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Metoclopramide
An Updated Review of its Pharmacological Properties and Clinical Use

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Contents

Summary

Synopsis: *Since previously reviewed in the Journal (Vol. 12, No. 2), metoclopramide has been confirmed as an effective drug in treating and preventing various types of vomiting and as a useful agent in oesophageal reflux disease, gastroparesis, dyspepsia, and in a variety of functional gastrointestinal disorders. Of considerable importance is the recent evidence of its efficacy when administered intravenously in high dosages in preventing severe vomiting associated with cisplatin. Good results have been achieved in patients not previously treated with cisplatin, but further studies are needed to determine its level of efficacy in patients who have experienced severe vomiting during earlier courses of cytotoxic therapy. Side effects consisting of mild sedation, diarrhoea and reversible extrapyramidal reactions have occurred, but are tolerated by many patients.*

Pharmacodynamic Studies: Pharmacodynamic studies in man have shown that oral and intravenous metoclopramide rapidly influences gastrointestinal tract motility. The effect of the drug in increasing lower oesophageal sphincter pressure is more marked in volunteers than patients with reflux oesophagitis or pregnant patients, and appears to be directly related to basal pressure, dose and route of administration. Gastric emptying studies employing radioisotope-labelled liquid and solid meals have demonstrated increased emptying in patients with delayed gastric emptying associated with diabetes, vagotomy and other gastric surgery. The effect of metoclopramide on gastric contractions is most pronounced in the antrum. Metoclopramide stimulates contraction of intestinal smooth muscle, resulting in a decreased transit time through the small intestine, but any effect on colonic activity remains to be clarified. Metoclopramide is effective in preventing apomorphine-induced vomiting in man, and in animals prevents vomiting induced by apomorphine, hydergine, reserpine, tetrodotoxin and copper sulphate, by raising the threshold for vomiting at the chemoreceptor trigger zone as well as by peripheral mechanisms. Other effects on the gastrointestinal tract are thought to result from inhibition of dopaminergic receptors, potentiation of cholinergic effects and/or a direct action on smooth muscle.

The neuroleptic-like central nervous system effects of metoclopramide probably result from blockade of cerebral dopamine receptors by the parent drug rather than by a metabolite.

Oral or intravenous metoclopramide stimulates prolactin release in all recipients.

Pharmacokinetics: Peak plasma metoclopramide concentrations occur within 1 hour of oral administration. On average, concentrations 1 hour after 20 and 40mg doses are about 40 and 80 ng/ml, respectively, but may show interindividual variation because of 'first-pass' hepatic metabolism. In crossover studies, relative bioavailability was lower after rectal administration of 40mg than after an oral dose of 26.7mg. The mean volume of distribution is about 2 to 3 L/kg. Metoclopramide readily enters breast milk where drug concentrations exceed those in plasma 2 hours after oral administration. 80% of an oral dose is excreted in the urine within 24 hours, either as unchanged drug (20%) or sulphate and glucuronide conjugates of metoclopramide. Elimination half-life has been reported as 2.6 to 5 hours in healthy subjects and around 14 hours in patients with moderate to severe renal impairment.

Therapeutic Trials: Controlled trials have shown oral metoclopramide 30 to 40mg daily to alleviate the symptoms of gastro-oesophageal reflux relative to placebo and in some studies to also increase lower oesophageal sphincter pressure. However, as with many other drugs used in oesophageal reflux disease, endoscopic healing of oesophagitis has still to be adequately demonstrated with metoclopramide.

Some patients with gastroparesis associated with diabetes mellitus or vagotomy have benefited from treatment with metoclopramide 40mg daily. However, there are no established criteria to predict which patients may benefit most and gastric emptying rates are not a reliable indication of response.

Metoclopramide has been successfully used to treat dyspepsia, being more effective than placebo, the anticholinergic drug pipenzolate and the antiemetic agent prochlorperazine. Similarly, metoclopramide appears to be useful in a variety of functional gastrointestinal disorders including irritable bowel syndrome, spastic constipation, and functional diarrhoea but studies in these conditions and in dyspepsia have generally been poorly designed. There is no firm evidence that the drug promotes the healing of peptic ulcer.

