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The Role of Cisapride in the Treatment of Pediatric Gastroesophageal Reflux

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Article Outline

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Abstract

Background: Cisapride is a gastrointestinal prokinetic agent that is used worldwide in the treatment of gastrointestinal motility-related disorders in premature infants, full-term infants, and children. Efficacy data suggest that it is the most effective commercially available prokinetic drug.

Methods: Because of recent concerns about safety, a critical and in-depth analysis of all reported adverse events was performed and resulted in the conclusions and recommendations that follow.

Results: Cisapride should only be administered to patients in whom the use of prokinetics is justified according to current medical knowledge. If cisapride is given to pediatric patients who can be considered healthy except for their gastrointestinal motility disorder, and the maximum dose does not exceed 0.8 mg/kg per day in 3 to 4 administrations of 0.2 mg/kg (not exceeding 40 mg/d), no special safety procedures regarding potential cardiac adverse events are recommended. However, if cisapride is prescribed for pateints who are known to be or are suspected of being at increased risk for drug-associated increases in QTc interval, certain precautions are advisable. Such patients include those:(1) with a previous history of cardiac dysrhythmias, (2) receiving drugs known to inhibit the metabolism of cisapride and/or adversely affect ventricular repolarisation, (3) with immaturity and/or disease causing reduced cytochrome P450 3A4 activity, or (4) with electrolyte disturbances. In

such patients, ECG monitoring to quantitate the QTc interval should be used before initiation of therapy and after 3 days of treatment to ascertain whether a cisapride-induced cardiac adverse effect is present.

Conclusions: With rare exceptions, the total daily dose of cisapride should not exceed 0.8 mg/kg divided into 3 or 4 approximately equally spaced doses. If higher doses than this are given, the precautions above are advisable. In any patient in whom a prolonged QTc interval is found, the dose of cisapride should be reduced or the drug discontinued until the ECG normalizes. If the QTc interval returns to normal after withdrawal of cisapride, and the administration of cisapride is considered to be justified because of its efficacy and absence of alternative treatment options, cisapride can be restarted at half dose with control of the QTc interval. Unfortunately, at present, normal ranges of QTc interval in children are unknown. However, a critical analysis of the literature suggests that a duration of less than 450 milliseconds can be considered to be within the normal range and greater than 470 milliseconds as outside it.

The effective function of the gastrointestinal tract depends on a coordianted pattern of propulsive motor activity running from the esophagus to the colon. Disordered motor activity is associated with gastroesophageal reflux disease (GERD), delayed gastric emptying, dyspepsia, intestinal pseudo-obstruction, irritable bowel syndrome, and constipation. These disorders are prevalent among pediatric populations; for example, approximately 20% to 40% of all infants have increased regurgitation or other symptoms attributable to GERD [(1,2)].

Cisapride is a gastrointestinal prokinetic agent that acts as a postganglionic serotonin 5-HT_4 receptor agonist. It belongs to a subgroup of substitute benzamides and does not possess dopamine receptor-blocking or direct cholinergic receptor-stimulating properties [(3)]. The mechanism of action of cisapride might, for the most part, be explained by an enhancement of the physiologic release of acetylcholine at the level of the myenteric plexus.

Cisapride has been available for prescription since 1988 and can be obtained in more than 90 countries. To date, cisapride has been prescribed for more than 140 million patients, of whom 18% were in the age group younger than 1 year and 8% were among the 1- to 20-year age group (data provided by the company).

Side effects of cisapride treatment are reported to be rare, transient, and generally benign [4,5]. Recent reports of cardiac adverse events such as prolongation of the QTc interval and proarrhythmias [6-8] have raised the issue of its safety in premature, newborn, and infant populations, resulting in suggestions that cisapride may be contraindicated in these patients. Moreover, in a recent publication by Schwartz et al., a prolonged QTc interval was suggested to be associated with sudden infant death [9]. In Western societies, sudden infant death is ranked among the most frequent causes of infant death [10], thus causing speculation regarding potential adverse effects of the wide use of cisapride.

Back to Top | Article Outline

EFFICACY OF CISAPRIDE IN PEDIATRIC POPULATIONS

Recently, extensive overviews on the efficacy of cisapride in children have been published [3,4,11]. Studies indicate that cisapride may have a positive effect in the treatment of infant regurgitation, esophagitis, chronic respiratory disease, gastrointestinal manifestations of cystic fibrosis, functional dyspepsia, chronic idiopathic pseudo-obstruction, postoperative ileus, constipation, and fecal incontinence [4,11]. Cisapride has also been shown to be effective in reducing regurgitation and in improving gastric emptying in premature babies, and also in treating neonatal postoperative ileus [4,12,13].

