Pharmacy Benefits Management Strategic Healthcare Group
and
Medical Advisory Panel
Drug Class Review
Prokinetic Agents

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OBJECTIVE

To review the safety, efficacy and administration of the currently available prokinetic agents in the treatment of gastric motility disorders, primarily gastroesophageal reflux disease (GERD).

Table 1 Available agents in the US

Generic Name	Trade Name	Generic Available	Manufacturer	Dosage Forms
Cisapride	Propulsid®	No*	Janssen	**Tablets:** 10mg (scored), 20mg
Metoclopramide	Reglan®	Yes	Robins / various	**Tablets:** 5mg, 10mg **Syrup:** 5mg/mL **Injection:** 5mg/mL

*Patent expiration date unavailable

I INDICATIONS and CONTRAINDICATIONS [1-5]

Prokinetic agents have been shown to be effective in the treatment and prophylaxis of gastroesophageal reflux disease (GERD) and gastroparesis. Cisapride is not currently approved for the treatment of gastroparesis, however, clinical studies suggest that this agent is efficacious. Metoclopramide possess additional indications for chemotherapy-induced nausea and vomiting, prophylaxis of post-operative nausea and vomiting and may be used as an adjunct in gastrointestinal radiography and small bowel intubation. Table 2 summarizes the current FDA approved indications for these agents.

Table 2: Current FDA approved indications

INDICATION		CISAPRIDE	METOCLOPRAMIDE
GERD	**Treatment**	Yes	Yes
	Prophylaxis	Yes*	No
Diabetic Gastroparesis		No†	Yes
Antiemetic	**Chemotherapy induced**	No	Yes
	Post Operative prophylaxis	No	Yes
Adjunct to radiologic examinations		No	Yes
Adjunct for small bowel intubation		No	Yes

* Recommended per USPDI † Janssen currently not pursuing FDA approval for this indication

Prokinetic agents are contraindicated in patients in whom increased gastrointestinal motility would pose a danger (e.g. presence of gastrointestinal hemorrhage, mechanical obstruction or perforation) and in patients with hypersensitivity or intolerance to these agents. Cisapride is contraindicated in patients receiving medications that inhibit the CYP450 3A4 enzyme system such as azole antifungal agents (e.g. ketoconazole, itraconazole, fluconazole, miconazole) or macrolide antibiotics (e.g. erythromycin, clarithromycin) due to potential development of cardiac arrhythmias such as ventricular tachycardia, ventricular fibrillation and torsades de pointes. Metoclopramide should be avoided in patients with pheochromocytoma secondary to the possible development of hypertensive crisis as well as in patients taking antiepileptic agents or agents associated with development of extrapyramidal symptoms (EPS) as the incidence of seizures or severity of EPS may be intensified.

II PHARMACOLOGY [1-8]

Prokinetic agents stimulate gastrointestinal motility and although their mechanisms of action vary, the net effects are similar. Metoclopramide is a synthetic, substituted piperidinyl derivative which stimulates upper gastrointestinal tract motility, therefore, accelerating gastric emptying and intestinal transit time. Metoclopramide does not stimulate the secretion of biliary, gastric or pancreatic enzymes. Although its mechanism of action is unclear, metoclopramide appears to exert its effect via tissue sensitization to acetylcholine. In patients with GERD, metoclopramide increases lower esophageal sphincter pressure (LESP), which aids in alleviating reflux symptoms. Additionally, metoclopramide's antiemetic properties are due to its direct effect at the

chemoreceptor trigger zone (CTZ). This mechanism of action is secondary to agonization of dopamine receptors which accounts for the incidence of extrapyramidal symptoms (EPS).

Cisapride is chemically related to metoclopramide but lacks dopaminergic activity. Therefore, this agent does not possess antiemetic activity and has not been associated with EPS. Cisapride appears to exert its effect by facilitating acetylcholine release from postganglionic neurons in the mesenteric plexus resulting in increased gastrointestinal tract motility from the esophagus to the large bowel. *In vitro* studies suggest that in addition to its effect on acetylcholine release, cisapride appears to effect serotonin receptors, acting as an agonist at the 5-HT_4 receptor and as an antagonist at the 5-HT_3 receptor. Similar to metoclopramide, cisapride increases LESP resulting in decreased GERD symptoms.

