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*Review*

# Prokinetic agents: current aspects with focus on cisapride

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## SUMMARY

**Prokinetic agents are substances which, through various mechanisms, stimulate gastrointestinal motor activity, e.g. cholinergic agonists, macrolide antibiotics (such as erythromycin), dopamine receptors antagonists (metoclopramide) and substituted benzamides (domperidone and cisapride). Cisapride is the only prokinetic agent which increases the motility of both the small and large bowel. Since 1993 when it was introduced to the pharmaceutical market, cisapride has been widely used with remarkable success in a variety of gastrointestinal diseases such as: gastro-oesophageal reflux disease, gastric ulcer, chronic idiopathic constipation, irritable bowel syndrome, intestinal pseudo-obstruction. Its major side-effects are gastrointestinal (abdominal pain, diarrhoea) and cardiovascular. Although it has always been considered an effective and rather safe medication, the large number of reports referring to serious and even fatal adverse effects on the cardiovascular system (Q-T interval extension, torsades de pointes, ventricular fibrillation) have prompted manufacturing company to withdraw the drug from the U.S. market as of July 12, 2000, pending further research.**


**Key words:** prokinetic agents, gastrointestinal hypomotility, pharmacodynamics, pharmacokinetics, drug interactions, side-effects

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## 1. INTRODUCTION

Gastrointestinal hypomotility includes a number of clinical disorders very commonly faced by gastroenterologists, such as: Gastro-Oesophageal Reflux Disease (G.E.R.D), gastroparesis (idiopathic or diabetic), irritable bowel syndrome, chronic and acute colonic pseudo-obstruction (Ogilvie's syndrome), chronic idiopathic constipation. The medical management of patients with gastrointestinal hypomotility usually includes the administration of a prokinetic agent. Prokinetic agents are substances which, through various mechanisms, stimulate gastrointestinal motor activity, e.g. metoclopramide, domperidone and cisapride. The cholinergic agonist betanechol is known to improve postoperative ileus but its clinical use is very limited because of its side-effects. The motilin agonist erythromycin is used in the treatment of diabetic gastroparesis, colonic pseudo-obstruction and postoperative ileus. Naloxone, an opioid antagonist, gave hopeful results when administered to patients with irritable bowel syndrome, small intestinal pseudo-obstruction and constipation. Dopamine antagonists such as domperidone are very effective when administered to hypomotility disorders of the proximal gastrointestinal tract, such as gastro-oesophageal reflux disease and gastroparesis, but their pharmacodynamic effects on the colon are minimal. Metoclopramide (combines cholinergic agonist and dopamine antagonist action) is used in current therapeutics for upper gastrointestinal tract hypomotility disorders only. Finally, cisapride is unique among the other prokinetic agents, for it can be administered to hypomotility disorders of both the proximal and distal gastrointestinal tract with equally good results.

Cisapride is a substituted piperidinyl benzamide with a chemical structure that is related to the procainamidic derivative metoclopramide. It appears to exert its pharmacological actions in the gastrointestinal tract as a partial agonist of 5-HT serotonin receptors, thus stimulating the release of acetylcholine from the postsynaptic

nerve endings of the myenteric plexus in the lengthwise muscle of the gastrointestinal tract. The fact that these actions are demonstrated throughout the entire length of the gastrointestinal tract, from oesophagus to rectum, makes cisapride unique amongst the rest of the prokinetic agents.[1-5]

Since September 1993 when cisapride was introduced into the pharmaceutical market by Janssen-Cilag (Propulsid® in USA - Alimix® in Greece), it has been widely used by clinicians, principally because of its lack of antidopaminergic or cholinergic side-effects, which have restricted the extensive use of other prokinetic agents.

Numerous researchers have documented the efficacy of cisapride (greater than placebo and similar to or superior to other therapeutic agents) in the symptomatic relief of patients with gastric dysmotility. Todate it has been considered to be a significant agent for the medical management of gastro-oesophageal reflux disease (especially accompanied by oesophagitis), functional dyspepsia, gastroparesis and chronic idiopathic constipation.[2,6,7] Furthermore, it has been proven to be effective in the therapy of other pathological conditions, such as chronic intestinal pseudo-obstruction, irritable bowel syndrome and gastric ulcer. Overall, cisapride has exhibited a low incidence of undesirable side-effects but concern over the growing numbers of reports pertaining to serious adverse effects on the heart prompted a large scale study of this problem by its manufacturing company Janssen-Cilag, culminating in its pending withdrawal from the market.

The present article presents a brief report on prokinetic agents in general, followed by a more detailed review of the pharmacokinetics, clinical uses, side-effects and drug interactions of cisapride which account for its current status in the therapy of gastrointestinal hypomotility.

## 2. CLASSIFICATION OF PROKINETIC AGENTS

Prokinetic agents are classified into three categories, according to their mechanisms of action.[4,5,7-11]

A) **Agents that increase the release of stimulating neurotransmitters:** Cholinergic agonists, 5 $HT_4$ receptor agonists.

B) **Agents that inhibit the action of inhibitory neurotransmitters:** Antidopaminergic agents, opioid antagonists.

C) **Agents that act as agonists on gastrointestinal hormones receptors:** Agonists of motilin receptors (macrolide antibiotics), somatostatin agonists (octreotide).

### *2.1. Cholinergic agonists*

Cholinergic agonists act on muscarinic cholinergic $M_2$ type receptors which can be found throughout the length of the gastrointestinal tract. They act by increasing the muscular tone, the tension of contractions and the peristaltic activity of the bowel. Their prime representative is bethanehol, which acts principally on the upper section of the gastrointestinal system, increasing the pressure of the lower oesophageal sphincter and the strength of oesophageal peristaltic contractions. Clinical trials involving betanechol in the treatment of gastro-oesophageal reflux disease have demonstrated both symptomatic and endoscopic improvement in oesophagitis. It was also found that although betanechol has a minor effect on accelerating small bowel transit, it improves the symptoms of postoperative ileus. It must be emphasized that although betanechol could have a place in the therapeutic management of gastro-oesophageal reflux disease and postoperative ileus, currently its use is limited by the many side effects evoked by its cholinergic action.[1,8,12] Cholinergic agonists do not have a role in the treatment of intestinal pseudo-obstruction or chronic idiopathic constipation.

### *2.2. Macrolide antibiotics*

Macrolide antibiotics act as agonists of motilin receptors that can be found throughout the length of the gastrointestinal tract, from the oesophagus to the large bowel. Motilin is released by stimulation of the vagus and by the transit of food through the duodenum. It increases both the motility of the stomach (not after a meal) and the small bowel while simultaneously increasing gallbladder contractions. The main representative of the macrolide antibiotics is erythromycin. Erythromycin (after I.V. infusion) binds with motilin receptors on the gastrointestinal smooth muscle membranes, inhibiting motilin binding. In this way it causes powerful dose-dependent peristaltic contractions in the antrum, accelerating the gastric emptying of both solids and liquids in healthy volunteers and in patients with diabetic gastroparesis. Erythromycin also accelerates colonic transit and stool frequency. Therefore it can be used successfully in the treatment of gastrointestinal dysmotility due to diabetic gastroparesis, intestinal pseudo-obstruction, chronic idiopathic constipation and postoperative ileum.[1,8] On the contrary, erythromycin administration did not produce remarkable results in the treatment of gastro-oesopha-

geal reflux disease. Prolonged per os use causes a significant incidence of gastrointestinal side-effects (abdominal cramping, nausea, vomiting and diarrhea) and may result in bacterial or mycotic hyperplasia and allergic reactions (urticaria, cutaneus eruptions, anaphylaxis).[13] Also, erythromycin is known to inhibit the hepatic microsomal oxidative metabolism, through cytochrome P450, of many co-administered drugs, increasing their levels in plasma and thus the risk of toxicity (e.g. theophylline).