Results of studies in the prevention of postoperative vomiting have been variable, with metoclopramide proving effective and comparable with the peripheral dopamine antagonist domperidone when administered intravenously immediately prior to general anaesthesia. As with other drugs used in prevention of postoperative vomiting, response to metoclopramide has been influenced by the interval between administration and induction of anaesthesia, the anaesthetic drugs, postoperative use of narcotic analgesics and variation in surgical procedures.

Recent well conducted studies have shown high dose intravenous metoclopramide (1 to 2 mg/kg for 5 or 6 doses) to be effective in preventing the severe vomiting caused by cisplatin therapy (50 to 120 mg/m^2). Best results to date have been achieved in patients not previously exposed to antineoplastic drugs, and in patients previously treated with cisplatin whose initial vomiting had been well controlled. In patients receiving cisplatin for the first time, high dose metoclopramide was superior to placebo, intramuscular prochlorperazine and oral tetrahydrocannabinol.

Metoclopramide has been used to control vomiting associated with narcotic analgesics, radiation therapy, pregnancy, gastroenteritis, gastric carcinoma, hepatic and biliary disorders, chronic renal failure, cardiac disease and alcoholism. The delayed absorption caused by poor gastric emptying associated with migraine attacks appears to be corrected by metoclopramide, resulting in earlier attainment of therapeutic plasma concentrations of concomitantly administered analgesics, but this has yet to be confirmed in appropriately designed controlled trials.

The drug has been widely used as an adjunct in radiological examination of the small bowel to facilitate the passage of barium, and is useful in facilitating intubation and in speeding the passage of biopsy capsules across the pylorus.

Side Effects: At usual therapeutic doses metoclopramide is well tolerated. Side effects are generally mild and transient and seldom necessitate withdrawal of the drug. They consist principally of drowsiness, restlessness, bowel disturbances, dizziness and faintness after oral or parenteral administration. At usual doses, extrapyramidal effects are infrequent in adults, but occur more often at the higher dosages used to prevent vomiting caused by antineoplastic drugs and in patients with renal failure. These reactions respond to reduction of dose, withdrawal of the drug, or treatment with intramuscular benztropine, diphenhydramine or diazepam. A dose-related increase in drowsiness is evident with high intravenous doses used to treat cisplatin-induced vomiting. Further experience is needed to determine the incidence of side effects with high and intermediate doses of intravenous metoclopramide, particularly in children and young adults.

Dosage: The usual oral intramuscular or intravenous dose in adults is 10mg 3 or 4 times daily before meals or before symptoms are likely to occur. Children under 14 years should receive 0.1 mg/kg per dose, the total daily dose not to exceed 0.5 mg/kg/day.

For diagnostic purposes, the adult dose is 20mg orally 20 minutes before examination or 10 to 20mg parenterally 5 minutes before examination.

For the prevention of cisplatin-induced vomiting in adults, metoclopramide should be diluted in 50ml of an intravenous solution and infused over a period of at least 15 minutes. At present it is recommended that administration should begin 30 minutes before cisplatin and be repeated 2-hourly for 2 doses and 3-hourly for 3 doses. The initial doses should be 2 mg/kg, and if vomiting is controlled, subsequent doses may be decreased to 1 mg/kg. However, the optimum dosage recommendations, particularly in children and young adults, remain to be established.

1. Pharmacodynamic Studies

Nearly 20 years have elapsed since the use of metoclopramide was first evaluated. Metoclopramide is related to procainamide (fig. 1), but is virtually devoid of antiarrhythmic or local anaesthetic activity in doses used clinically. The pharmacological effects of metoclopramide are most evident in the gastrointestinal tract (altered gastrointestinal motility and antiemetic effects), although increased prolactin secretion and production of extrapyramidal symptoms have also been demonstrated. The nature of the gastrointestinal effects produced has led to the use of the drug in a variety of clinical settings. The pharmacological properties and clinical use of metoclopramide have previously been reviewed (Pinder et al., 1976). This paper will summarise previously reviewed data and present recent information in more detail.