III PHARMACOKINETICS [1-7]

A. Absorption

Cispride and metoclopramide undergo rapid and complete absorption following oral administration. Cisapride undergoes extensive first-pass metabolism as indicated by its bioavailability of 40-50%. The presence of food enhances the bioavailability of cisapride, but the rate of absorption is not affected. Oral metoclopramide exhibits a bioavailability of 80 $\pm$ 15.5%, relative to a 20mg intravenous dose. For both agents, the onset of action after oral administration is seen within 30-60 minutes and peak concentrations occur 1-2 hours after administration. In regards to parenteral metoclopramide, the onset of action after intramuscular administration is seen within 10-15 minutes and the effect after intravenous administration is seen 1-2 minutes after administration.

B. Distribution

Cisapride and metoclopramide undergo extensive tissue distribution as evidenced by their large volumes of distribution of 2.4 L/kg and 3.5 L/kg, respectively. Cisapride is 98% bound to plasma proteins, primarily albumin, while metoclopramide is not extensively protein bound with only 30% bound to plasma proteins.

C. Metabolism and Excretion

Cisapride is hepatically metabolized via the CYP450 3A4 enzyme system to three metabolites; norcisapride through N-dealkylation and 3-fluoro-4-hydroxycisapride and 4-fluoro-2 hydroxycisapride through aromatic hydroxylation. Norcisapride is the only active metabolite, possessing 1/6 the activity of cisapride. Cisapride is eliminated both renally and fecally with <10% eliminated unchanged in the urine. The elimination half-life is approximately 7-10 hours after single and multiple doses. Metoclopramide undergoes hepatic biotransformation and renal excretion with 85% of the oral dose renally excreted unchanged or as glucuronide conjugates. Metoclopramide's elimination half-life is approximately 4-6 hours after oral administration.

The following table summarizes the pharmacokinetic parameters of these agents.

Table 3: Summary of pharmacokinetic parameters

VARIABLE	CISAPRIDE	METOCLOPRAMIDE
Oral bioavailability (%)	40-50	80 ± 15.5
Onset (minutes)	30-60	30-60
Time to peak effect (hours)	1-2	1-2
Vd (L/kg)*	2.4	3.5
Protein bound (%)	98	30
t½ (hours)†	7-10	4-6
Metabolism	Hepatic	Hepatic
Active metabolite	Norcisapride	None
Elimination	Renal and Fecal	Renal

*Vd = volume of distribution; † t½ = half-life

IV CLINICAL TRIALS

A. Gastroesophageal Reflux Disease

Cisapride and metoclopramide are both effective in the treatment of gastroesophageal reflux disease. Comparative trials indicate that cisapride and metoclopramide provide similar symptom relief, however, cisapride is generally better tolerated due to the lower incidence of central nervous system side effects. The majority of clinical trials dosed cisapride and metoclopramide 3-4 times daily 15-30 minutes before meals and bedtime. Additionally, all trials assessed the main symptoms of reflux disease (heartburn, regurgitation, day or night). The trials suggest that both agents are efficacious in healing mild to severe reflux disease, however, patients with more severe disease require longer treatment periods (up to 12 weeks).

When compared to H_2 receptor antagonists, cisapride is as effective as cimetidine and ranitidine in controlling reflux symptoms and promoting esophageal healing. The three agents are well tolerated with similar side effect profiles. One study suggests that cisapride may be associated with fewer side effects than cimetidine. There are currently no clinical trials comparing the effect of metoclopramide to the H_2 receptor antagonists in the treatment of GERD. However, two studies address the efficacy of combination therapy with metoclopramide in treatment refractive reflux disease.

Metoclopramide has been combined with both cimetidine and ranitidine in treatment refractive GERD patients. When compared to placebo, the combination significantly reduces reflux symptoms and promotes esophageal healing. However, when compared to omeprazole and ranitidine monotherapy, the combination of metoclopramide and ranitidine merely increases the incidence of adverse effects without significantly improving patient symptoms. Cisapride has not currently been studied in this population. Additionally, many patients, including treatment refractive patients, require long term therapy to prevent symptom relapse.

Cisapride is the only prokinetic agent, to date, that has been studied for greater than 12 weeks. Compared to placebo, cisapride is more effective in reducing relapse rates. In the 6 to 12 month follow up periods, cisapride was well tolerated, with mild gastrointestinal problems as the major complaint. Cisapride monotherapy has also been compared to omeprazole and ranitidine monotherapy as well as in in combination with those agents. Although each regimen is efficacious

in preventing relapse, omeprazole monotherapy or the combination of omeprazole and cisapride is slightly superior in relapse prevention.

The following tables summarize the clinical trials addressing gastroesophageal reflux disease.