### *2.3. Opioid antagonists*

These act as antagonists of the μ-receptors of the gastrointestinal system, with naloxone as their prime representative. Naloxone antagonizes the action of morphine on the upper gastrointestinal tract (where it mainly increases smooth muscle tone in the oesophagus and accelerates gastric emptying) as well as on the lower gastrointestinal tract, where its action is more intense: it reduces the transit time in the large bowel without increasing the number of the enteric movements, it reduces the endolumen enteric pressure and increases the number of emptyings. Naloxone is used in the therapy of enteric pseudo-obstruction, chronic idiopathic constipation and irritable bowel syndrome.[14] It is considered to be relatively safe but it has the disadvantage of high cost.[15]

### *2.4. Somatostatin Agonists*

Somatostatin receptors are scattered throughout the gastrointestinal system, regulating the endocrine and exocrine secretion, the motility of the gastrointestinal tract and the visceral blood flow to a significant extent. The substance acetic octreotide exhibits a long duration of action. It increases the pressure of the lower oesophageal sphincter and the strength and the speed of oesophageal peristalsis and reduces the transit time of the small and large bowel up to the rectosigmoid. In clinical trials it has been used in patients with postoperative ileum (where it has been found to reduce the production of neurotransmiters e.g. substance P that inhibits enteric motility) and systemic sclerosis. Its probable use in other diseases, where reduction of enteric motility is present, is currently being studied in other clinical trials.[16,17]

### *2.5. Dopamine antagonists – Benzamides*

As has been previously mentioned, the prokinetic agents have been used successfully in the medical management of conditions resulting from dysfunction and/or lack of synchronism of gastrointestinal motility. Metoclopramide, a procainamidic derivative that does not show antiarrhythmic or topical anesthetic activity was primarily used as an antiemetic agent. Later it was found to be capable of stimulating the motility of the upper gastrointestinal tract. In larger dosages it exhibits neuroleptic action as well.[1,18] The pharmacodynamic potency of metoclopramide and its extrapyramidal unwanted effects are due to its antagonistic action on dopaminergic receptors in the Central Nervous System (C.N.S.). This action is not detected only on the central system but also on the peripheral nervous system. Dopamine receptors have been found throughout the length of the gastro-intestinal tract, especially in the stomach, pancreas, mesenteric artery and lower segment of the gastrointestinal tract. Inhibition of dopamine secretion increases the release of acetylcholine from the nerve endings of the myenteric plexus and increases the motility and the synchronism of the peristaltic waves in the gastrointestinal system. By means of this mechanism, metoclopramide increases the pressure of the lower oesophageal sphincter, increases the strength of contraction of the oesophagus and accelerates gastric emptying. In the small and large bowel metoclopramide stimulates motility and reduces transit time. Metoclopramide has been used mainly in the treatment of gastro-oesophageal reflux, diabetic gastroparesis or other forms of gastroparesis related to neuropathies, and in postoperative ileum as well. Its use in diseases related to large bowel dysmotility is limited (enteric pseudo-obstruction, constipation).

Side effects are reported in about 20% of patients who take metoclopramide, but are usually temporary, mild and reversible after termination of administration. They include: stress, somnolence, fatigue, increased mammary glands, galactorrhea and menstrual disorders. Extrapyramidal symptoms are developed in about 1-2% of patients but only after long term administration (usually exceeding 12 months).[19] Metoclopramide should not be administered to patients who take monoamine oxidase inhibitors, tricyclic antidepressants, sympathomimetic agents, phenothiazines or have a history of epilepsy or extrapyramidal syndromes.

Domperidone is a compound with powerful antagonistic action on $D_2$ peripheral dopamine receptors.[20] Stimulation of these receptors reduces the levels of cyclic A.M.P., in this way reducing the motility of the oesophagus, stomach and large bowel. Domperidone exhibits a powerful antiemetic action but unlike metoclopramide it does not penetrate the blood-brain barrier and thus does not act on the central nervous system even in very high dosages.[21,22]

Domperidone can be used for gastro-oesophageal reflux therapy, but it is more effective in gastroparesis

treatment, as it increases the duration of contractions at the level of the pyloric antrum and duodenum, increasing gastric emptying, and enlarges the diameter of the pyloric sphincter. It does not affect the motility of the large bowel and therefore is not used in the treatment of irritable bowel syndrome, enteric pseudo-obstruction or in chronic idiopathic constipation. Domperidone is administered to patients with Parkinson's disease in order to minimize the side-effects of L-Dopa, as it exerts a powerful antagonistic action on $D_2$ peripheral dopamine receptors.

Unwanted effects of domperidone include galactorrhea, menstrual disorders, dry mouth, headache, diarrhea and cutaneus eruptions. Domperidone should not be coadministered with monoamine oxidase inhibitors, because of the risk of hypertensive crisis.[1,23]

The efforts of researchers to synthesize a derivative without antagonistic properties against dopaminergic receptors[24] but with the prokinetic properties of domperidone and metoclopramide, resulted in the development of cisapride.[20]

## 3.0. CICAPRIDE

### *3.1. Chemical Structure*

Cisapride is a substituted piperidinyl benzamide which lacks the antidopaminergic or direct cholinergic effects characteristic of other benzamide derivatives.[1,2,3,8] Its efficacy and safety have been documented by clinical trials in more than 1700 patients with gastro-oesophageal reflux and other motility disorders of the gastrointestinal system.[25-28]

Cisapride's chemical structure resembles that of the procainamidic derivative metoclopramide. Its complete chemical name is: cis - 4 - amino - 5 - chloro - N - {1 - [3 - (4 - fluorophenoxy) propyl] - 3 - methoxy - 4 - piperidyl} - 2 - methoxy - benzamide monohydrate (R 51619).

### *3.2. Mechanism of action*

The first review article on cisapride (Mc Callum, Drugs, 1988) mentioned that the drug increases motility in the gastrointestinal tract by indirectly facilitating acetylcholine release from the myenteric plexus-longitudinal muscle of the bowel (mediated by postsynaptic nerve fibers).[3] As acetylcholine is the final chemical mediator of smooth muscle motility, the administration of atropine or other antimuscarinic agents is expected to antagonize the pharmacological actions of cisapride. This hypothesis was experimentally confirmed.[7]

Craig and Clarke in 1990 confirmed the observation of Dumuis in 1989 that cisapride is simultaneously an agonist and antagonist of serotonin receptors (5 - hydroxy - tryptamine).[2,29] Cisapride's pharmacological actions are due to its 5-$HT_4$ receptors agonist action.[30-33] It enhances the size of the rapid stimulating nicotinic postsynaptic potentials (Excitatory Post Synaptic Potentials - E.P.S.P.) that constitute the final part of the myoneural enteric microcircuit.[1] Cisapride also exerts an antagonistic action on 5-$HT_3$ receptors. Originally researchers considered that the prokinetic action of cisapride could be justified by this action. Later they came to the conclusion that the pharmacological properties of cisapride may result from its agonistic action on 5-$HT_4$ receptors, rather than 5-$HT_3$ receptor blockade. This conclusion was reinforced by the observation that other known antagonists of 5-$HT_3$ receptors had rather a small effect on motility and peristalsis throughout the length of gastrointestinal tract.[5,7]

Cisapride does not display antagonistic action on dopamine receptors: After single administration of 5 or 10 mg of cisapride 3 or 4 times daily during prolonged therapy, prolactin plasma levels remained normal in healthy volunteers as well as in patients.[34] Also, cisapride does not exhibit non-eclectic cholinomimetic action: After intravenous administration in healthy volunteers or after per os administration in patients with regressive ulcer, an increase of gastric fluid secretion was not observed.[34] Moreover, cisapride exhibits or shows antagonistic action on the 5-$HT_1$ receptors of the enteric neurons, but the prokinetic action of this drug is not related to this action.[35] Finally cisapride administration provokes increased levels of endorphin, motilin and pancreatic polypeptide, while it reduces the levels of substance P and cholecystokinin.[36,37]

## 4.0. PHARMACOLOGICAL PROPERTIES OF CISAPRIDE

As previously mentioned cisapride has a unique characteristic that distinguishes it from the rest of the prokinetic agents: Its ability to increase motility extends from the small bowel to the large bowel, but is more obvious in the oesophagus and stomach.[2,7]

### *4.1. Oesophagus*

Effects on Lower Oesophageal Sphincter Pressure (L.O.S.P.)

After per os or intravenous administration of cisapride, basal L.O.S.P. increases by about 20-50%. This

increase has been documented in patients with gastro-oesophageal reflux, in infants with idiopathic apnea and in patients with systematic sclerosis.[26,38] This effect of cisapride is statistically more powerful than that of placebo administration and antagonizes the action on the lower oesophageal sphincter evoked by atropine, neostigmine and theophylline but is similar or more powerful (and more prolonged) than the corresponding actions of metoclopramide.

*Effects on oesophageal motility*

In healthy adult volunteers, as well as in patients with gastro-oesophageal reflux, cisapride increases the amplitude of the oesophageal peristaltic contractions by about 20-50%.[3,39]

*Effects on oesophageal pH*

The measurement of oesophageal pH has shown that cisapride, in adults with reflux oesophagitis, maintained a pH of >4, reducing gastric acid reflux during both day and night.[2,3]

Studies in infants with gastro-oesophageal reflux showed that cisapride exhibits similar efficacy with famotidine and omeprazole and superior efficacy to metoclopramide.[38]

### *4.2. Effects on gastric emptying*

Gastric emptying of solids takes place in two major phases. Gastric accommodation consists of tonic contractions which forward the bolus of solid food towards the antrum. There, in the first phase, peristaltic movements cut the food into smaller pieces. Finally, during the second phase, the gastric contents empty gradually into the duodenum. Gastric emptying of liquids depends on tonic contractions of the stomach.