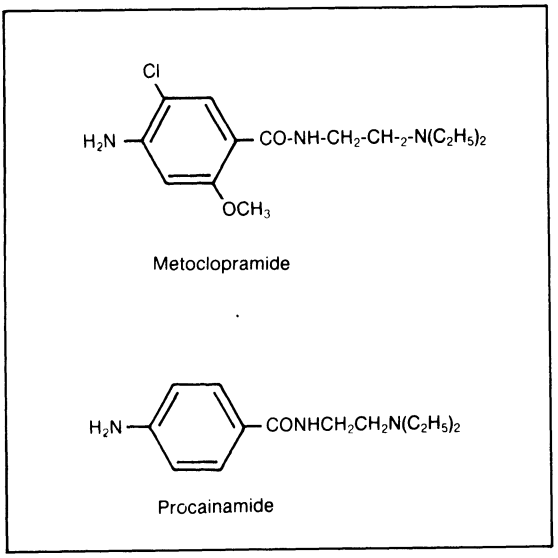

Fig. 1. Structural formulae of metoclopramide and procainamide.

1.1 Gastrointestinal Effects

Metoclopramide has a pronounced effect upon gastrointestinal motility in both animals and man after either oral or intravenous administration (Pinder et al., 1976; Schulze-Delrieu, 1981). The effects of metoclopramide include an increase in the amplitude of oesophageal contractions and of lower oesophageal sphincter pressure, as well as increased amplitude and frequency of antral contractions. Metoclopramide has no effect on gastric secretion. In the small bowel, metoclopramide improves the coordination of duodenal with antral contractions and causes an increase in the amplitude of duodenal contractions. These effects result in accelerated gastric emptying with reduced small bowel transit time. No consistent effect upon colonic motility has been demonstrated *in vivo*.

1.1.1 Effects on the Oesophagus

Intravenous administration of metoclopramide (10 to 20mg single doses) to healthy volunteers, pregnant women with and without heartburn, and patients with hiatus hernia with and without gastro-oesophageal reflux has resulted in a significant increase in lower oesophageal sphincter pressure as determined by intraluminal pressure techniques. After administration, the onset of the elevation in lower oesophageal sphincter pressure begins in 2 to 5 minutes, reaches a peak in 10 to 20 minutes and this effect lasts for at least 90 minutes. With oral administration the duration of increased pressure (120 minutes), and the time to onset of effect (10 to 20 minutes) and to peak effect (40 minutes) are longer (Baumann et al., 1979; Cohen et al., 1976; Pinder et al., 1976).

An average increase in lower oesophageal sphincter pressure of 16.9mm Hg (range of 3.0-34.0mm Hg) after intravenous or oral administration of metoclopramide 10 to 20mg was demonstrated in healthy volunteers (Baumann et al., 1979; Bremner and Bremner, 1972; Cohen et al., 1976; Guelrud, 1974; Heitmann and Moller, 1970), which is somewhat higher than the mean increase in lower oesophageal sphincter pressure seen in patients with gastro-oesophageal reflux. In such patients with hiatus hernia an average pressure increase of 10.9mm Hg occurred (range 6.1-19.4mm Hg) [Behar and Biancani, 1976; Bremner and Bremner, 1972; Guelrub, 1974], while in patients without hiatus hernia the average pressure increase was 10.1mm Hg (range 7.0-15mm Hg) [Cohen et al., 1976; Stanciu and Bennett, 1973; Winnan et al., 1980]. Pregnant women, either with or without heartburn, also exhibit a smaller mean increase in lower oesophageal sphincter pressure than healthy volunteers after receiving metoclopramide (13.4mm Hg; range 10.2-15.2mm Hg) [Brock-Utne et al., 1978; Hey and Ostick, 1978]. A significantly lower mean response is observed in patients with progressive systemic sclerosis (4.47mm Hg) [Ramirez-Mata et al., 1977].