Published placebo-controlled or comparative studies consistently indicate that cisapride reduces gastroesophageal reflux in various conditions associated with disordered gastrointestinal motility, at least for some of the end points of the studies

[4,11,14]. This contrasts with evidence for the efficacy of other prokinetic drugs such as metoclopramide or domperidone, which is weaker than for cisapride [5,15]. If prokinetic medication is indicated, we consider cisapride (in comparison to other therapeutic intervention options) to be the first choice because of its superior efficacy profiel [5]. Side effects are observed more frequently with prokinetics such as metoclopramide than with cisapride [5].

Back to Top | Article Outline

THE METABOLISM OF CISAPRIDE

The hepatic cytochrome P450 3A4 enzyme is quantitatively the most important cytochrome P450 (CYP) isoform, and is responsible for the metabolism of numerous drugs, including cisapride, cyclosporin, estradiol, lidocaine, nifedipine, and quinidine [16]. The cytochromes P450 are a superfamily of haem proteins and consist of the subfamilies CYP1A, CYP2B, CYP2C, CYP2D, and CYP3A [17]. The CYP3A subfamily comprises up to 40% of the total cytochrome P450 content present in both the adult human liver and small intestine [18], and consists of at least three isoforms in humans (i.e., CYP3A4, CYP3A5, and CYP3A7), capable of metabolizing numerous drugs and endogenous substrates [16,17,19,20]. As recently reviewed by Leeder and Kearns, CYP3A5 is polymorphically expressed (in contrast to CYP3A4, which is monomorphically expressed) and is present in approximately 25% of adult liver samples [21]. CYP3A7 is the fetal form of CYP3A, where it comprises 30% to 50% of total hepatic cytochrome P450 content in the fetus and is responsible for catalyzing the biotransformation of selected endogenous (e.g., DHEA) and exogenous (e.g., carbamazepine) substrates. Shortly after birth, a virtually complete shift in activity from CYP3A7 to CYP3A4 appears to occur [22], although CYP3A7 may be expressed to varying degrees in the adult liver.

The ontogeny of CYP3A4 has been studied both in vitro [22] and in vivo [23].

Recently, Lacroix et al. [22] demonstrated that the extent of catalytically active CYP3A4 present in the liver of infants at 1 month of postnatal age was approximately 30% of adult activity. Levels of CYP3A4 activity in infants appear to approach adult values by approximately 6 to 12 months of age and, based on pharmacokinetic studies of selected CYP3A4 substrates, may exceed adult values between 1 to 4 years of age [21]. It is important to note that CYP3A4 is also characterized by substantial intersubject variability [19,24,25] in both hepatic enzyme content (i.e., up to 10-fold) and constitutive activity (i.e., up to 20-fold [21]).

Previous reports of pharmacokinetic interactions between cisapride and compounds known to inhibit the activity of CYP3A4 (e.g., erythromycin, clarithromycin, azole antifungals, cimetidine, grapefruit juice) have provided indirect evidence that CYP3A4 is responsible for cisapride biotransformation. Very recently, Gorschall et al. provided in vitro evidence using human hepatic microsomes and heterologously expressed human cytochromes P450 that CYP3A4 is responsible for catalyzing the biotransformation of cisapride to its major metabolite, norcisapride [26]. Norcisapride is a compound that possesses approximately 15% of the prokinetic activity of cisapride, is extensively excreted by renal mechanisms, and has no intrinsic activity on myocardial conduction [27]. Furthermore, these investigators demonstrated that cisapride biotransformation to norcisapride or either 3-fluoro-4-hydroxy cisapride or 4-fluoro-2-hydroxy cisapride was not catalyzed by either CYP3A7 or CYP315 [27].