Gastric emptying is accelerated by cisapride to a statistically greater extent than the placebo in healthy adults and patients with gastroparesis.[3] Gastric emptying of both solid and liquid food is accelerated.[40] In all clinical studies cisapride has proven to be more effective than metoclopramide regarding accelerated gastric emptying, while it shows similar efficacy to domperidone. It must be pointed out that unlike metoclopramide and domperidone, cisapride continues to have the same powerful effect on gastric emptying after long term administration.[28]

### *4.3. Effects on pyloric antrum and duodenum motility*

Cisapride decreases the threshold, that is, the minimum required volume of gastric contents that sets off the motor function of the pyloric antrum, and also reinforces the motor function of the gastrointestinal system during digestion. An increase in the frequency as well as the amplitude of contractions of both the pyloric antrum and duodenum has been observed in healthy volunteers and patients with functional dyspepsia.[3,8] Also the motility of the pyloric antrum and duodenum increases after cisapride administration in patients with diabetic gastroparesis, a condition in which pyloric antrum hypomotility and absence of phase III is frequently observed.[41]

### *4.4. Effects on small and large bowel and on colonic transit time*

Comparisons with placebo have shown that the transit time through the small and large bowel is significantly reduced after administration of cisapride, in healthy adult volunteers as well as in patients with enteric motility disorders. Improvement of small bowel motility has been documented in patients with diabetic neuropathy of the autonomic nervous system, while large bowel electromyography of the descending colon and the sigmoid colon has shown an increase in the promotional peristaltic movements and a corresponding decrease in reflux motility. Transit time of mouth-to-caecum was significantly reduced after cisapride administration both in quadriplegic patients and in patients with gastro-oesophageal reflux who had been operated on for its therapy. A decrease in caecum and ascending colon transit time after administration of cisapride in patients with chronic idiopathic constipation and in patients who underwent cholecystectomy has been reported.[42]

Enck in 1989 and Wienbeck in 1992 suggested that enhanced defecation observed after the administration of cisapride in patients with chronic idiopathic constipation, could be partly attributed to the decrease in anal sphincter tone.[2] Berger in 1989 expressed the opinion that the observed increase in the number of emptyings is due to the direct kinetic effect of cisapride and not to an indirect action, which may include malabsorption of water, fats and cholic acids.[2]

### *4.5. Effects on Gallbladder*

The effect of cisapride on the gallbladder is not yet clear. The results of various studies have usually been contradictory: A number support the opinion that cisapride decreases contractions of the gallbladder, while others report that cisapride has the exact opposite action, increasing gallbladder contractions and thus minimizing the volume of bile.

### *4.6. Other effects*

After per os administration of cisapride 5-10 mg 3 times daily for up to 2 weeks, no prolactin secretion is observed in healthy male volunteers because of the lack of antidopaminergic activity of cisapride.[20] Also, after single administration of cisapride, plasma levels of human pancreatic polypeptide and cholecystokinin increased, but not after repeated cisapride administration.[2,3] Cisapride does not significantly influence glucose levels in normal volunteers. However, improved glycemic control has been reported in patients with unstable diabetes mellitus followed by delayed gastric emptying and this may result from an increase in gastric motility.[43] Launspach and Saffer in 1996 administered 10 mg of cisapride daily for 3 days to healthy volunteers. They observed that postprandially, the saliva volume and buffering ability increased relative to placebo to statistically significant extents.[44] In the fasted state no statistically significant increase was observed. The two researchers believe that cisapride increased saliva flux thus provoking an increase in saliva swallowing. Also, the increase in saliva buffering ability is caused by an increase in its content of bicarbonate ions ($HCO_3^-$) which in combination with increased swallowing contributes to neutralizing larger quantities of gastric acid in patients with gastro-oesophageal reflux. This action, in combination with increased oesophageal peristalsis, explains the efficacy of cisapride in these patients.

## 5.0. CISAPRIDE PHARMACOKINETICS

### *5.1. Per os absorption*

Almost all pharmacokinetic data relating to cisapride have been obtained from studies in adults. Very little is known about its pharmacokinetics in children, but great differences are not expected.[26]

The absorption of cisapride after per os administration is reduced in patients with decreased gastric emptying. Administration of cisapride 15 min before meals does not change the rate but increases the extent of its absorption. The bioavailability of cisapride increases about 30% under these circumstances compared to administration 2 hours before a meal.

Cisapride bioavailability also decreases in cases of gastric hypochlorhydria evoked by $H_2$ receptor antagonists and after administration of sodium bicarbonate ($NaHCO_3$).[2,3,45] The above effect of the $H_2$ receptor antagonists may be eliminated if cisapride is administered 15 min before meals.

Following per os administration of cisapride, peak plasma concentrations ($Cp_{max}$) are reached after 1 to 2 hours. $Cp_{max}$ values increase when cisapride is administered with food, but the majority of clinical researchers suggest administration 15-30 min before meals.[1-3] The absolute bioavailability (F) of cisapride is about 50%. $Cp_{max}$ and A.U.C. values following administration of various dosage regimens of the drug are provided in table 1.

The usual initial dose of cisapride is 10 mg 4 times daily, but can be increased to 20 mg 4 times daily in serious cases that do not respond to usual dosages. In pediatric patients the suggested dosage of cisapride suspension is 0,1-0,3 mg/kg every 6-8 hours.

Pharmacokinetic data following administration of 10 mg cisapride is very well documented.[2,45] The bioequivalence of two 10 mg tablets and one 20 mg tablet has also been proved.

Pharmacokinetic data found after per os administration of 20 mg cisapride (Honghui Zhou et.al, 1998), were as follows:[46] After a single dose- $T_{max}$ 1,5 h, $Cp_{max}$ 61 ng/ml. After two 20 mg doses the steady state was reached in 3 days, while $Cp_{min}$ remained stable after the second day of administration. Data analysis showed linear pharmacokinetics and the time to $Cp_{max}$ ($T_{max}$) was the same in both cases while:

- The $A.U.C._{0\text{-}12\ h}$ after 5 days of administration twice daily was 70% higher than that observed after single dose administration (average 646 ng/ml.h and 381 ng/ml.h respectively).
- The $Cp_{max}$ showed an increase of 43%, from 61 ng/ml after a single dose to 87 ng/ml after twice daily administration.
- Only the half-life of the drug did not correspond to the linear pharmacokinetic profile as it increased 35% (from 8,4 h to 11,4 h).

A comparison of pharmacokinetic data following administration of 20 mg of cisapride twice daily and 10

**Table 1.** $Cp_{max}$ and A.U.C. values obtained after administration of different doses of cisapride

| Dose of Cisapride | $Cp_{max}$ (μg/L) | A.U.C. (ng/ml.h) |
|---|---|---|
| 10 mg single dose | 45-65 | 325-673 |
| 10 mg 3 times daily | 60-80 | - |
| 10 mg 4 times daily | 53-99 | 796-1590 |

$Cp_{max}$: Maximum concentration (μg/ml)

A.U.C.: Area under the curve (ng/ml.h)

mg 4 times daily, is given in table 2.

At steady-state the concentrations of cisapride with both dosage regimens were similar. This was significant, as the administration of 20 mg twice daily instead of 10 mg four times daily improves patient compliance.[46]

### *5.2. Rectal Absorption*

The pharmacokinetics of cisapride after administration of a suppository of the drug (30 mg) was studied for the first time by Hedner and his associates in 1990[47]. The time to peak plasma concentration was 3,8 hours ($T_{max}$), indicating a slower absorption than after per os administration. The time required for completion of absorption was around 8 hours, while absolute bioavailability (F) was 20-25%.

### *5.3. Absorption after intramuscular administration*

After intramuscular administration the absorption of cisapride is complete and rapid. $T_{max}$ fluctuates between 10 to 30 min.[2,45]

### *5.4. Distribution of cisapride*

The apparent volume of distribution of cisapride ($V_d$) is 2,4 L/kg. Protein binding *in vitro* is 98%, with albumin being its main binding protein.[2,48]

Tissue distribution data in humans are not available. In rats, the highest concentrations of cisapride were found in the liver, stomach and wall of the small intestine.[48] Concentrations of cisapride in brain tissue were 2 to 3 times less than in plasma. In sheep, cisapride readily transferred across the placenta after intravenous administration. Sheep placenta is less permeable than human placenta, thus cisapride may be transferred across the human placenta with even greater ease and it is reasonable to assume that cisapride may be transferred across the maternal placenta to the fetus. This is a possibility which should be taken into consideration if cisapride administration during pregnancy is decided. The F.D.A. (Food and Drug Administration) has placed cisapride in the C category of drugs. Considering that only a few studies have been carried out, cisapride should be administered during pregnancy only when it is thought absolutely necessary.