The elevation in lower oesophageal sphincter pressure after metoclopramide in normal volunteers and patients (except pregnant women) is related to basal pressure, dose and administration route; a higher basal pressure, higher dose or the intravenous route of administration results in a larger mean increase in lower oesophageal sphincter pressure (Baumann et al., 1979; Behar and

Biancani, 1976; Cohen et al., 1976; Engstrom and Rhodes, 1977; McCallum et al., 1975b; Ramirez-Mata et al., 1977; Winnan et al., 1980). Thus, patients who have disease states associated with lower oesophageal sphincter incompetence (hiatus hernia, gastro-oesophageal reflux, progressive systemic sclerosis) show smaller mean increases in lower oesophageal sphincter pressure after metoclopramide. Also, there is a significantly greater response of both healthy volunteers and patients with oesophageal reflux to an oral metoclopramide dose of 20mg compared with the response to 10mg (Cohen et al., 1976; McCallum et al., 1975b) [fig. 2].

Patients with progressive systemic sclerosis ('scleroderma') who characteristically demonstrate diminished lower oesophageal sphincter pressure and hypo- or aperistalsis of the oesophagus, show a small increase in lower oesophageal sphincter pressure following metoclopramide. Their response is small because the underlying pathology of progressive systemic sclerosis causes extremely low basal lower oesophageal sphincter pressure. Those patients who possess some remaining oesophageal peristaltic function will exhibit improvement after metoclopramide, but it is uncertain whether those with aperistalsis will respond. After intravenous injection of metoclopramide 10mg, an average pressure of 4.47mm Hg was demonstrated in 7 of 14 patients with systemic sclerosis who had no previously detectable lower oesophageal sphincter pressure (Ramirez-Mata et al., 1977). Engstrom and Rhodes (1977) observed a mean increase of 4.1mm Hg (from 5.9 to 10.0mm Hg) in lower oesophageal pressure after intravenous metoclopramide 10mg in 4 of 9 patients with progressive systemic sclerosis, but no increase in pressure was observed in the remaining 5 patients who had no basal peristaltic activity. However, metoclopramide 10mg intravenously was shown by manometric study to cause pressure waves in 5 of 11 patients with aperistalsis, and a 3-fold increase in amplitude of pressure occured in 3 patients with hypomotility (Ramirez-Mata et al., 1977).

After 8 weeks of metoclopramide treatment (10mg orally 4 times daily), McCallum et al. (1977) could demonstrate no change in basal lower oesophageal sphincter pressure in 31 patients with gastro-oesophageal reflux. However, lower oesophageal sphincter pressure was not measured until between 9 and 48 hours after therapy was discontinued when little, if any, of the drug would be present in plasma. This would suggest metoclopramide does not result in a permanent change or improvement in lower oesophageal sphincter pressure.

1.1.2 Effects on the Stomach

The acute effects of metoclopramide on the human stomach include significant acceleration of gastric emptying and an increase in the amplitude of gastric contractions. This has been demonstrated in single-dose studies utilising various laboratory measurement methods after oral, intramuscular or intravenous administration of metoclopramide 10 to 40mg. The effects of metoclopramide on the stomach are most readily demonstrated in patients who have abnormally slow rates of gastric emptying and/or weak antral and small duodenal contractions. Such effects are less readily seen in individuals with normal rates of gastric emptying, a normal gastric contraction pattern, or no sig-

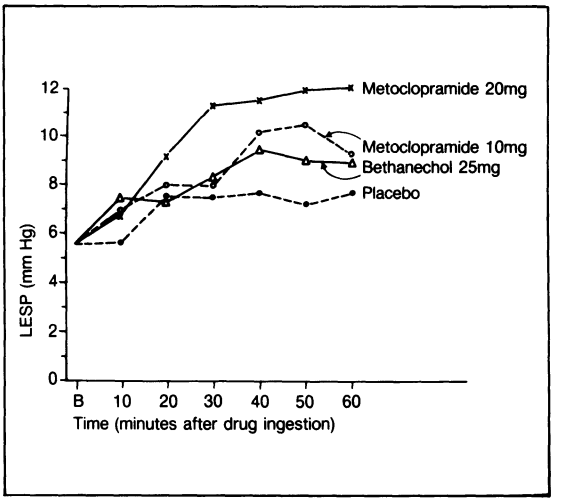

Fig. 2. Changes in lower oesophageal sphincter pressure in patients with oesophageal reflux following oral administration of metoclopramide 10 and 20mg or bethanechol 25mg (after McCallum et al., 1975b).

nificant antral or duodenal contractions (Behar and Ramsby, 1978; Berkowitz et al., 1976; Davidson et al., 1977; Miller et al., 1980; Perkel et al., 1981; Pinder et al., 1976; Saleh and Lebwohl, 1980).