Based on the aforementioned information, it would be anticipated that the developmental pattern of cisapride biotransformation (and plasma clearance) would mirror the ontogeny of CYP3A4 and thereby, make the very youngest and most immature infants at greatest risk for accumulation of cisapride plasma concentrations during therapy. This anticipated "pattern" of pharmacokinetics has not, however, been observed in an initial study of 100

premature and term neonates who were given cisapride doses ranging from 0.8 to 1.2 mg/kg/d, which produced steady state plasma concentrations of the drug that were similar to those observed in adults taking therapeutic doses of the drug [28-30]. The bioavailability of orally administered cisapride is approximately 40% to 50%. Cisapride is 97.5% bound to plasma proteins, mainly to albumin [27]. Therefore, theoretically severe hypoalbuminemia may increase the free fraction of cisapride, which may increase the availability of the drug for metabolism and/or renal excretion [27]. However, it is important to note that the developmental pharmacokinetics of cisapride during the first year of life, which include its bioavailability and protein-binding characteristics, have not been completely characterized. Until such data are available, it appears prudent to use cisapride with caution and vigilance in sick, premature infants who, because of age or concomitant pathophysiology, may be at increased risk for drug-associated adverse effects produced on either a pharmacokinetic or pharmacodynamic basis.

Cisapride may also be subject to drug-food interaction. Grapefruit juice has been shown to increase the bioavailability of several drugs metabolized by CYP3A4 present in the gut wall [31]. Although this effect appears to be clinically irrelevant for cisapride [32] (but relevant for cyclosporine and FK506 [33]), it seems logical to recommend a different vitamin C source in infants taking cisapride or any other drug that is metabolized by cytochrome P450 3A4.

Back to Top | Article Outline

SAFETY OF CISAPRIDE

Adverse, side, or unwanted effects of cisapride are unusual, but may be both gastrointestinal and extraintestinal.

Back to Top | Article Outline

Noncardiac Adverse Events

The most commonly reported side effects, which are loose stools, diarrhea, borborygmi, and abdominal cramps, occur in approximately 2% of treated

patients [5,34]. These side effects are usually self-limiting and fit with the pharmacologic profile of the drug. According to the package insert, headache and dizziness may also occur, but with the same frequency as placebo. Isolated cases of anorexia and enuresis have also been reported as adverse events [35].

Several publications describe the occurrence of extrapyramidal reactions associated with cisapride treatment, both in children and adults [36,37]. Isolated, single case reports of hallucinations [38], paroxysmal dystonia [37], fine tremor [39], torticollis [40], and slurred speech [41] exist, although the case of torticollis occurred during coadministration with trimetubine, and in the case of slurred speech, cisapride was present in overdose. In infants under the age of 1 year, isolated cases of mild sedation, apathy, and atony are reported. Hyperprolactinemia has also been reported [42].

Studies on the use of cisapride in infants receiving anticonvulsive drugs have not suggested a direct cause-effect relationship between cisapride administration and seizures in epileptic patients [43]. The exacerbation of bronchospasm and asthma has been reported among pediatric populations, although this effect is rare [44,45].

Two publications describe the development of a pruritic rash during cisapride treatment [46,47]. One case occurred in a 2-month-old boy, in whom anal irritation and a rash on the buttocks appeared following the initiation of cisapride after therapeutic failure of cimetidine. However, these signs and symptoms may be attributed to the effect of cimetidine in altering the intestinal flora and hence causing acid stools [46]. The other case involved an adult patient with drug-induced hepatic disease after treatment with cisapride [47]. One report suggests that cisapride treatment may be associated with liver impairment in very low birth weight infants younger than 34 weeks of gestational age [48], but this has been contradicted by other reports [13,49,50]. Because premature infants have multiple risk factors for liver impairment, it seems very unlikely that cisapride is associated with an increased

risk of liver impairment.

Back to Top | Article Outline

Cardiac Side Effects

QTc Prolongation: Clinical Relevance

The QT interval represents the period from the beginning of depolarization (QRS complex, at the onset of the Q wave) to the end of repolarization (T wave) of the ventricles. The QT interval varies with the heart rate, lengthening at slower rates and shortening at faster rates [(51)]. It also varies with age, exercise, and the degree of autonomic tone. Prolongation of the QT interval may be either congenital or acquired. The congenital long QT syndrome is very rare, occurring in 1 in 10,000 to 1 in 15,000 individuals. Recent studies have identified 5 gene loci responsible for the congenital long QT syndrome. Examples include the Romano-Ward syndrome (autosomal dominant) and the Jervell-Lange-Nielsen syndrome (autosomal recessive) [(52-54)]. Villain et al., examining the natural history of these disorders, found that of 15 neonates with congenital prolonged QTc interval, four died (probably because of the prolonged QTc interval), and in five, the QTc interval returned to normal [(55)]. QTc remained prolonged but asymptomatic in the other six neonates [(55)]. In a series from Taiwan, a prolonged QTc syndrome (median 530, range 460-590) was considered responsible for sudden death (two children), seizures (six children), and syncope (three children) [(56)]. Their electrocardiogram (ECG) abnormalities included torsades de pointes (seven children), sinus bradycardia (four children), T-wave abnormalities (four children), monomorphic ventricular tachycardia (two children), and congenital complete atrioventricular block (one child) [(56)]. In a follow-up period of 0.5 to 6 years, six children were free of symptoms, one died of ventricular tachycardia, and two had recurrent syncope [(56)].