**Table 2.** Pharmacokinetic data obtained following administration of different doses of cisapride

| Dosage | $Cp_{max\ ss}$ (ng/ml) | $A.U.C._{0-24}$ (ng/ml.h) |
|---|---|---|
| 10 mg 4 times daily | 76 | 646 |
| 20 mg twice daily | 87 | 1193 |

**$Cp_{max\ ss}$ :** Maximum steady-state concentration (ng/ml)

**$A.U.C._{0-24}$ :** Area under the curve between 0-24h after administration (ng/ml.h)

### *5.5. Metabolism*

After per os administration, cisapride is subjected to extensive first pass metabolism in the liver and intestinal wall.

Cisapride is metabolized extensively in the liver. Oxidative-N-dealkylation which yields the major metabolite norcisapride and aromatic hydroxylation are the two most important metabolic reactions and are catalysed by the microsomal enzyme cytochrome P450 system and more specifically by the subfamily P450 3A4.[48,49] Cisapride's metabolites exhibit very little pharmacological activity.[1,2,48] Naturally, the enzyme inhibitors of cytochrome P450 3A4 increase the levels of cisapride in the blood.

### *5.6. Excretion*

In 1988 Meuldermans reported that after administration of radiolabelled cisapride, 1-3% of the parent drug was excreted unchanged (non-metabolized) in urine and about 5% in faeces.[48]

Cisapride is excreted in small amounts, i.e. 0,1% of the initial dose, in human breast milk.

Cisapride's half-life in healthy volunteers following both single and multiple dose administration, ranges between 7-10 hours. Steady state levels are accomplished within 2-3 days. Cisapride half-life may be prolonged in patients with hepatic disease or in some elderly subjects, but not in patients with renal impairment.[45,48]

Finally, in 22 patients with severe renal failure undergoing haemodialysis, cisapride was not removed during dialysis.

## 6.0. INTERACTIONS OF CISAPRIDE WITH OTHER CO-ADMINISTERED DRUGS

Cisapride affects the pharmacokinetics of co-administered drugs in three ways: it increases their $Cp_{max}$ and decreases their $T_{max}$ and A.U.C.

These effects of cisapride, which are due mostly to its ability to increase the motility of the gastrointestinal tract and thus affect the rate of absorption of other drugs, have been documented for the following drugs:

acetylsalicylic acid, anticoagulants, diazepam, digoxin, cyclosporine, L-dopa, lithium, paracetamol, propranolol, ranitidine, cimetidine, tetracycline, anticoagulants per os. Monitoring blood levels of these drugs during co-administration with cisapride is advisable.

### *6.1. Interactions of cisapride with $H_2$ antagonists*

When cisapride is administered with $H_2$ antagonists, it increases their rate of absorption. The interaction of cisapride with ranitidine and cimetidine have been well documented. In a study carried out by Rowbotham et al in 1991 a statistically significant decrease in the $T_{max}$ and $A.U.C._{0\text{-}8hr}$ was reported following cisapride and ranitidine administration in healthy volunteers.[50] The $Cp_{max}$ values were unaffected. Co-administration of cisapride with cimetidine had the same results except for a statistically significant increase in $Cp_{max}$ as well. Cimetidine, due to its ability to increase the gastric pH values, provokes an increase in the $Cp_{max}$ and A.U.C. parameters of cisapride.[51]

### *6.2. Interactions of cisapride with antiarrhythmic drugs*

Co-administration with cisapride caused an increase in the absorption rate constant of disopyramide ($K_a$) while the A.U.C. and half-life of disopyramide remained stable. Cisapride also antagonized the anticholinergic actions of disopyramide in the gastrointestinal system.[51] In patients with atrial fibrillation who received cisapride, an increase in flecainide absorption was observed.[51]

### *6.3. Interaction with cyclosporin*

In 10 patients who had undergone a transplant operation, an increase in cyclosporin absorption was observed ($Cp_{max}$ and A.U.C. increased while $T_{max}$ decreased with simultaneous administration of cisapride). Close monitoring of cyclosporin levels in plasma is unconditionally recommended.[52]

### *6.4. Interaction with alcohol*

Cisapride administration increased the absorption rate of ethyl alcohol, leading to increased ethanol concentrations in plasma (ethanol $Cp_{max}$ increased 34% and $A.U.C._{0\text{-}4hr}$ increased 24%).[51]

### *6.5. Interaction with morphine*

Rowbotham in 1991 reported that cisapride increased the absorption of morphine from a controlled release formulation administered to 20 patients prior to surgery.[53] The $Cp_{max}$ of morphine increased but no statistically significant change was noted in the $T_{max}$. The increase in morphine plasma concentration had no clinical consequence, probably because of the low dose of morphine administered. With a larger dose there may have been an increase in its sedative action.

### *6.6. Interaction with anticholinergic drugs*

Anticholinergic drugs (such as atropine, dicyclomine, propantheline) antagonize the desirable pharmacological actions of cisapride in the gastrointestinal tract. Other drugs with similar antagonistic action are tricyclic antidepressants and opioids.[51]

### *6.7. Interaction with per os anticoagulants*

When cisapride is administered with anticoagulant agents, it increases their coagulation time, after 1 week of concomitant drug therapy. More specifically, in a study carried out by Daneshmend et al in 1990, cisapride (10 mg 4 times daily) was administered to 12 adults who received warfarin. To achieve the desired anticoagulant activity the administered dose of warfarin had to be increased from 44,5 to 49 mg, but the results were not statistically significant.[54] When the same dose of cisapride was administered to 24 healthy volunteers who were given a single dose of phenprocoumon on the fourth day of therapy, no change in the pharmacokinetic parameters of the anticoagulant was observed.[55] In contrast when cisapride (10 mg 3 times daily) was administered to 22 patients on asenocumarol an increase in coagulation time was noted. The mechanism of the interaction is unknown, but closer monitoring of prothrombin time is recommended during the coadministration of cisapride with asenocumarol.[56]

### *6.8. Interaction with paracetamol*

When 10 and 20 mg of cisapride were administered per os with 1500 mg of paracetamol in 12 healthy young volunteers in a fasted state, no change was observed in the pharmacokinetic parameters of paracetamol.[51,57] But when cisapride (10 mg) was administered I.M. to patients prior to surgery, it reversed the delayed absorption of paracetamol evoked by morphine. The average $Cp_{max}$ of paracetamol was increased from 14,6 to 22,6 mg/L, while its average $A.U.C._{0\text{-}90\ h}$ was also increased from 787 to 1151 mg/L·min.[58] This effect of intramuscular cisapride was more pronounced than that of intramuscular metoclopramide.[59]

Cisapride (30 and 60 mg) in suppository form did not reverse the delayed absorption of paracetamol evoked by morphine.[60]

### *6.9. Interaction with diazepam*

Cisapride (8 mg) was intravenously administered to 8 healthy volunteers who also received 10 mg of diazepam per os. The result was that the diazepam $Cp_{max}$ increased from 368,6 μg/L to 433,5 μg/L, an increase of 17,6%. Diazepam $t_{max}$ was reduced from 46 to 33 min, while $A.U.C._{0\text{-}1\ h}$ was increased to a statistically significant extent from 253 to 328 μg/L·h.[61]

### *6.10. Interaction with digoxin*

In one study in which cisapride was co-administered with digoxin, no effect on the pharmacokinetic parameters of digoxin was reported.[51] Other researchers have reported that the absorption of digoxin is reduced and have suggested precautions for their co-administration.[62]

### *6.11. Interaction with L-Dopa*

One of the most documented and interesting cases of cisapride interaction with another drug is undoubtedly that of L-dopa. This interaction is of special clinical importance, considering that through L-dopa cisapride could be used as an adjunctive medicine in Parkinson therapy, because of its ability to increase the efficacy of L-dopa. It is known that the acceleration of gastric emptying caused by antagonists of dopamine $D_2$ peripheral receptors, increases the percentage of L-dopa absorbed. Of those substituted benzamides (metoclopramide, clebopride, tiapride) with antagonistic action on dopamine $D_2$ receptors, only domperidone is of clinical use in Parkinson's disease, as it is the only one that does not block dopamine receptors in the central nervous system. As many patients with Parkinson disease suffer from chronic and severe constipation and therefore receive cisapride for symptomatic treatment, Diaz - Neira et al in 1994 decided to study the clinical consequences of the pharmacokinetic interaction between L-dopa and cisapride.[63] 14 patients (average age 65 years) on L-dopa and carbidopa for about 5,7 years who had an inadequate response to L-dopa treatment (no improvement of parkinsonian akathisia and "wearing off" syndrome) and who also suffered from chronic constipation (less than 3 bowel movements or defecations per week) took part in the study. The duration of the study was 2 weeks. During the second week cisapride was added to the treatment protocol in a dose of 10 mg 3 times daily, 15 min before meals.