Table 4: Cisapride vs. Metoclopramide

CLINICAL TRIAL	IMPORTANT CRITERIA	DOSES	OUTCOME	COMMENTS
Manousos ON et. al. 4 wk randomized, double-blind trial w/ 1 wk single blind placebo run in phase [9] Greece	-30 pts w/ chronic ($\geq$ 3 mo) h/o heartburn, regurgitation or both + esophagitis - assessment of reflux symptoms and global clinical response before & after run in phase & at weeks 2 & 4	metoclopramide: 10mg po tid cisapride: 10mg po tid	-significant reduction in reflux scores of both groups at wks 2 & 4 ($p < 0.01$) -Greater decrease in symptoms in cisapride group at wks 2 ($p = 0.003$) & 4 ($p=0.031$) -Global clinical response favored cisapride ($p = 0.05$) -Adverse events: cisapride: 0/15 metoclopramide: 3/15	-no significant difference in pt groups based on sex, weight or mucosal damage -no pt characteristics reported -cisapride group had a longer h/o of reflux symptoms & reported higher baseline symptom scores - adverse events: asthenia, somnilence, numbness -all pts w/ metoclopramide induced side effects withdrew
Arabehety JT et. al. 4 wk, multicenter, randomized, double-blind trial w/ 1 week single blind placebo run in phase [10] Argentina, Brazil, Columbia	-114 pts, avg age 46yrs w/ GERD symptoms $\geq$ 3 mos, total symptom severity score $\geq$ 4 -subjective assessment of reflux symptoms and global clinical response before & after run in phase & at wks 2 & 4	metoclopramide: 10mg po tid cisapride: 5mg po tid cisapride: 10mg po tid	-significant symptom improvement in all 3 groups beginning at wk 2 ($p < 0.001$) -Initial symptoms worse in cisapride groups, especially the 10mg group. -Total adverse events: more common in metoclopramide group (events included CNS, abdominal cramping, loose stools, pruritis) -CNS adverse events more common with metoclopramide (fatigue, somnolence. dysarthria)	-14 pts excluded from statistical analysis due to symptom score <4 or due to study withdrawal -38 male / 72 female -all 114 patients analyzed for adverse events - 3 pts in metoclopramide group withdrew due to CNS effects & 3 due to pruritis, nausea & dyspepsia -1 pt / cisapride group withdrew due to pruritis

Table 5. Cisapride vs. H_2 Antagonists

CLINICAL TRIAL	IMPORTANT CRITERIA	DOSES	OUTCOME	COMMENTS
Galmiche JP et. al. 6-12 wk randomized, double-blind with 1 wk placebo run in phase[11] France	-73 pts with GERD sx + endoscopically proven Grade I-III esophagitis -assessment of GERD symptoms & esophageal healing at run in phase & wks 6 & 12	cimetidine 400mg po qid cisapride -10mg po qid	-Cisapride and cimetidine are effective in reducing GERD symptoms and promoting esophageal healing -Both cimetidine and cisapride significantly decreased the intensity of GERD sx ($p<0.01$) -56% of cisapride pts & 57% cimetidine pts exhibited mucosal healing end of tx -Both agents well tolerated Cimetidine associated w/ slightly more adverse events (nervousness, insomnia, diarrhea, headache, fatigue)	-pts continued 12 wks of tx if mucosal healing not seen at wk 6 -groups well matched for age, sex, severity of symptoms & social history -at entry, 2/3 each group grade I esophagits -1 pt receiving cisapride & 2 pts receiving cimetidine withdrew due to adverse events
Maleev A et. al. 8-12 wk randomized, double-blind w/ 1 wk washout period[12]	-129 pts (80 male) avg age 46 yrs w/ endoscopically documented erosive esophagitis and GERD symptoms -endoscopy performed at selection visit & wks 8 & 12 -Sx assessed at initial visit & every 4 wks	cisapride 10mg po qid (40mg/day) 10mg po bid w/ 2 placebo (20mg/day) cimetidine 400mg po qid (1600 mg/day) 400mg po bid w/ 2 placebo (800 mg/day)	-cisapride is as effective as cimetidine in relieving GERD sx and promoting mucosal healing -cisapride 10mg po qid tends to provide the most symptom relief -significant decrease in esophagitis (per endoscopy) in all groups ($p<0.001$) -significant decrease in GERD severity scores for all groups at wk 4 ($p<0.05$) & wk 8 ($P<0.01$) -healing rates slightly higher w/ cisapride but not statistically significant	-lasted 12 wks if endoscopic improvement not seen by wk 6 -groups well matched for age, sex, social history & severity of symptoms -esophageal symptoms less severe in cisapride 10mg bid than cimetidine 1600mg/day ($p=0.03$)
Arvanitakis C et. al. 8wk double-blind, randomized trial[13] Greece	-40 pts w/ GERD sx $\geq$ 4 wks , severity score >9 & endoscopically proven grade I-III esophagitis -GERD sx assessed at wks 4, 8 & 12 (4 wk f/u visit) -upper endoscopy peformed before and after treatment	cisapride 10mg po qid ranitidine 150mg po bid	-both cisapride & raniditine effective in controlling GERD symptoms -both agents well tolerated -both cisapride & ranitidine resulted in increased esophageal healing at wk 8 ($P<0.001$) -healing sustained at 4wk f/u visit	-37 pts included in final analysis -2 cisapride pts withdrew due to vertigo & noncompliance, 1 raniditine pt withdrew due to anaphylaxis -groups well matched for age, sex , symptoms social history - cisapride group: shorter duration of symptoms slightly more females in group