The QT interval corrected for heart rate, the QTc, is obtained by using Bazett's formula (dividing the QT interval by the square root of the R-R interval). However, when the heart rate is above

60 beats per minute, as is the case in infants, the Bazett formula may wrongly overestimate the duration of the QTc interval [57-59]. Therefore, other proposed methods of estimating the QTc are being evaluated [60,61]. Studies have shown that the duration of the QTc interval exhibits a high degree of intraindividual variability that makes a strict definition of normal and abnormal ranges difficult, especially in newborns and young infants. Moreover, the exact measurement of the QT interval can be difficult because the T wave often ends with a gentle slope or is followed by a poorly defined U wave. The 95th percentile of the QTc is 430 milliseconds in adult men and 450 milliseconds in women; values of more than 450 milliseconds and 470 milliseconds, respectively, are considered prolonged [62]. Normal ranges of the QTc in children have been published [51,63]. The mean value of corrected QT remains at about 400 milliseconds throughout all age groups. In 95% of the subjects the corrected QT is less than 450 milliseconds, and in 98% less than 480 milliseconds with the exception of the first day of life, when the values are slightly higher [51]. According to Schwartz et al. the normal QT interval is 451 milliseconds on day 4, 454 milliseconds at 2 months, 451 milliseconds at 4 months, and 442 milliseconds at 6 months of life (mean + 3 SD) [63].

Many drugs, both cardiac and noncardiac, influence cardiac repolarization and hence the QT interval. Cisapride does not appear to influence the depolarization phase even though the repolarization phase is modified (Belli DC, personal data). Most medications that cause QT prolongation have direct or indirect action on the cardiac potassium channels. Medications for noncardiac applications, such as cisapride, have direct concentration-dependent effects on the potassium channels in animal studies [64]. Recent experimental evidence suggests that cisapride, in studies examining its effects on single cardiac myocytes, blocks the delayed rectifier potassium channel (IKr), whereas in whole heart experiments, increased action potential durations and afterdepolarizations have been observed

[(65)].

Excessive QTc prolongation can induce arrhythmias, or be proarrhythmic and degenerate into the potentially fatal ventricular arrhythmia known as "torsades de pointes." This French word means turning or twisting around a point, reflecting the characteristics ECG feature of the tachycardia: a continuous undulation of the QRS axis around the isoelectric line. The arrhythmia is clinically significant because it is associated with a severe reduction in cardiac output, resulting in syncope or sudden death. It may also deteriorate into ventricular fibrillation.

No absolute value of QTc interval is predictive of or present in all episodes of torsades de pointes. The transition between clinically irrelevant or antiarrhythmic and proarrhythmic prolongations of the QTc interval is not well defined or understood. However, judged on the body of evidence, a prolongation of the QTc interval above 500 milliseconds is thought to carry undue risk for torsades de pointes, particularly when associated with slow heart rates. Additional risk factors thought to predispose to torsades de pointes include cardiac disease, congenital long QT syndrome, hypokalemia, hypomagnesemia, intracerebral abnormalities (especially hemorrhage), and concurrent administration of drugs known to prolong the QT interval. Aside from some cardiovascular pharmaceutical agents that are well recognized to be proarrhythmic in certain circumstances, there are a number of other therapeutic classes of compounds such as psychotropic agents, H1-antihistamines, and some classes of antibiotics, such as the macrolides, which have the potential to prolong the QT interval and induce torsades de pointes.

One could speculate that it is not the QT or QTc interval that represents a determinant risk factor for the torsades de pointes, but rather the QT dispersion. QT dispersion is a measure of the heterogenicity of the ventricular repolarization process [(66)]. Nonuniform recovery of ventricular excitability is considered essential in triggering malignant ventricular arrhythmias, because if some segments repolarize

earlier than others, the risk of inducing alternative circuits resulting in ventricular arrhythmias is higher. Among subjects who developed ventricular tachyarrhythmias such as torsades de pointes after taking certain pharmaceutical agents, no association with the degree of QT prolongation has been observed [67]. Moreover, drugs that induce a marked QT prolongation, such as amiodarone, do not necessarily precipitate torsades de pointes, in contrast with the modest increases of the QT interval seen with class Ia arrhythmics [67], drugs that are known to be associated with induction of torsades de pointes through QT dispersion. Amiodarone is associated with less QT dispersion [68,69].