The results were that cisapride increased the $Cp_{max}$ of L-dopa 37% and the average L-dopa levels in plasma 13%. Because of the acceleration in gastric emptying produced by cisapride, the $t_{max}$ was reduced from 160,7 to 94,3 min. Furthermore, due to great interindividual and intraindividual fluctuations in L-dopa levels, the plasma levels of 3-O-methyldopa were measured (a stable metabolite with long half-life), as these levels indirectly reflect L-dopa absorption, and these were also found to be increased. Increased L-dopa absorption increases patient response to therapy (i.e. it improves eye - hand synchronism as well as walking ability).

Cisapride also relieves the constipation that often troubles patients with Parkinson's disease. However it also increases unwanted effects e.g. it increases the frequency of inadvertent movements, nausea, vomiting, stimulation of the cardiovascular system. Finally, an interesting observation made by the researchers is that cisapride reduces the levels of levodopa in plasma 6 hours after the morning dose and 1 hour after the noon dose, thus increasing enteric L-dopa absorption.

### *6.12. Interactions with drugs that alter the pharmacokinetics of cisapride*

Cisapride co-administration with drugs which inhibit hepatic oxidative metabolism by 3A4 P450 enzymes should be avoided. These are:

- **Antibiotics:** Erythromycin per os or I.V., clarithromycin, troleandromycin (greater inhibitory action than the previous two macrolidic antibiotics).[51]
- **Antidepressants:** Nefazodone.
- **Antifungals:** Fluconazole I.V. or per os, itraconazole, ketoconazole per os, miconazole.
- **Protease inhibitors:** Indinavir, ritornavir.

To date no drug interaction with cisapride has been found to affect its absorption or binding to plasma proteins.[65]

## 7.0. CLINICAL USES OF CISAPRIDE

### *GENERAL*

Until today cisapride has held an important position in the therapy of many pathological conditions of the upper and lower gastrointestinal system. Its efficacy in gastro-oesophageal reflux disease, functional (non-ulcer) dyspepsia, gastroparesis due to diabetic neuropathy or postoperative compications and chronic idiopathic constipation is well documented.[2-4,7] In numerous clinical trials cisapride efficacy has been compared to placebo, other prokinetic agents (metoclopramide, domperidone), antagonists of $H_2$ receptors such as cimetidine and rani-

tidine and antacid formulations. More recently following extensive clinical trials more indications for cisapride therapy have been added, such as chronic enteric pseudo-obstruction, irritable bowel syndrome, gastric ulcer and reduced aspiration of gastric contents during operations with opioid analgesics (mainly morphine).

In the majority of the studies cisapride was generally administered in doses of 10-20 mg 3 times daily. In some cases remission was achieved even after low doses of cisapride e.g. 2,5 mg 3 times daily.

The main therapeutic indications of cisapride will be discussed in more detail below.

### *7.1. Gastro-oesophageal Reflux Disease (G.O.R.D.)*

Gastro-oesophageal reflux disease is a widespread disease affecting a large number of people.[45,66] Its prevalence in America is indicative of the size of the problem: 44% of American adults suffer from symptoms of the disease at least once a month, while 7-10% suffer once or more weekly with obvious consequences on their quality of life. Factors which contribute to the pathophysiology of G.O.R.D., alone or in combination, are: incompetent lower oesophageal sphincter, irritant effects of the refluxate (pH<2, presence of pepsin and conjugated bile salts), abnormal oesophageal clearance and delayed gastric emptying.

Cisapride treatment of gastro-oesophageal reflux is mainly recommended in mild cases, due to its ability to enhance lower oesophageal sphincter tone, to increase peristalsis of oesophageal smooth muscle and to accelerate gastric emptying. Statistically, 75% of patients with G.OR.D. respond positively to cisapride therapy, while 91% of those who respond positively report a good to excellent response.[2]

#### *Efficacy of cisapride in G.O.R.D.*

Cisapride's efficacy in the treatment of G.O.R.D. is similar to cimetidine, ranitidine and similar or superior to metoclopramide.[3] In pediatric patients cisapride produced symptomatic relief and mucosal healing similar to metoclopramide or alginate derivatives.[26,38] In severe cases of G.O.R.D., after discontinuation of the administered proton pump inhibitors, relapse of erosive esophagitis within 6 months is observed in 80% of the patients. Cisapride has been used in long term maintenance therapy in order to prevent relapse of oesophagitis, administered twice daily alone or in combination with an $H_2$ receptor antagonist, but a successful symptomatic remission is observed in less than 50% of cases.[67,68] Therefore, chronic maintenance therapy should include the administration of a proton pump inhibitor, e.g. omeprazole 20-40 mg daily or lansoprazole 15-30 mg daily. More recent cost-effectiveness studies suggest that in cases of uncomplicated G.O.R.D. with fewer than three symptomatic recurrences per year, it is less expensive to administer a proton pump inhibitor for 8-12 intermittent week courses instead of chronic maintenance therapy. It must be pointed out that approximately 10% of patients with moderate or severe G.O.R.D. do not respond to standard doses of proton pump inhibitors. In such cases, the addition of cisapride has been proven to be effective.

Cisapride has also been used in the treatment of more specific oesophageal reflux cases, such as those associated with cystic fibrosis (frequent occurrence in children and adults who suffer from the disease) and the reflux which accompanies chronic respiratory disease in children (for example chronic bronchopulmonary disease and premature neonatal apnea with sleep disorders).[26] In both cases cisapride was found to be more effective than placebo.

### *7.2. Functional Dyspepsia*

The term dyspepsia is very general and could be described by a number of symptoms such as:

- Epigastric discomfort or pain
- Feeling of fullness after meals
- Abdominal distension
- Early satiety
- Belching
- Regurgitation of gastric content
- Heartburn (specially with gastro-oesophageal reflux)

Dyspepsia is a very common clinical syndrome. It is estimated to affect about 25% of the adult population, but its actual prevalence is likely to be higher than estimated since a large number of patients with dyspeptic complaints do not seek medical attention.[69,70]

#### *Aetiology - Kinds of dyspepsia*

Dyspepsia is a multifactorial clinical syndrome. Its aetiology is varied· thus its classification is based mainly upon the coexisting symptomatology. Factors which may be responsible for the onset of symptoms of dyspepsia are described below.[71,72]

- ***Intolerance to drugs.*** Dyspeptic complaints appear after short or long term administration of various

drugs, such as aspirin or other non-steroidal anti-inflammatory drugs, corticosteroids, antibiotics (mainly erythromycin and metronidazole), digoxin, theophylline and iron salts. it is known from common experience that chronic alcohol uptake and the overuse of caffeine could lead to what people call «dyspepsia».

- ***Diseases of the gastrointestinal tract.*** 5-15% of patients with dyspepsia show signs of gastro-oesophageal reflux disease, while 15-25% suffer from active peptic ulcer. Rarely (1%) stomach cancer is diagnosed, but usually in patients over 45-years-of age. Other diseases of the gastrointestinal tract that probably lead to dyspepsia are gastroparesis (mainly in persons who suffer from diabetes mellitus), intolerance to lactose and other malabsorption syndromes and also parasitic infections, especially from *Giardia* and *Strongyloides* species. The role of chronic active gastritis due to helicobacter pylori infection in the pathogenesis of chronic dyspepsia remains debatable.[70,71]

- ***Other diseases and conditions.*** Diseases of the pancreas such as pancreatic carcinoma and chronic pancreatitis, diseases of bile canaliculi, diabetes mellitus, thyroid disease, ischemia of the coronary arteries, congestive heart failure, malignant neoplasm of ventral area, vascular diseases, pregnancy, uremia and pneumonic tuberculosis.

## *Functional (non-ulcer) dyspepsia*

This is the most common form of dyspepsia. It can be defined as a discomfort often described as indigestion, gaseousness, fullness or gnawing or burning pain localized to the upper abdomen or chest that has no specific cause on diagnostic evaluation: patients who suffer from the disease (approximately 2/3 of the total number of patients with dyspeptic complaints), do not have obvious organic or biochemical causes for their symptoms that can be determined by upper endoscopy or abdominal ultrasonography.[69,71,73] The aetiology of functional dyspepsia has not been fully clarified but the disease's pathophysiology includes a number of factors such as: increased visceral sensory sensitivity, intolerance to specific foods, changes in the familial environment and in the professional status, decreased gastric and intestinal motility (this finding has been reported for about 50% of the patients with functional dyspepsia). Some patients with non-ulcer dyspepsia complain of other symptoms which lead to irritable bowel syndrome, a fact that supports the opinion that functional dyspepsia is a generalized gastrointestinal motility disorder.

Functional dyspepsia is at least twice as frequent as peptic ulcer, since it affects 20-30% of the general population, but characteristically only 20-30% of the patients seek medical advice.[72-74] The patients' history, physical and laboratory examinations (including the test for Helicobacter pylori) and imaging techniques (endoscopy and ultrasound) are used for its accurate diagnosis.