Table 5. Cisapride vs. H_2 Antagonists - continued

CLINICAL TRIAL	IMPORTANT CRITERIA	DOSES	OUTCOME	COMMENTS
Janisch HD et. al. 6-12 wk randomized, double-blind trial[14] Germany	-65 pts w/ endoscopically proven grade I-II esophagitis -52 pts included in analysis -endoscopic evaluation at wks 6 & 12 - GERD sx & post prandial sx assessed at wks 0, 3 ,6 and at the end of the trial	cisapride 10mg po qid ranitidine 150mg po bid w/ 2 placebo	-Cisapride is as effective as ranitidine in controlling reflux symptoms and promoting esophageal healing as ranitidine -Both agents were well tolerated (mild adverse events reported: diarrhea, headache, fatigue) -Both agents significantly decreased the severity of esophagitis ($p<0.0001$) & improved GERD sx at wk 3 ($p<0.01$)	- lasted 12 wks if endoscopic improvement not seen by wk 6 -9/65 pts withdrew before 6 wk follow up -pts well matched for age, sex, severity of symptoms and duration of disease -adverse events included all patients

Table 6: Combination Therapy

CLINICAL TRIAL	IMPORTANT CRITERIA	DOSES	OUTCOME	COMMENTS
Lieberman DA, Keeffe EB 8wk randomized, double-blind, placebo-controlled trial w/ 4wk initial phase open-label trial for pts who fail therapy during trial [15]	-60 pts w/ chronic reflux sx for avg 13yrs in initial phase -25 pts refractory to initial therapy in initial phase -compliance & GERD sx assess every 2 wks -endoscopy at baseline & end of trial -10 pts in open label study	initial phase: cimetidine 300mg po qid antacid 15mL 4-7x/day treatment cimetidine 300mg po qid w/ metoclopramide 10mg po qid **or** placebo open label metoclopramide 10mg po qid	-The combination of cimetidine and metolclopramide is effective in the treatment of refractory GERD, however, side effects are more common -cimetidine + metoclopramide more effective in improving GERD symptom score ($p=0.04$) -cimetidine + metoclopramide more effective in improving endoscopic appearance ($p<0.05$) -adverse events more common w/ metoclopramide ($p<0.02$) (somnolence, fatigue, anxiety, restlessness)	-pts w/ severe symptoms after 4wk initial phase included in tx phase -both groups well matched for age, sex, social history & duration of disease. -1pt in metoclopramide tx phase withdrew due to side effects (disorientation, confusion) -3/10 pts in open label study withdrew due to side effects (prolonged somnolence)
Richter JE et. al. 8wk multicenter, randomized, open-label stratified study [16]	-290 pts avg age 49yrs w/ symptomatic GERD refractory to an 8wk trial of ranitidine -236 pts completed trial -Daily assessment of GERD sx by pt -Global sx assessment and endoscopy at baseline & wks 4 &8 -37% pts grade 0-II esophagitis	omeprazole 20mg po qam ranitidine 150mg po bid raniditine + metoclopramide 10mg po qid	-omeprazole more effective in providing GERD sx relief and esophageal healing -the addition of metoclopramide increased side effects -Significantly more omprazole pts completely healed & symptom free at end of study ($p<0.001$) -Significantly more pts receiving ranitidine + metoclopramide reported side effects ($p<0.05$) (CNS effects) 25% d/c therapy	-61% pts male, 88% Caucasian -sig more non-Causacions pts in omeprazole group ($p<0.05$) -Social history sx similar between groups -Duration of dx not reported -asymtpomatic pts did not undergo final evaluation at wk 8 -Adverse events included all pts