After ingestion of an ordinary mixed meal the intragastric aqueous, solid and oil phases each have a characteristic pattern of emptying. It is therefore important to study the action of drugs on the emptying of both liquids and solids. It is well established that liquids are emptied from the stomach more rapidly than solids, and also that they are emptied by different mechanisms. It has been proposed that the body of the stomach, in accommodating increasing volumes of liquid, undergoes vagal-mediated receptive relaxation, without increasing intragastric pressure. Increasing evidence indicates that tonic fundal activity may be primarily responsible for the emptying of liquids (Malagelada, 1979), whereas the antral contractions and pyloric relaxations in coordination with duodenal contractions regulate gastric emptying of solids. Until solid material is appropriately liquefied and mixed, food is retained in the stomach by an unspecified antro-pyloric mechanism (Perkel et al., 1981). Since the rate of emptying of liquids may not be slowed in patients with gastric motor disorder, the diagnosis is confirmed by demonstrating impaired gastric emptying of a solid meal. Two accepted methods of measuring gastric emptying of solid meals include the radiological study of a test meal incorporating barium sulphate ('barium burger') and the gamma camera evaluation of the rate of disappearance from the stomach of a radioisotope-labelled meal (Malagelada, 1982). Although both methods are useful in assessing gastric emptying, a major criticism of the barium test meal is that it only measures total emptying time and does not demonstrate the pattern of gastric emptying (Perkel et al., 1981). Many of the studies of the effect of metoclopramide on gastric emptying have employed the radioisotope-labelled meal method with solid (Brady and Richardson, 1977; Berkowitz et al., 1976; Wright and McGregor, 1979) or both liquid and solid meals (Behar and Ramsay 1978; Campbell et al., 1977; Millar et al., 1980; Saleh and Lebwohl, 1980; Perkel et al., 1981).

Gastric Contractions

Metoclopramide's effect upon gastric contractions in normal individuals and patients with gastric motility abnormalities are most pronounced in the antrum. They appear within an average of 5 minutes of intravenous infection, and last for about 30 minutes. Metoclopramide has been found to induce pronounced antral contractions, followed by duodenal contractions (see section 1.1.3) as well as coordination of the antral and duodenal wave complexes (Pinder et al., 1976).

The effects of metoclopramide on antral activity have varied in different patient groups. In 13 patients with reflux oesophagitis, oral metoclopramide 15mg increased antral contractions from 26 to 41 (mean) per hour (Behar and Ramsby, 1978). Similarly, in 9 postoperative patients who received intravenous metoclopramide 10mg, contractile activity returned to normal in 5 patients who had no evident baseline contractions and gastric contractions increased in the other 4 patients (Davidson et al., 1977).

Fox and Behar (1980) studied the effect of intravenous metoclopramide 10mg on gastric contractions in 7 normal individuals, 7 diabetics with symptoms of delayed gastric emptying and 4 diabetic patients without such symptoms. A significant increase in the amplitude and duration (but not frequency) of antral activity occurred in normal and asymptomatic diabetic subjects. In diabetics with delayed gastric emptying there was an increase in the number of antral contractions or in total antral activity but the change was not statistically significant. In these same patients, however, bethanechol 5mg (subcutaneously) produced a marked increase in the number of antral contractions and in cumulative antral activity, to near normal values.

Interdigestive motor motility after intravenous metoclopramide 10mg was studied in 17 patients with delayed gastric emptying (10 post-vagotomy and 7 diabetic). Phase III activity (a burst of high amplitude contractions) was often observed in the fundus of post-vagotomy patients immediately after intravenous metoclopramide but was not seen in patients with severe diabetic gastroparesis (Mala-

gelada et al., 1980). However, such diabetics have experienced symptomatic improvement (see section 3.1.2) in the absence of marked measurable effect.