## *Pharmaceutical treatment of functional dyspepsia*

More than half of patients show symptomatic relief following administration of placebo, a fact that is indicative of the important role psychological factors play in the pathophysiology of functional dyspepsia. Originally, $H_2$ inhibitors were prescribed for treatment but their efficacy is marginally greater than that of placebo and these agents demonstrate better results in the symptomatic treatment of dyspepsia related to gastro-oesophageal reflux disease.[74-76] Prokinetic agents such as cisapride 10 mg 3 times daily before meals and metoclopramide 10 mg 3-4 times daily, have documented efficacy, since an improvement in the symptoms of 60-80% of patients has been observed. It is characteristic that treatment with prokinetic agents does not produce a statistically significant delay in gastric emptying time. But cisapride therapy for 4-8 weeks has been reported to definitely reduce the frequency and severity of symptoms of functional dyspepsia. After the termination of cisapride administration patients are re-assessed for possible relapse of symptoms.[69]

## *Cisapride efficacy in the pharmaceutical treatment of functional dyspepsia*

*Comparisons with placebo*: 63-86% of patients receiving cisapride for treatment of functional dyspepsia reported good to excellent relief of symptoms compared with the correspond percentage after receiving placebo.[3] Many patients responded to 5 mg 3 times daily for 3-6 weeks, while others required 10 mg 3 times daily. Cisapride administered in a 10 mg dose 3 times daily for one month, relieved flatulence and epigastric discomfort in 71% of the patients vs. 20% receiving placebo.[77] De Nutte (1989) reported that cisapride therapy (5 mg 3 times daily) for up to one month, alleviated chronic epigastric pain (reducing or disappearing in 82% of the patients vs. 43% after receiving placebo) and the beneficial results remained for up to 2 weeks after the end of the clinical trials.[78] Furthermore, when cisapride was administered in a 0,6 mg/kg dose to pediatric patients for up to a month, the symptoms of functional dyspepsia improved in 75% of patients within two weeks compared with 50% receiving placebo.[79] In a dosage of 10 mg 3

times daily for up to 4 weeks, cisapride improved symptoms in 87% of patients with functional dyspepsia and gallbladder hypomotility after a meal (early satiety, nausea, epigastric pain, flatulence) compared with 48% on placebo.[80] Cisapride had the same efficacy when administered to patients with dyspepsia and hypomotility of the pyloric antrum and duodenum, i.e. 33% vs. 14% on placebo.[41]

Many researchers have emphasized that cisapride efficacy relative to placebo is higher after 2 weeks of treatment (47% vs. 30%) compared with 4 weeks of treatment (50% vs. 40%).[81-83] Cisapride improved more symptoms (epigastric pain, discomfort, nausea, retrosternal burn feeling, flatulence) than the placebo did.[81] Finally, cisapride administration of 10 mg 3 times daily for 2 weeks, relieved functional dyspepsia symptoms in 65% of patients non-respondent to former administration of metoclopramide or domperidone, compared with 22% on placebo.[84]

*Comparison with other drugs:* Cisapride demonstrates similar efficacy to that observed with other prokinetic agents, like metoclopramide and domperidone.[3] When cisapride was administered in a dose of 5 mg 3 times daily for up to 2 months, it showed similar efficacy to metoclopramide (10 mg 3 times daily) and ranitidine (150 mg twice daily). However, the two prokinetic agents relieved symptoms such as acid regurgitation, retrosternal burning and retrosternal pain to a greater extent.[85] In another clinical study, when cisapride was administered in a 5 mg dose 3 times daily it had the same efficacy as metoclopramide in a 10 mg dose 3 times daily (the total treatment duration was 1 month). But two weeks after discontinuation of treatment, only the patients who had received cisapride continued to have moderate symptoms. The researchers credited this to its prolonged duration of action.[86]

When cisapride was administered in a dose of 10 mg 3 times daily for 2 or 4 weeks, it demonstrated the same efficacy as the prokinetic agent clebopride (0,5 mg 3 times daily).[87] Koelz in 1993 published an article where he reported similar efficacy with cisapride and tripotassium dicitrate bismuthate (bismuth subcitrate) 120 mg 4 times daily.[69] Compared with 200 mg of cimetidine 4 times daily, 5 mg of cisapride administered for 1 month produced better symptomatic relief of non-ulcer dyspepsia, in particular in patients with gastrointestinal hypomotility.[88] In a study carried out by Lewin-van De Broek et al in 1999, statistical analysis of 263 patients with dyspepsia showed that cisapride was equally effective with omeprazole and the combination of an $H_2$ receptor antagonist and a prokinetic agent after 8 weeks of treatment.[89] Finally, co-administration of 2,5 mg of cisapride 3 times daily and 10 mg of domperidone 3 times daily for 1 week improved gastrointestinal symptoms (epigastric fullness, eructations) more than cisapride monotherapy.[90]

*Estimation of cisapride's efficacy in functional dyspepsia with clinical trials:* First of all, it must be pointed out that the results of the statistical analysis of data collected from studies involving patients with functional dyspepsia treated with cisapride or other medications, should be interpreted having in mind the factors that decrease the credibility of these clinical trials: there is often absence of homogeneity in patient groups, evaluation of the treatment results is carried out using different methods, the percentage of response to the placebo administration is high, the number of patients participating and the duration of the studies is relatively small. Generally the percentage of patients who respond to cisapride therapy fluctuates at about 80% in all types of dyspepsia (with gastrointestinal hypomotility, with gastro-oesophageal reflux, ulcer-like or functional dyspepsia), but Inoue observed that only ΄52% of patients with ulcer-like dyspepsia responded.[91,92]

Heyse in 1993 administered 5 or 10 mg of cisapride 3 times daily for 2-4 weeks to 600 patients.[93] The percentages of patients who responded to treatment were the following: 67% of patients who had not received any other treatment in the past, 72% of patients who had received prokinetic agents, 60% of patients who used antacid compounds, 48% of patients who had been administered $H_2$ receptor antagonists, 80% of patients with acute dyspepsia and 50% of patients with chronic dyspepsia. About 30% of patients who participated in the study had recurrent dyspeptic symptoms during the 6 month follow-up, but the majority (88%) responded to subsequent cisapride administration. Factors associated with symptom recurrence were: pretreatment duration, efficacy of current cisapride treatment.

Fehr in 1993 reported good to excellent responses in 75%-80% of 1071 patients with dyspeptic symptoms.[94] Among them, 405 had functional dyspepsia and were treated with 5 mg of cisapride 3 times daily for 28 days, while 666 had gastro-oesophageal reflux and received 10 mg of cisapride 3 times daily for the same period. Coadministered medicines did not affect the final outcome (antacids, b-blockers, antidepressants, calcium antagonists), neither did concomitant disease. But patients under nonsteroidal antiinflammatory drug (N.S.A.I.D.) treatment did not demonstrate significant symptom improvement.

*Dyspepsia associated with duodenogastric reflux*

Duodenogastric reflux is a result of a change in the motility of the pyloric antrum. As a result duodenal material flows back into the stomach and because of its bile salts and pancreatic enzymes damages the gastric mucosa, resulting in dyspeptic complaints. In patients with chronic antral gastritis and with proven duodenogastric bile reflux, cisapride administration (10 mg 4 times daily for up to 2 months) showed no statistically significant difference in frequency and severity of symptoms compared with placebo administration. However after 8 weeks of additional treatment, there was a great improvement in the patients who received cisapride and this was confirmed endoscopically.[2]

Finally, when cisapride was administered (10 mg 3 times daily) to patients with dyspeptic complaints due to duodenogastric reflux, a similar efficacy was observed to that of sucralfate in a dose of 2 mg twice daily.

### *7.3. Gastroparesis*

Gastroparesis is a motility disorder resulting in poor gastric emptying. The main symptoms of gastroparesis are epigastric pain, early satiety, nausea, vomiting, anorexia, flatulence and also reduced gastric emptying due to hypomotility of the pyloric antrum in the fed state, disordered synchronism of the pyloric antrum and duodenum. Cisapride's efficacy in gastroparesis seems to correspond with that of metoclopramide and domperidone. It accelerates gastric emptying and improves symptoms in patients with gastroparesis, in short as well as long term studies. Administered in a dose of 10 mg 3 times daily, for 3 to 6 weeks, the patients' main symptoms (epigastric pain, flatulence, prolonged digestion) were relieved to a greater extent with cisapride compared with placebo. The increase in gastric emptying is particularly obvious at the proximal area of the stomach.

Cisapride administration had positive results in cases of diabetic gastroparesis as well.[2,43] Improvement of the patients' symptoms (statistically more significant than placebo administration) was observed after 10 mg of cisapride administration 4 times daily after 4, 16 and 48 weeks of treatment.

The same results were obtained using cisapride in serious cases of idiopathic or diabetic gastroparesis, refractory to metoclopramide administration.[95]

Gastroparesis is frequently observed in patients who suffer from anorexia nervosa. These individuals suffer from epigastric fullness or discomfort after meals which is relieved by provoking vomit.[2,7] Cisapride administration of 10 mg per os 3 times daily or 4 mg slow intravenous injection increased the power of gastric contractions and the emptying of semisolid meals.