Table 7: Maintenance therapy with cisapride

CLINICAL TRIAL	IMPORTANT CRITERIA	DOSES	OUTCOME	COMMENTS
Blum AL et. al. 12 mo randomized, double-blind, placebo-controlled intention to treat [17] France, Italy, Austria, Switzerland	-443 pts (66% male, avg age 48yrs) w/ endoscopy confirmed healed esophagitis with antisecretory tx -symptoms assessed at least every 2 months -endoscopy at months 4 & 12	cisapride 10mg po bid cisapride 20mg po qpm + placebo q am placebo bid	-cisapride is effective in preventing relapse of healed esophagitis & is well tolerated -both cisapride regimens prolonged time to symptomatic relapse (p=0.012) -pts w/ less severe dx had increased duration of remission (p=0.038) -12 mo endoscopic relapse rate 32% cisapride 20mg qpm p<0.005 34% cisapride 10mg bid p=0.02	-groups well matched for age, sex, duration of symptoms & social history -95% of pts originally healed w/ H_2 agent -8 placebo pts and 30 cisapride pts withdrew due to side effects (diarrhea, abdominal pain, nausea & vomiting)
Toussaint J et. al. -8wk open label treatment phase w/ 6 month randomized, double-blind, placebo-controlled maintenance phase Belgium, Brussels[18]	-163 pts avg age 52yrs w/ endoscopically diagnoised grade I-IV esophagitis (62% grade II-IV) -138 pts in tx analysis 80 pts in maintenance -severity of sx & post prandrial discomfort assessed at each visit & control endoscopy at trial end	treatment: cisapride 10mg po qid maintenance: cisapride 10mg po bid or placebo	-cisapride is effective in healing esophagitis & preventing relapse & is well tolerated -treatment: healing tended to occur faster in pts w/ less severe esophagitis -maintenance significant sx improvement w/ cisapride at wk 8 (p<0.001) cumulative % pts in remission higher w/ cisapride (p=<0.06)	-groups well matched for age, sex, symptom duration & social history -2 phase trial: open label healing phase for all pts, therapy continued for 12-16wks in pts not healed by wk 8, if no improvement by wk 16, therapy stopped pts healed by wks 8-16 included in maintenance trial
Vigneri S et. al. 4-8wk open-label healing phase w/ 12 month randomized, prospective, stratified maintenance trial intention to treat[19]	-175pts avg age 45yrs w/ grade I-III esophagitis & presence of ≥ GERD sx -symptoms assessed every 8 wks or per telephone -endoscopy completed at month 6 & 12	healing phase omprazole 40mg qd maintenance ompeprazole (O) 20mg po qd cisapride (C) 10mg po tid ranitidine (R) 150mg po tid omperazole or ranitidine + cisapride (O/C & R/C)	-all 5 regimens effective in improving remission rates -omeprazole and omeprazole + cisapride significantly improved remission rates compared to the other regimens O vs.C p=0.02, O vs.R p=0.003 O/C vs C p=0.003, O/C vs. R p<0.001 O/C vs R/C p=0.03 omeprazole & omeprazole sig improved symptoms (p<0.001)	-pt groups well matched for age, sex, severity & duration of symptoms & social history -5pts discontinued treatment due to adverse events (diarrhea, abdominal pain)

B. Diabetic gastroparesis

Metoclopramide is the only prokinetic agent with FDA approval for the treatment of diabetic gastroparesis. Clinical studies have shown that metoclopramide doses of 40mg / day are effective in improving gatsroparesis symptoms (nausea, vomiting, abdominal pain, bloating) as well as gastric emptying rates. This agent is generally well tolerated in diabetic patients, with mild central nervous system effects being the most common complaints. Currently, there are no comparitive trials between metoclopramide and cisapride in the management of diabetic gastroparesis. However, cisapride monotherapy has been evaluated.

Clinical trials assessing the effects of cisapride in diabetic gastroparesis have yielded conflicting resuts. There is a trend toward symptomatic improvement and increased gastric empyting rates, however, further trials are needed to assess the role of cisapride therapy in diabetic gastroparesis.

The following tables summarize the clinical trials.