Thus, the effect of metoclopramide on gastric contractile activity appears to be more pronounced, and therefore more easily demonstrated, in patients with oesophageal reflux, vagotomy or other gastrointestinal surgery, and in asymptomatic diabetic patients.

Gastric Emptying

Metoclopramide 10mg given in single intravenous, intramuscular or oral doses to diabetic patients with gastroparesis has been shown to increase significantly gastric emptying of both solid (fig. 3) and liquid meals, by isotope-labelled (e.g. Berkowitz et al., 1976; Brady and Richardson, 1977; Campbell et al., 1977) and radiological methods (Braverman and Bogoch, 1978; Perkel et al., 1981). Enhancement of gastric emptying after metoclopramide 10 to 30mg orally or parenterally has also been shown in patients with idiopathic and postinfectious delayed gastric emptying, and that associated with vagotomy and other gastric surgery, anorexia nervosa and gastric ulcer (Davidson et al., 1977; Millar et al., 1980; Perkel et al., 1981; Rhodes et al., 1979; Saleh and Lebwohl, 1980). Levodopa administration to normal individuals has been shown to reduce gastric emptying, and single-dose metoclopramide antagonises this effect, returning gastric emptying to normal (Berkowitz and McCallum, 1980). Metoclopramide has been shown to accelerate gastric emptying in women in labour, as discussed in a previous review (Pinder et al., 1976).

Multiple-dose studies in post-vagotomy patients as well as in patients with diabetic gastroparesis indicate that intramuscular or oral metoclopramide 10 to 15mg 3 or 4 times daily accelerates the rate of gastric emptying (Battle et al., 1979; Hartong et al., 1977; Longstreth et al., 1977; Metzger et al., 1976; Millar et al., 1980; Wright and

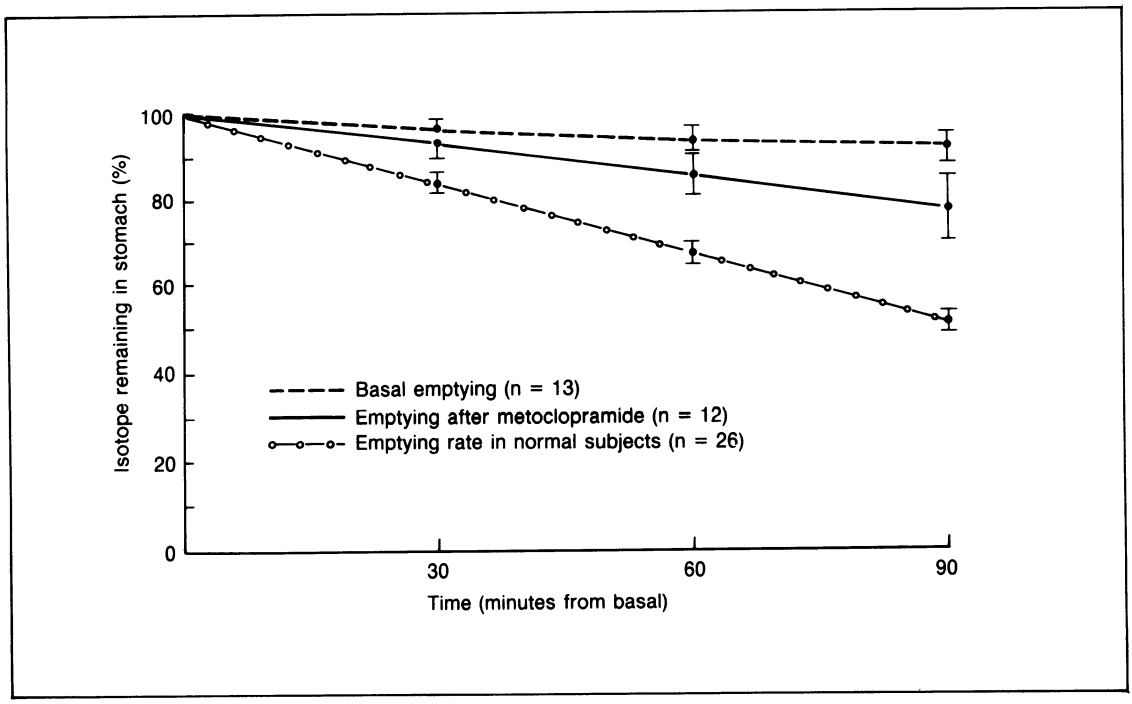

Fig. 3. Effect on gastric emptying of intramuscular metoclopramide 10mg in 13 diabetic patients with gastric stasis given an isotope-labelled egg salad sandwich meal (mean values ± SEM).

