and colleagues[1] are deserving of comment.

GOR in young children is a common occurrence. In the vast majority of children reflux is harmless, self limiting, and can be viewed as a physiological variant rather than a disease. This form of GOR is best managed with reassurance and ongoing clinical monitoring. In a minority of cases GOR is complicated by oesophagitis, respiratory symptoms, Sandifer syndrome or failure to thrive, and it is then referred to as GOR disease (GORD). Under such circumstances, medical and/or surgical intervention is usually necessary. The pathophysiology of GOR in children is still poorly understood. In particular the relation between GOR and GORD is far from clear.

The prokinetic agent cisapride induces a number of gastrointestinal motility changes and effects on sphincter function that are mediated through 5-HT_4 receptors and/or acetylcholine release.[3] Consequently, cisapride has been used in a variety of gastrointestinal disorders.[3] Following encouraging results from early studies, the use of this drug in children with GOR gained widespread acceptance. Guidelines published in 1993 cited cisapride as the first line medication for the management of GOR in children (both GOR and GORD).[4] Reports of cisapride toxicity causing sudden death in association with the ingestion of other drugs, notably antifungals, started to appear in the early 1990s. Nevertheless, this drug continued to be prescribed widely for children with GOR, a condition that would have resolved without treatment in the vast majority of cases. It is likely that many parents were not routinely informed of the potential side effects of the drug or the benign nature of the condition.

A randomised prospective multicentre Canadian trial,[5] published in 1999 cast doubt on the clinical efficacy of cisapride for the treatment of reflux related vomiting in young children. This trial was the largest and arguably the most comprehensive study of the use of cisapride to treat GOR. Subsequently, a study by Cohen and colleagues[6] that also failed to show a benefit from cisapride over placebo for relief of symptoms in children with uncomplicated GOR appeared to receive more widespread exposure in the paediatric literature.[7] Taken together with concerns regarding cardiovascular toxicity, these studies finally forced a reappraisal of the usefulness of this drug in paediatric GOR.

In 1999, the European and North American Societies of Paediatrics, Gastroenterology and Hepatology, and Nutrition published medical position papers on the role of cisapride in the treatment of paediatric GOR.[8 9] These reviews focused on the safety of cisapride. In addition, both statements were supportive of a role for cisapride in relieving childhood GOR, and while acknowledging the potential toxicity of cisapride, the conclusions of both groups overall were reassuring. For example, the European guideline stated that "cisapride (in comparison to other therapeutic intervention options) should be first choice because of its superior efficacy profile".[8]

Against this background the systematic review undertaken by the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group of cisapride treatment for GOR in children was a welcome undertaking. The authors of this report defined their primary outcomes as change of symptoms at the end of treatment, occurrence of adverse events, occurrence of clinical complications, and weight gain. The secondary endpoints were physiological measures of GOR or histological evidence of oesophagitis. They included only randomised controlled trials comparing cisapride with placebo or other non-surgical treatments. Eight trials met the inclusion criteria. The principal finding of the study was that cisapride did not improve symptoms of GOR compared with placebo. The odds ratio for symptoms being "the same or worse" versus "improved" at the end of treatment for cisapride and placebo was 0.34. The authors also point out from their funnel plot analysis that substantial publication bias favouring studies showing a positive effect of cisapride was evident in the literature.

Even the most ardent cisapride enthusiast will find little of comfort in this report. The single main positive finding of the study was that cisapride produces a statistically significantly reduction in the reflux index, a measure of the time pH is less than 4. However, other parameters of oesophageal pH monitoring did not reach significance and a beneficial effect of cisapride on oesophageal inflammation could not be shown. The cessation of cisapride marketing in the USA from July 2000[2] means that larger studies of the effectiveness of cisapride which might have addressed weaknesses and heterogeneity within the existing studies are no longer possible.

An important question that arises is why children frequently had cisapride prescribed for GOR. It is quite possible that the profusion of publications and practice guidelines/consensus statements suggesting a benefit from cisapride may have influenced the decisions of physicians to use this drug, rather than them considering the rationale for prescribing drugs to well babies. Similarly, if parents were routinely informed of the benign nature of GOR in most infants, its natural history to resolve, the lack of adequate studies of the efficacy of the drugs used to treat reflux, and their potential side effects, it is difficult to believe that many parents would have chosen drug therapy as an option.

The fall out from the demise of cisapride as a treatment for GOR reaffirms the necessity for well designed, appropriately conducted studies of drug efficacy as a basis for clinical practice. The undertaking of such trials poses particularly difficult challenges for paediatricians for a variety of reasons. Apart from the obvious ethical issues affecting research on minors, there is often reluctance by the pharmaceutical industry to conduct expensive trials on children because the financial incentive is less. Recent changes to FDA guidelines requiring pharmaceutical companies to undertake trials in children of new drugs before they are approved may result in an improvement in the quality of data on which paediatricians will base therapeutic decisions in future.

The cisapride controversy also underscores the importance of standards for those who develop and publish practice guidelines. As recently highlighted,[10] guidelines must be multidisciplinary, based on systematic review of published work, and should explicitly link recommendations to the supporting evidence. Evidence based guidelines developed by subspecialty groups should be able to provide evidence of their own validity so that potential users are in a position to assess their applicability. Medical journals need to encourage the introduction of minimum standards for the reporting of clinical practice guidelines. Furthermore, where symptoms are not harmful to the child and are likely to resolve spontaneously in time, the decision to use any medication, even if effective, needs to be carefully evaluated.

Arch Dis Child 2002;**86**:71–72

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