Back to Top | Article Outline

Cisapride and the QTc Interval

The first reported cardiac effect of cisapride was sinus or supraventricular tachycardia [41,70,71]. However, epidemiologic data in adults and children have not confirmed an increased risk of serious ventricular arrhythmias associated with cisapride treatment. Prescription-event monitoring of arrhythmias and other cardiac rhythm disorders has demonstrated a lower incidence with cisapride treatment than that obtained for the large majority of other drugs frequently prescribed [72-74]. In the case of pediatric subjects, Cheron et al. did not find any effect of therapeutic doses of cisapride on the cardiac conduction in term neonates [75]. This findings was confirmed in a study enrolling 20 children and 10 premature infants, to whom cisapride 0.8 mg/kg/d was given. No prolongation of QTc interval was found after 1 month of treatment [76]. Zamora et al. report a QT prolongation of more than 450 milliseconds in 4 of 20 infants receiving cisapride [25].

Bernardini et al. showed in a prospective trial that cisapride administered at doses of 0.42 to 1.6 mg/kg/d induced a significant increase in QTc interval in a group on neonates at 25 to 41 weeks of gestation, although prolongation above 450 milliseconds (occurring in 7 of 49 neonates) remained clinically asymptomatic [6]. Furthermore, there was no correlation

between the length of the QTc before and after cisapride therapy, gestational age, and birth weight [6]. Six of the seven infants with a prolonged QTc had a gestational age under 33 weeks, and in no case were cardiac rhythm disturbances observed [6].

Lewin et al. [8] reported the case of a 2-month-old patient with a 2:1 atrioventricular conduction block and prolonged QTc of 510 milliseconds who was receiving cisapride at a dose of 1.2 mg/kg/k. Of note, he was born at a gestational age of weeks [8]. Evidence for the effects of dosage on the incidence of QTc prolongations is found in a report on seven neonates (one full term, two mature preterms, and four preterms) with prolonged QTc intervals (mean interval of 486 milliseconds) in whom the cisapride dose was 1.31 mg/kg/d [7]. Cisapride therapy was discontinued in five of the children and continued in two others at a reduced dose of 0.8 mg/kg/d. In all patients, the QTc interval returned to what the authors considered to be within normal, ranges of less than 440 milliseconds [7].

Several studies have examined the influence of risk factors on the development of QTc prolongation in children treated with cisapride. In the study of Khongphatthanayothin et al. [77], ECGs were performed in 30 children before and during cisapride treatment. A mean increase in the QTc of 15.5 ± 4.6 milliseconds was demonstrated. The same authors also performed ECGs in 101 patients receiving cisapride for more than 2 days, and found repolarization abnormalities (QTc prolongation above 440 milliseconds) in 13 patients (13%) [77]. However, risk factors that may have contributed to QTc prolongation were present in 11 of 13 patients (85%), including prematurity, heart disease, liver failure, and treatment with furosemide, erythromycin, or fluconazole. At least seven infants had a combination of different risk factors [77]. Hill et al. reported a prolonged QTc interval (> 450) in 11 of 35 children (31%) receiving cisapride (mean 0.67 mg/kg/d, range 0.30-1.68), although the mean QTc of the 35 children was below 430 [78]. Two children developed torsades de pointes; both were concomitantly treated with macrolides

[(78)]. In a recent prospective study involving 201 infants, aged 1 to 12 months, a statistically significant prolongation of the QTc in a subgroup of infants younger than 3 months of age on cisapride therapy was found (454 versus 421 milliseconds, $p < 0.01$), whereas in the older infants the QTc approximated 420 milliseconds, and the differences was not significant from controls [(79)]. The authors postulate that this may be due to a reduced CYP3A4 activity in infants under the age of 3 months, and/or a direct combined class III antiarrhythmic effect on the delayed potassium rectifier IKr channel [(22,79-82)]. Electrolyte disorders, such as hypokalemia, hypomagnesemia, and hypocalcemia may cause QTc prolongation, torsades de pointes, and ventricular tachycardia [(83-85)].