Table 8: Cisapride in gastroparesis

CLINICAL TRIAL	IMPORTANT CRITERIA	DOSES	OUTCOME	COMMENTS
Troels H et al. 8 wk randomized, double-blind, placebo-controlled, crossover trial[20]	-10pts w/ IDDM & delayed gastric emptying w/ minimal symptoms -gastric emptying measured before and after each tx period -symptoms recorded 1 wk prior to study (baseline) & wks 2.4.6.8 & 12 (f/u visit)	cisapride 10mg po qid placebo po qid pts switched therapies at wk 4	-trend towards symptomatic improvement with cisapride -cisapride significantly improved sx of vomiting & pain ($p<0.05$ compared to baseline) -both agents sig improved sx of nausea & anorexia ($p<0.05$ compared to baseline) -no statistically significant difference in gastric emptying	
Richards RD et. al. 2 wk single-blind placebo run in phase followed 6 wk randomized, double-blind, placebo-controlled trial. intention to treat[21]	-43 pts (95% male, avg age 38.5yrs) w/ sx of gastroparesis & documented delayed gastric emptying -38pts in trial -symptoms assessed every 2 wks, daily sx recording by pt -final gastric emptying study at end of trial	placebo tid x 2wks cisapride 20mg po tid or placebo tid x 6 wks	-cispride significantly improved solid gastric emptying time compared to baseline ($p=0.005$) -no statistical significance between cisapride & placebo in gastric emptying -improvement of gastroparesis symptoms was not statistically significant with cisapride.	-5/43 pts excluded due to placebo resonse -Gastroparesis etiology DM n=7, scleroderma n=2 idiopathic n=29 -pt groups well matched for age, gastroparesis etiology and baseline emptying scores -3 cisapride pts & 7 placebo withdrew due to lack of symptomatic improvement
Horowitz M et. al. randomized, double-blind placebo-controlled single-dose assessment followed by a 4 wk randomized, double blind trial[22]	20 pts (avg age 45yr) w/ IDDM, sx of gastroparesis & documented delayed gastric emptying -22 controls (avg age 34yr) w/out IDDM -assessment of sx at baseline & at least every 2 wks -gastric (solid & liquid) / esophageal empyting studies completed at baseline, after single dose & at completion of trial	single po dose of cisapride 20mg or placebo x 2 days followed by cisapride 10mg po qid or placebo qid	Single dose administration: -Cisapride increased gastric and esophageal empting -Cisapride increased solid & liquid gastric emptying ($p<0.001$) and esophageal empyting ($P<0.01$) Chronic administration: -cisapride is effective in reducing sx of gastroparesis -cisapride increased gastric emptying ($p<0.001$) compared to placebo, but not esophageal emptying ($p>0.2$) -sig improvement in upper GI sx w/ cisapride ($p<0.05$)	-only IDDM pts randomized to receive cisapride or placebo -controls used for baseline gastric / esophageal emptying comparisons--equally matched w/ tx groups for age & wt. -majority of pts with mild sx

Table 9: Metoclopramide in gastroparesis

CLINICAL TRIAL	IMPORTANT CRITERIA	DOSES	OUTCOME	COMMENTS
Snape WJ et. al. 6 wk randomized, double-blind, placebo-controlled, crossover trial [23]	-10 pts (avg age 31.4yrs) w/ IDDM & sx of gastroparesis -gastric emptying & symptoms assessed at baseline, wks 3 and 6	placebo qid metoclopramide 10mg po qid pts switched therapies at wk 3	-metoclopramide improved gastric emptying and sx in diabetic pts -mean rate of gastric emptying sig improved after 3 wks metoclopramide ($p<0.01$) -overall sx improved in 7/10 pts on metoclopride & 0/10 placebo -vomiting decreased in 9/10 pts and stopped in 6/10 pts on metoclopramide compared to 1/10 pts on placebo	-pt characteristics not reported -statistical significance for symptoms not reported
Ricci DA et. al. 6 wk randomized, double-blind, placebo-controlled, crossover trial optional open label metoclopramide at end of trial [24]	-13 pts (avg ag yrs) w/ IDDM and sx of gastroparesis & evidence of delayed gastric emptying weekly symptom assessment -gastric emptying studies completed at baseline, after im metolopramide -7/13 pts included in open label trial	one time dose of metoclopramide 10mg im followed by metoclopramide 10mg po qid or placebo qid pts switched therapies at wk 3	-metoclopramide significantly improved gastric emptying and pt symtoms -generally well tolerated -gastric emptying significantly improved after im metoclopramide ($p<0.05$) -symptom improvement of 52.6% from baseline with po metoclopramide ($p<0.01$) -significantly less gastric retention compared to basline in open label group ($p<0.05$)	-1 wk wash-out period between trials -6 male, 7 female -6 pts type I DM 7pts type II DM