Cisapride may have a place in the therapeutic management of gastroparesis, but its safety and efficacy after long term treatment compared to placebo or other drugs has to be documented further.

### *7.4. Postoperative gastrointestinal atony*

A number of studies have examined the possible efficacy of cisapride in gastrointestinal atony observed after major abdominal surgery, cholecystectomy and gastrojejunostomy.[3] Many patients who undergo this kind of surgery demonstrate a plethora of unpleasant symptoms, such as postprandial abdominal pain, epigastric fullness, nausea and vomiting, probably due to delayed gastric emptying. Administration of 10 mg of cisapride 4 times daily for 3 weeks has helped improve these symptoms.

Cisapride administration has proved to be even more effective in the therapeutic treatment of postoperative paralytic ileum: Tollesson et al. administered cisapride intravenously for 3 days every 12 hours to 40 adult patients following cholecystectomy.[96] They ascertained that the recurrence of bowel motility was faster than in patients who had not received cisapride. The same result was obtained by Tack in 1995.[28]

Finally, many patients who undergo cholecystectomy, complain of mild colic-like pain, symptoms of dyspepsia and flatulence. The usual administered dose of cisapride (10 mg 3 times daily for 1 month) to these patients, improved symptomatology and facilitated biliary drainage but did not alleviate pain originating in the bile duct. More clinical trials are required to clarify its role in post-operative gastro-intestinal atony.

### *7.5. Chronic idiopathic constipation*

Chronic idiopathic (non-organic) constipation is the result of non synchronized peristaltic movements and transit through the large bowel or disorders in the defecation mechanism at the anorectal level. The above mentioned mechanism dominates constipation in children.[97] Pharmacodynamic studies showed that cisapride restored colonic propulsive activity (through sequential, absolutely synchronized peristaltic movements) and accelerated colonic transit in the caecum and ascending colon. Anorectal manometric studies showed that of the prokinetic agents used today, only cisapride influences the parameters that are used by scientists to describe rectum motility. These parameters include: the recto-anal inhibitory reflex threshold (defined as the distension volume

for which an initial transient sensation is reported) and the conscious rectal sensitivity threshold (defined as the distension volume for which a minimal relaxation of 10 cm $H_2O$ occurs). It is also probable that cisapride increases the aqueous content of stools in the rectum, facilitating defecation in this way.

Contrary to the rest of the prokinetic agents, cisapride has proved to be effective in the therapeutic treatment of functional constipation, when usual first-line therapy fails. When cisapride is administered, it also reduces the use of purgative compounds. Cisapride is ineffective in cases of constipation due to neuropathic disorder of colonic motility or in cases with colonic inertia.[98]

Cisapride administration of 5-10 mg 3 times daily or 20 mg twice daily for up to 12 weeks, increased stool frequency and reduced the use of purgatives in adult patients to a greater extent than placebo administration.[3] Cisapride demonstrated the same efficacy when it was administered to pediatric patients in a dose of 0,2 mg/kg 3 times daily, increasing stool frequency and reducing the total bowel transit time.

For the treatment of constipation in adults with severe spinal cord injury studies in paraplegic patients showed satisfactory efficacy. In constipation after prolonged hospital stay, cisapride administration of 10 mg 4 times daily proved to be as effective as bisacodyl administration (5 mg once daily).

In conclusion, although cisapride has documented efficacy in cases of chronic idiopathic constipation, its efficacy compared with other pharmaceutical agents used in constipation treatment and also following long term therapy must be further evaluated.

### *7.6. Chronic intestinal pseudo-obstruction*

Chronic intestinal pseudo-obstruction is the most severe disorder of enteric motility. Symptoms and signs of intestinal obstruction are observed without visual indication of mechanical obstruction. The response to treatment with prokinetic agents is frequently disappointing.

Cisapride has given hopeful results in clinical trials, particularly in mild or moderate disease characterized by absence of autonomic Central Nervous System dysfunction, presence of migrating motor complexes in manometric studies, absence of extensive enteric distention in radiographic studies and reduced duodenal motility after meals.

Patients with the neurogenous type of pseudo-obstruction are more likely to respond to treatment with cisapride than those who suffer from the myogenous type.[7] Because intestinal pseudo-obstruction is a chronic, progressively developing disease, cisapride administration must be extended for long periods. The reduced absorption of the medication in cases of severe gastric and jejunal stasis is a common clinical problem. Rectal administration is a possible solution, since there is no available stable form for I.V. administration of cisapride.

Cisapride efficacy in the treatment of pseudo-obstruction in adults, children and premature neonates is well documented, while in very recent studies, it has given hopeful results in patients with Ogilvie syndrome (acute colonic pseudo-obstruction).[99]

### *7.7. Irritable bowel syndrome*

This syndrome, due to non-synchronized motility of the small bowel, results in constipation, abdominal distension, pain, flatulence, defecation urge and diarrhoea. Cisapride increases small bowel motility and reduces its transit time and therefore may be useful in the treatment of symptoms of irritable bowel syndrome.

Van Outryve in 1991 administered 5 mg of cisapride, 3 times daily for a total duration of 3 months and observed that it produced an increase in stool frequency and a reduction in the intensity and frequency of abdominal pain and distension compared to placebo, when the dominant clinical manifestation of the irritable bowel syndrome was constipation[2]. When the main manifestation was flatulence, 10 mg of cisapride 3 times daily for a month, improved the symptom to a greater extent than the placebo.

### *7.8. Other indications*

*Gastric ulcer: In* clinical trials cisapride has been shown to be effective in healing gastric ulcer and may prevent duodenal ulcer relapse after healing. The reduced emptying capacity of the stomach is known to be important in the pathogenesis of gastric ulcer. Thus, the ability of cisapride to improve gastrointestinal motility and to facilitate gastric emptying is likely to contribute to its efficacy in treating gastric ulcer.

Cisapride administration, in a 10 mg dose 3 times daily for 2 months, demonstrated similar efficacy to 150 mg of ranitidine administered twice daily for gastric ulcer treatment. Ulcer healing was proven endoscopically in both cases and it was similar[2]. Both drugs caused rapid and effective alleviation of symptoms such as: epigastric pressure, flatulence, nausea. In another study, 20 mg of cisapride administered as monotherapy twice daily demonstrated similar healing rates of gastric ulcer relative to

150 mg of ranitidine (twice daily) and relative to a combination of both drugs.[100]

Finally, cisapride (10 mg twice daily for 1 year) is more effective than placebo in the maintenance therapy of duodenal ulcer. In order to establish gastric ulcer as another indication for cisapride administration, more clinical trials are required.

*Cystic fibrosis:* When cisapride was administered in a pilot study to 17 patients with cystic fibrosis for a duration of 6 months, it demonstrated greater efficacy than the placebo in reducing the gastrointestinal complaints which accompany cystic fibrosis i.e. flatulence, epigastric fullness, nausea. But, it did not improve other parameters such as the patients food consumption, respiratory function, quantity and synthesis of stools and loss of fat with the stools.[101]

## 8.0. ADVERSE EFFECTS OF CISAPRIDE

### *8.1. Adverse effects from the gastrointestinal system*

These constitute the most usual adverse effects of cisapride. Statistical analysis showed that the percentages of patients who demonstrated adverse effects from the gastrointestinal system after receiving cisapride (1024 patients) or placebo (686 patients) were the following (Table 3).

In other clinical trials (double-blind studies) diarrhoea was reported to be the most frequent adverse effect, appearing in about 4% of the patients who received cisapride and 3% of the patients after receiving placebo. The diarrhoea was not dose related.[89,91,92]

Finally the frequency of side effects is similar to that of cimetidine and ranitidine and does not seem to differ following long or short term treatment (Blum, 1993).[67]

**Table 3.** % percentage of gastrointestinal side-effects after cisapride or placebo administration

| Adverse effects | Cisapride percentage % (1024 patients) | Placebo percentage % (686 patients) |
|---|---|---|
| Diarrhoea | 14,2 | 10,3 |
| Abdominal pain | 10,2 | 7,7 |
| Nausea | 7,6 | 7,6 |
| Constipation | 6,7 | 3,4 |
| Abdominal distension | 3,5 | 3,1 |
| Dyspepsia | 2,7 | 1 |

### *8.2. Adverse effects from the Central Nervous System*

Central nervous system adverse effects following administration of cisapride are less frequent i.e. only 1,5% compared with 15,2% after receiving metoclopramide.[2] The most frequent are somnolence and fatigue. Rarely confusion, depression, stress, nervousness, headache, paraesthesia and even suicidal tendencies have been reported.