To date, available reports in infants and young children demonstrate that serious ventricular dysrhythmias have been reported uncommonly in patients receiving cisapride in the absence of any known or suspected risk factor that might predispose to adverse cardiac effects previously associated with the drug (file data, Janssen Research Foundation). Since the introduction of cisapride in Europe and North America, it is estimated that up to 140,000,000 courses of therapy have been prescribed over an approximately 12-year period. The approximate incidence of the congenital QT syndrome associated with genetic defects of the IKr channel function is approximately 1:10,000. If cisapride's potential to alter the action of the IKr potassium channel [(86)] would be assumed to have an additive effects between congenital long QT syndrome and the development of serious ventricular arrhythmias, thousands of cases of long QT syndrome should have been reported in the huge population treated with cisapride. This calculated incidence is clearly not substantiated.

Back to Top | Article Outline

CISAPRIDE OVERDOSE

Side effects are more commonly reported in patients receiving accidental overdose of cisapride [(81)], especially if cisapride is given in combination with inhibitors of CYP3A4 [(87)]. Nevertheless,

serious side effects are rare and have been only sporadically reported even in children with documented overdoses. In the cases of two children in whom a 10-fold dose of cisapride (2 mg/kg/dose) had been given [88,89], the ECG remained normal in one child, whereas in the other child a transient prolongation of the QTc to 497 was observed, returning to a baseline of 436 after 2 days [89]. In a 7-month-old child who was given a quadruple dose of cisapride (0.8 mg/kg/dose), intussusception was reported [90]. It was hypothesized that hyperperistalsis induced by the excessive cisapride dose might have caused the intussusception. The majority of children with a prolonged QTc received a total daily dose of 1.2 to 1.3 mg/kg of cisapride [7,8].

Back to Top | Article Outline

DRUG INTERACTIONS WITH CISAPRIDE

Interactions between cisapride and other drugs have been extensively analyzed [91]. Because cisapride enhances gastric emptying and accelerates gastrointestinal transit time, the absorption of many drugs is slightly greater when cisapride is coadministered [16]. For example, cisapride increases peak ethanol levels in fasting conditions [92]. One case report describes a 75-year-old man in whom the addition of cisapride increased the anticoagulation effect of warfarin [93]. In formal pharmacokinetic studies, cisapride has been shown to increase the absorption of the H2-receptor antagonists, cimetidine and ranitidine [91]. At therapeutic plasma concentrations, cisapride has neither inducing nor inhibitory effects on the hepatic cytochrome P450 system and it is therefore unlikely that cisapride will influence the pharmacokinetics of other drugs.

In vitro and in vivo studies indicate that a number of commonly used drugs can inhibit CYP3A4. Coadministration may therefore result in increased plasma cisapride levels. It is notable that the majority of the patients discussed in case reports that suggest a causal role for drug interactions in potentiating the side effects of cisapride have other risk

factors, such as metabolic disorders (e.g., renal failure, diabetes mellitus) [78]. For example, one patient was receiving 12 different medications [94], another patient had four concomitant medical conditions [87], and a third patient was receiving extracorporeal life support [95]. Initially, 12 patients were reported to the Food and Drug Administration's Adverse Drug Experience Reporting System [96]. The majority of these patients were chronically ill, had other potential risk factors for arrhythmias, or were receiving more than one drug [96].

The inhibition of the metabolism of cisapride by the azole antifungals miconazole, ketoconazole, and itraconazole, and by the antidepressive drug nefazodone, if given orally or parenterally, occurs with subtherapeutic plasma levels of these drugs, and is therefore clinically relevant. However, this is not valid for the topical or cutaneous application of the antifungals, because their absorption is very limited. Fluconazole is also known to inhibit the metabolism of cisapride. In vitro studies do suggest a clinically relevant interaction between cisapride and protease inhibitors such as ritonavir and indinavir, but not with saquinavir [97,98].

Most macrolide antibiotics inhibit CYP3A4 by the metabolic formation of a stable iron-metabolite complex [99,100]. Their inhibitory effect on cisapride metabolism is clinically relevant because of the formation of these stable complexes. Erythromycin, clarithromycin, and troleandromycin seem to be relatively potent inhibitors [87,101-103], whereas azithromycin does not appear to have a clinically significant effect [104].