V ADVERSE EFFECTS [1-7]

Cisapride and metoclopramide are well tolerated in most patients. The most frequently reported untoward effects include gastrointestinal complaints (transient diarrhea and abdominal cramping) followed by central nervous system effects. These side effects are generally self-limiting and reversible upon treatment discontinuation. Compared to metoclopramide, cisapride has a lower incidence of CNS effects (drowsiness, fatigue) and has rarely been associated with the development of extrapyramidal symptoms. For both agents, the frequency of adverse effects appears to be dose related. Additionally, the incidence of metoclopramide associated adverse effects appears to correlate with treatment duration.

The following table summarizes the adverse effects associated with the prokinetic agents.

Table 10

ADVERSE EFFECT	CISAPRIDE (%)	METOCLOPRAMIDE (%)
Gastrointestinal	Overall incidence not reported	Overall incidence 2-9%*
Diarrhea	14.2†	2-9
Abdominal pain	10.2†	2-9
Nausea	7.6†	2-9
Constipation	6.7†	2-9
Flatulence	3.5	2-9
Dyspepsia	2.7	2-9
Central Nervous System	Overall incidence not reported	Overall incidence 12-24%‡
Headache	19.3	<10
Drowsiness	<1	10
Anxiety	1.4	1-9
Restlessness	<1	10
Dizziness	>1	3
Insomnia	1.9	<10
Extrapyramidal Symptoms	Rare	Overall incidence 1-9%
Acute dystonic reactions	Rare	0.2§

*) Overall incidence increased to 81% in patients receiving high dose metoclopramide (2mg/kg)
†) More frequent in patients receiving 20mg cisapride per dose
‡) Overall incidence increased to 43% in patients receiving high dose metoclopramide (2mg/kg)
§) In chemotherapy patients, incidence increased to 2% in patients $\geq$ 30 years of age and to 25% in patients not receiving prophylactic diphenhydramine

VI DRUG INTERACTIONS [1-7]

The use of prokinetic agents may affect the absorption and bioavailability of many agents due to the increased gastrointestinal transit time. Therefore, patients receiving agents with narrow therapeutic indexes or agents requiring special monitoring (e.g. digoxin, warfarin, cyclosprine) should be frequently monitored. Table 11 summarizes the pertinent drug interactions.

Table 11: Summary of pertinent drug interactions

PROKINETIC AGENT	DRUG(S)	INTERACTION
Cisapride	***Azole antifungals**** ketoconazole itraconazole fluconazole miconazole (iv)	Inhibition of cisapride metabolism resulting in increased AUC with potential QT interval prolongation on ECG and arrhythmias (ventricular tachycardia/fibrillation, torsade de pointes)
Cisapride	***Macrolide antibiotics**** erythromycin clarithromycin troleandomycin	Inhibition of cisapride metabolism resulting in increased AUC with potential QT interval prolongation on ECG and arrhythmias (ventricular tachycardia/fibrillation, torsade de pointes)
Metoclopramide	Alcohol* CNS depressants*	Increased sedation
Cisapride **Metoclopramide**	Anticholinergic agents*	May counteract the effect of prokinetic agents
Cisapride	Cimetidine	Cimetidine can increase plasma concentrations of cisapride

Metoclopramide	Narcotic analgesics	May counteract the effect of metocloprmide

*clinically significant interactions

VII PREGNANCY AND LACTATION [1-5]

There is a lack of clinical trials assessing the safety of prokinetic agents in pregnant or lactating females. Currently, cisapride is listed as Category C and metoclopramide as Category B. Both cisapride and metoclopramide are excreted in breast milk with cisapride concentrations approximating 1/20 of the observed plasma concentrations and metoclopramide concentrations approximating twice the plasma concentration 2 hours post dose. Until well-controlled clinical trials determine the true safety of these agents, prokinetic agents should be administered cautiously in pregnant or lactating females and should be used only in those instances in which the benefits of therapy outweigh the potential risks to the fetus.

VIII DOSING AND ADMINISTRATION [1-7]

The doses and duration of prokinetic therapy vary based on treatment indications, and pharmacokinetic parameters suggest that dose adjustments are necessary in the presence of severe hepatic or renal insufficiency. Neither agent is significantly removed by hemodialysis, therefore, redosing is not necessary. Additionally, metoclopramide is not removed by continuous ambulatory peritoneal dialysis (CAPD). Tables 12 and 13 summarize this information.