### *8.3. Adverse effects from the urinary tract*

Incontinence and increased frequency of urination has been reported by adults on cisapride. These effects are thought to be due to increased cholinergic activity in the bladder. Rarely, an increased frequency in urinary tract infections has been reported following cisapride administration.[102]

### *8.4. Adverse effects from the respiratory tract*

They are rare and include: Rhinitis, nasosinusitis, increased frequency of infections in the upper respiratory tract, pharyngitis and cough. In one instance a patient, who suffered from asthma and received a single dose of 10 mg of cisapride, felt a tightening in the chest, stridor and experienced a reduction of the maximum expiratory flux.[103]

### *8.5. Adverse effects from the cardiovascular system*

The adverse effects of cisapride on the cardiovascular system have led to a great deal of controversy within the scientific community in the last ten years. From July 1993, when cisapride was introduced in the U.S. pharmaceutical market, through December 1999, 341 cases of cardiac arrhythmias such as ventricular tachycardia, ventricular fibrillation, torsades de pointes and Q-T prolongation in patients who had undergone cisapride treatment were reported. Of these 341 incidents, 80 were fatal. Until very recently, the side-effects of cisapride from the cardiovascular system were attributed exclusively to co-administration of other medications which are known to increase cisapride plasma levels by inhibiting its hepatic metabolism or to predisposing (risk) factors of the patients, e.g. cardiopulmonary disease, severe renal impairment and electrolyte disorders. The view that cisapride would not have cardiovascular side-effects if the risk factors mentioned above could be detected in any patient prior to cisapride treatment and handled accordingly, has been generally accepted by the medical community until now. However, recent evaluation of these data demonstrated that in approximately 85% of cis-

apride cardiovascular side-effects the risk factors mentioned above were present, while the remaining 15% could not be attributed to any other factor but the drug itself. In the past few years, the Food and Drug Administration (F.D.A.) in collaboration with Janssen-Cilag pharmaceutical company, organized public advisory committee meetings in order to evaluate the accumulated data regarding cisapride's cardiac side-effects. After each meeting, both the F.D.A. and the company issued guidelines, via talk papers or "letters to the healthcare providers", in order to minimize the incidence of cardiac side-effects and the risk after cisapride administration. Although cisapride was widely considered a safe and effective medication, Janssen-Cilag very recently and rather unexpectedly decided that "continued general U.S. prescription access to the drug poses unacceptable risks" because the incidence of cardiac events not only could not be decreased, despite continious medical briefing and education, but also, a significant proportion of these events remained unexplained (could not be attributed to any known risk factor or co-medication). An F.D.A. talk paper issued on March 23, 2000 announced the decision of the company to stop marketing cisapride in the United States. On April 12, 2000 Janssen-Cilag announced the termination of cisapride marketing in the U.S. pharmaceutical market as of July 14, 2000 and its distribution only through an investigational limited access program and strictly for the following indications: *Gastro-Oesophageal Reflux Disease (G.O.R.D.), gastroparesis, pseudo-obstruction and severe chronic constipation in adults; Refractory G.O.R.D. associated with failure to thrive, asthma, bradycardia and apnea to pediatric patients; Feeding intolerance to neonates.* Although cardiac side-effects provoked by cisapride have been reported since 1989, the recent dramatic events were rather unexpected and make a brief historical review of this matter quite interesting and useful:

Between 1989 and 1991, based on data accumulated by the World Health Organization (W.H.O.), 7 patients demonstrated disorders in heart rhythm following cisapride administration.[104] More specifically, 4 complained of beats, 1 of tachycardia, 1 of hypertension and 1 of ectopic beats.

In a study carried out by Inman and Kubota in 1992, in which more than 13.000 patients were evaluated after taking cisapride, the frequency of adverse effects from the cardiovascular system was found to be 0,8 per 1000 patients, a much smaller frequency than that reported in previous studies i.e. 2,5 per 1000.[105]

The most probable mechanism of cisapride cardiac effects from a pharmacological point of view is reported to be its partial agonist activity at the 5-$HT_4$ receptors.[105] Stimulation of these receptors provokes an increase in cyclic A.M.P. levels, resulting in positive chronotropic and inotropic actions on the myocardium. This theory appears to be more acceptable to the scientific community than the previous one proposed by Olsson and Edwards,[104] who proposed that the possible arrhythmogenic effect of cisapride on the myocardium was due to a procainamide type of action (due to similarities in their chemical structures).

Later studies increased the concern for cisapride effects on the heart: from September 1993 to April 1996, 36 patients who had received cisapride for different length of time, among them 7 children and 1 teenager, demonstrated torsades de pointes (polymorphic ventricular tachycardia, directly life-threatening, in which the morphology of the QRS complex varies) while another 23 demonstrated extension of the Q-T period; 4 of these patients died, while 16 needed cardiorespiratory resuscitation after heart failure.[106]

On June 29th 1998, the Janssen-Cilag pharmaceutical company in the F.D.A. Medical Products Reporting Program web page (Medwatch), specifically mentioned that cisapride can provoke serious cardiac arrhythmias, such as: Ventricular tachycardia, ventricular fibrillation, torsades de pointes and extension of the Q-T period. The above abnormalities in many patients are due to simultaneous administration of other drugs, causing inhibition of the cytochrome P450 3A4 enzymes responsible for the hepatic metabolism of cisapride. These are: antibiotics such as erythromycin, clarithromycin, troleandromycin, antidepressants such as nefazodone, antifungals such as fluconazole I.V. or per os, itraconazole and ketoconazole per os, and also protease inhibitors (anti- H.I.V. drugs) such as indinavir and ritornavir. Cisapride administration is strictly contraindicated in patients receiving the above mentioned drugs.

Other patients who exhibited cardiac adverse effects following cisapride administration were not taking the contraindicated drugs, but suffered from other conditions or disorders that are considered to be predisposing factors for the appearance of arrhythmias. These were:

- *A history of extended Q - T intervals on the electrocardiograms.*
- *Renal impairment (in 25% of cases).*
- *A history of ventricular arrhythmia and ischemic myocardiopathy in 39% of the patients.*

- *Congestive heart failure.*
- *Electrolyte disorders (hypokalemia, hypomagnesemia) in 13% of cases.*
- *Respiratory insufficiency.*
- *The administration of other drugs, which increase the Q - T interval and predispose to arrhythmias (12%), such as:* category IA (quinidine, procainamide) and III (sotalol, amiodarone) antiarrhythmics, tricyclic (amitriptyline) and tetracyclic (maprotiline) antidepressants, antipsychotics (phenothiazines, sertindole), astamizole, bepridil, sparfloxacin and terodiline.

In conclusion, to avoid the occurrence of cardiac adverse effects, the following guidelines were suggested:

- Avoidance of administration of high doses.
- Prohibited use in the pathological conditions previously mentioned and with simultaneous administration of the above mentioned drugs.
- Prohibited administration of cisapride with agents that produce hypokalemia, such as kaliopenic diuretics and insulin.
- An E.C.G. prior to cisapride administration, when a patient is suspected of exhibiting an extended Q-T interval.
- Strict contraindication of cisapride administration to patients with 2nd or 3rd degree atrioventricular block.

### *8.6. Adverse effects from other systems*

Adverse effects from other systems are extremely rare and have mainly been reported following cisapride doses of 20 mg rather than 10 mg. They include:

- Allergic reactions (bronchospasm, urticaria, angioedema, fever).
- Pain in the joints or muscles (pain -particularly in the back-, arthralgia, myalgia).
- Vision abnormalities.

### *8.7. Rare adverse effects in pediatric patients*

While the safety and the efficacy of cisapride in adults has been specifically documented, this can not be said for children with absolute certainty. Single cases of sudden deaths in infants, after administration of cisapride have been mentioned in the international bibliography, mainly due to cardiovascular disorders e.g. third degree atrioventricular block and ventricular tachycardia.

In one 3 month old infant, cisapride administration provoked an epileptic crisis, which resulted in the infant's death.

In isolated cases cisapride use in children has been reported to produce anti-nuclear antibodies, anemia, hemolytic anemia, methemoglobinemia, hypoglycemia accompanied by acidemia, hyperglycemia, inexplicable episodes of apnea, confusion, depression, apathy, absence of attention, visual changes, amnesia and photosensitivity.[107]

## 9.0. CONCLUSIONS

Cisapride is a prokinetic agent with proven efficacy in the treatment of disorders associated with decreased gastrointestinal motility, such as gastro-oesophageal reflux, functional (non-ulcer) dyspepsia and also gastroparesis. It has been found to relieve symptoms of irritable bowel syndrome and gastric ulcer as well. Compared to other drugs used in the treatment of these diseases, cisapride has demonstrated similar or superior efficacy. Cisapride's reputation for effectiveness in the above mentioned disorders remains undoubted. Furthermore it has demonstrated a low incidence of gastrointestinal, central nervous system and respiratory side-effects.[108-110] However, overwhelming evidence regarding its cardiovascular toxicity has rendered its continued use, at least for the present, completely unfeasible.

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