A pharmacodynamic interaction affecting the central nervous system or a pharmacokinetic effect of cisapride on bromperidol was suggested in one case report [38]. A number of adverse reports concern patients who were concomitantly administered cisapride and nefazodone [105]. Furthermore, an interaction between fluoxetine and cisapride has been postulated but not demonstrated [87]. The role of cisapride in premature infants given doxapram, which itself causes atrioventricular

heart block, is unclear [106].

Cimetidine mildly inhibits CYP3A4 and may thereby cause an increase in cisapride plasma levels that is not considered to be clinically significant [107]. QT prolongation was also reported in an infant receiving a combination of ranitidine and cisapride [108], although this effect is probably not attributable to the slight increase in cisapride plasma levels seen with concomitant ranitidine administration [109-111]. Omeprazole and cisapride are very frequently coadministered, and this association appears to be safe [112]. Only two cases of torsades de pointes have been reported [113]; in one case the patient was taking several drugs, including omeprazole, cisapride, and clarithromycin [113].

Another interaction that may be relevant in infants is the coadministration of anticholinergic compounds. Diphemanil methylsulfate (Prantal) is a synthetic atropine derivate, which itself prolongs the QT interval [114], and which is frequently prescribed in cases of suspected "vagal hypertonia" in some countries (France). Because anticholinergic compounds may compromise the beneficial effects of cisapride, concomitant use of these drugs and cisapride is not appropriate.

Back to Top | Article Outline

SAFETY OF OTHER MEDICATIONS FOR GASTROESOPHAGEAL REFLUX DISEASE

It is beyond the scope of this article to examine extensively the side effects of other antireflux medications. Some of these side effects are briefly mentioned in other review articles [5,115] . It is clear that the side effects of bethanechol, domperidone, and metoclopramide are more frequently observed than those occurring with cisapride treatment [5,15]. Some side effects also occur with H2-receptor antagonists and proton pump inhibitors [116-118]. Bronchospasm and acute dystonic reactions have been reported with ranitidine [116,119], which is also associated with sinus node dysfunction, bradycardia, and increases in parasympatic tone [120,121]. Nizatidine

and famotidine may cause significant bradycardia and an increase of the pre-ejection period [122]. Cimetidine has also been reported to cause bradycardia in a small subgroup of patients [123], although in a study of 15 adult volunteers, it was concluded that cimetidine, famotidine, and ranitidine had no deleterious effect on exercise capacity or left ventricular systolic function [124]. Ranitidine has a positive inotropic effect [125].

Omeprazole is metabolized by CYP2C19, and to a lesser extent by CYP3A4 [16,126,127]. Proton pump inhibitors have been reported to cause hepatitis [128-130]. However, there is substantial evidence that omeprazole does not influence the metabolism of any other substrate by CYP3A4 [125]. Although pantoprazole has a theoretically lower drug-drug interaction potential than other proton pump inhibitors, based on in vitro studies [131], this has not been shown to be of clinical relevance. To date, omeprazole is the only proton pump inhibitor for which efficacy, dose-finding, and safety have been established in children [16,118].

Antireflux surgery is one of the other treatment options for GERD. However, in recent years, pediatric surgeons and others have documented high rates of failure and morbidity of surgery, and occasional mortality [132,133]. These problems occur especially in children with neurologic impairment, or repaired esophageal atresia, or chronic lung disease, and to a lesser degree in otherwise normal children. For example, in one study, compared with neurologically normal children, neurologically impaired children had more than twice the complication rate, three times the morbidity rate, and four times the reoperation rate of antireflux surgery, within a mean follow-up of only 1.6 year [134]. In another study [135], over 30% of neurologically impaired children had major complications or died within 30 days of surgery; within a mean follow-up of 3.5 years, 25% had documented operative failure, and overall 71% had return of one or more preoperative symptoms of GER. Although antireflux surgery does have a place in the management of GERD, i.e., reflux with a complication, increasingly there is recognition that in most cases

this should be performed only after failure of optimized medical management. The effect of prokinetics is limited in patients who have previously undergone surgery for esophageal atresia [(136)].

Back to Top | Article Outline

CONCLUSIONS

The evidence suggests that cisapride is a safe and efficacious agent in all age groups, including premature neonates [(137)]. It is the most effective prokinetic drug available on the market today, although not all data show a significant effect compared with placebo. Gastrointestinal side effects occur in about 2% of patients and are in line with the prokinetic activity of the drug (diarrhea, cramps, borborygmi). Nondigestive side effects such as rash, pruritus, urticaria, bronchospasm, extrapyramidal effects, headache, lightheadedness, dose-related increases in urinary frequency, hyperprolactinemia, and reversible liver function abnormalities are extremely rare. Cardiac side effects such as ventricular tachycardia, ventricular fibrillation, torsades de pointes caused by QTc prolongation, and QTc prolongation occur almost exclusively in rare patients with a known increased risk for arrhythmia. Most of the patients who have had cardiac side effects were receiving multiple medications and had pre-existing cardiac disease or risk factors for arrhythmias. The incidence of these side effects in large-scale surveillance studies has not exceeded that commonly reported in the general population.