Table12: Recommended dosage

INDICATION		CISAPRIDE*	METOCLOPRAMIDE†
GERD	**Treatment**	10-20mg po qid (ac & qhs) x 6-12 weeks	10-15 mg po up to qid x 6-12 weeks
	Prophylaxis	10mg po bid or 20mg po qhs	----------
Diabetic Gastroparesis		----------	10-15mg po qid 15 minutes ac [severe gastroparesis: iv up to 10days then po]
Antiemetic	**Chemotherapy-induced nausea and vomiting ‡**	----------	**Highly ematogenic**: 2mg/kg iv over 15 minutes q 2 hours x 2 doses then q 3 hours x 3 doses **Less ematogenic**: 1mg/kg iv over 15 minutes q 2 hours x 2 doses then q 3 hours x 3 doses
	Post operative propohylaxis §	----------	10-20mg im x 1 dose
Adjunct to radiological examinations		----------	10mg iv over 1-2 minutes
Adjunct for small bowel intubation		----------	10mg iv over 1-2 minutes

***** oral cisapride should be dosed at least 15 minutes before meals
† oral metoclopramide should be dosed at least 30 minutes before meals
‡ first dose to be administered 30 minutes prior to chemotherapy
§ dose to be given near the end of surgery

Table 13: Dosage adjustment in hepatic and renal failure

Variable	Cisapride	Metoclopramide*
Hepatic faiure	Reduce dose by 50%	Reduce dose by 50%
Renal Failure	Yes†	Reduce dose by 50% (CrCl < 40mL/min)

*Dose reduction recommended to avoid development of untoward effects, primarily EPS
†Inconclusive evidence to support dose reduction in renal failure. Patients should be monitored closely and the dosage titrated based on therapeutic effect and incidence of untoward effects

IX CONCLUSIONS

Efficacy / Outcomes:

A. Gastroesophageal reflux disease

Clinical studies have demonstrated the efficacy of prokinetic agents in the treatment of gastroesophageal reflux disease. Cisapride and metoclopramide provide similar symptom relief while promoting esophageal healing. Patients with mild to severe reflux disease respond to prokinetic therapy, however, patients with severe disease generally require longer treatment periods. Studies suggest that cisapride therapy is as effective as H_2 antagonists in the treatment of GERD and that combination therapy of metoclopramide and H_2 antagonists is effective for treatment refractive GERD patients.

Cisapride is the only prokinetic agent, to date, that has been evaluated for GERD maintenence therapy. For relapse prevention, cisapride monotherapy is more effective than placebo, however, in comparison to omeprazole monotherapy or combination therapy with omperazole and cisapride, cisapride monotherapy is not as effective.

B. Diabetic gastroparesis

Metoclopramide is currently the only prokinetic agent approved for the treatment of diabetic gastroparesis. Clinical studies have demonstrated its efficacy in improving gastric emptying rates and providing symptom relief. Cisapride has been studied in this population and appears to provide symptom relief and stimulate gastric emptying rates. However, head to head comparisons with metoclopramide are lacking and further studies are needed to assess the true effect of this agent in diabetic gastroparesis.

Safety and Tolerability:

The major side effects of the prokinetic agents are generally self-limiting and reversible upon treament discontinuation, with mild gastrointestinal problems being the most frequent complaint. Metoclopramide therapy has been associated with significantly more central nervous system adverse effects compared to cisapride. Additionally, metoclopramide induced extrapyradimal symptoms often warrent treatment discontinuation.

X RECOMMENDATIONS

As both metoclopramide and cisapride are efficacious in the treatment of gastroesophageal reflux disease and diabetic gastroparesis, the decision for first line therapy should be based on safety profiles and costs. Metoclopramide therapy is associated with an increased side effect profile compared to cisapride, however, the adverse effects of both agents are generally reversible upon treatment discontinuation. Metoclopramide is the only prokinetic agent currently generically available, which can result in decreased acquisition costs. Additionally, both parenteral and oral dosage forms are available.

Due to the cost difference between the agents and multiple dosage forms available, metoclopramide should be considered first line prokinetic therapy for patients with GERD or diabetic gastroparesis. Cisapride should considered second line therapy to be used in those patients with contraindications to metoclopramide therapy or in patients with intolerable metoclopramide induced side effects.

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