Back to Top | Article Outline

Recommendations for the Use of Cisapride

According to age and indications, three major patient groups can be identified: (1) regurgitation and reflux in otherwise healthy infants, (2) children with overt GERD, and (3) premature infants, full-term infants, and children at increased risk for side effects. As with any medical treatment, the risk-benefit ratio should always be considered, as should

alternative treatment.

Back to Top | Article Outline

Regurgitation and Reflux in Otherwise Healthy Infants

During infancy, regurgitation and GERD are usually self-limiting conditions. Therefore, a step-wise approach, as proposed by an "Ad Hoc Working Group" [5], starting with parental reassurance and dietary treatment is recommended to avoid the unnecessary use of medication [5]. Cisapride therapy is therefore, in general, not initiated during the first week of life [5]. However, in some of these infants or in some instances, medication may be necessary. Because of the lack of any other drug with a comparable demonstrated efficacy and safety in this age group, cisapride is the recommended therapeutic choice [4,5], at a dose not exceeding 0.8 mg/kg/d. Higher doses have been used but should be avoided. Preventive screening for risk factors known to increase the likelihood of side effects in this patient group and at this dose is not recommended if cisapride is given in otherwise healthy infants, with a negative family history of sudden infant death syndrome or serious, life-threatening events in siblings at a young age.

Back to Top | Article Outline

Children with Overt Gastroesophageal Reflux Disease

Cisapride therapy in doses of 0.8 mg/kg/d up to the maximum recommended adult dose of 40 mg/d can be administered safely to children in whom the diagnosis of GERD with or without a complication has been established, provided that these patients do not present with one of the risk factors listed in Tables 1 and 2.

Table 1
Image Tools

Table 2
Image Tools

Back to Top | Article Outline

Premature Infants, Full-Term Infants, and Children at Increased

Risk for Side Effects from Cisapride Administration

The risk of adverse cardiac effects of cisapride are rare and can be most effectively minimised by restricting the coadministration of drugs that can inhibit the cytochrome P450 3A4 enzyme, which is the most important elimination route of cisapride. Recommendations for contraindications and precautions to the use of cisapride are summarized in Tables 1 and 2, respectively.

If cisapride is given concomitantly with other medications capable of inhibiting CYP3A4 activity, the risk-benefit ratio of the combination should be strictly evaluated, and alternative medication should be considered. Patients suspected of having one of these risk factors should be closely evaluated before and during cisapride administration. Measurement of serum electrolyte levels when appropriate and determination of the QTc before initiation of cisapride therapy and undertaking repeat investigations 3 days later are highly recommended in these at-risk patients. If the QTc exceeds 470 milliseconds, cisapride should be discontinued; if the QTc interval is between 450 and 470 milliseconds, the risk-benefit ratio should be carefully weighed. A QTc interval below 450 milliseconds does not conclusively predict an increased risk for cardiac arrhythmias.

The risk that medication may cause a significant interaction with cisapride because of inhibition of CYP3A4, potentially resulting in prolongation of the QT interval, is valid for all the drugs listed in Table 1, and this includes agents such as macrolides, antifungals, and tricyclic antidepressants. Saquinavir, cimetidine, and ranitidine might all cause a slight increase in cisapride plasma levels, but these are not considered to be clinically significant. Population screening for the congenital QT syndrome, occurring at the most in 1 in 10,000 individuals, may in the future be an option. However, this is an issue of national health care policy that, at present, appears socioeconomically unjustified because of the high variability in QTc interval duration and inaccuracy at higher heart

rates, and the uncertain natural evolution of the QTc interval.

With adequate precautionary measures, particularly regarding the identification of pertinent risk factors, the potential benefits of cisapride therapy in pediatric populations far outweigh the potential risks, and provide strong justification for its continued clinical use. Presently, several safety studies are under way that will provide further information to update and re-evaluate the guidelines for the administration of cisapride.

Back to Top | Article Outline

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Back to Top | Article Outline

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Back to Top | Article Outline