MacGregor, 1979). However, in healthy controls and some patients with diabetic gastroparesis, no significant increase in gastric emptying was demonstrated (Metzger et al., 1976; Millar et al., 1980). Millar et al. (1980) failed to specify the dose of metoclopramide administered to his diabetic patients, and therefore it cannot be determined if it was sufficient to be expected to elicit a response.

Gastric Secretion

Studies in healthy volunteers, both pre- and post-vagotomy duodenal ulcer patients, and patients with reflux oesophagitis have shown that metoclopramide has no significant effect on gastric acid secretion or on serum levels of gastrin (Cohen et al., 1976; Pinder et al., 1976).

1.1.3 Effects on the Small Intestine

In animals, healthy volunteers, pregnant women and patients with impaired gastrointestinal motility, metoclopramide stimulates contraction of smooth muscle, resulting in a decreased transit time through the small intestine. These effects are antagonised by anticholinergic agents (Pinder et al., 1976).

The increase in frequency and amplitude of duodenal contractions in healthy individuals occurs within 15 minutes of intravenous administration of metoclopramide 10 to 20mg and lasts about 10 to 30 minutes (Banke, 1969). This effect was observed whether the resting duodenal pressure was high or low, and simultaneous recording of antral and duodenal contractions revealed that an antral contraction was usually followed by a series of duodenal pressure waves (Eisner, 1971). Metoclopramide-induced coordination of antral and duodenal contractions, as well as a significant increase in the amplitude of duodenal contractions, has also been observed in patients with disorders of digestion, but no change was evident in the number of contractions or in total activity. Metoclopramide had no effect in patients without basal duodenal activity (Johnson, 1971, 1973).

The stimulatory effect of metoclopramide on motility of the small intestine has been confirmed in studies measuring small intestine transit times. It is generally agreed that in dyspeptic patients the transit time of barium suspension from the pylorus to the ileocaecal valve is shortened by metoclopramide from about 160 to 60 minutes (Pinder et al., 1976; Schulze-Delrieu, 1979). Metoclopramide has been found to be a stronger stimulant of duodenal motility than pyridostigmine bromide (Oigaard and Fleckenstein, 1975).

1.1.4 Effects on the Large Intestine

The effect of metoclopramide upon colonic motility remains controversial. *In vitro,* metoclopramide increased the magnitude and frequency of contractions of circular strips of colonic smooth muscle from humans and animals (Schulze-Delrieu, 1979). In most studies *in vivo,* however, no consistent effect on colonic motility has been demonstrated. Whether metoclopramide is without consistent effects on the large intestine or the investigational methods are inadequate remains to be determined. Metoclopramide had no effect on motility in the canine intact colon, but effects were measured after administration of an anaesthetic which markedly decreased motility (Jacoby and Brodie, 1967). In patients, as judged by the position of a radiopill, metoclopramide had no effect on movement of luminal contents in the colon (Eisner, 1971).

However, in more recent studies in diabetic patients with severe autonomic neuropathy, Battle et al. (1980) demonstrated an increase in colonic 'spike' and motor activity after administration of 20mg of intravenous metoclopramide or intramuscular neostigmine. In this study, a stimulatory effect on colonic myoelectrical and motor activity was shown, suggesting metoclopramide may be of value in patients with constipation due to diabetic autonomic neuropathy.

In addition, intravenous metoclopramide 10mg stimulated colonic 'spike' potentials and contractile activity in 4 of 10 patients with progressive systemic sclerosis (Battle et al., 1981). The non-responders, who had long-standing progressive systemic sclerosis and severe systemic symptoms, had neither spontaneous colonic activity nor any response to either neostigmine or metoclopramide.

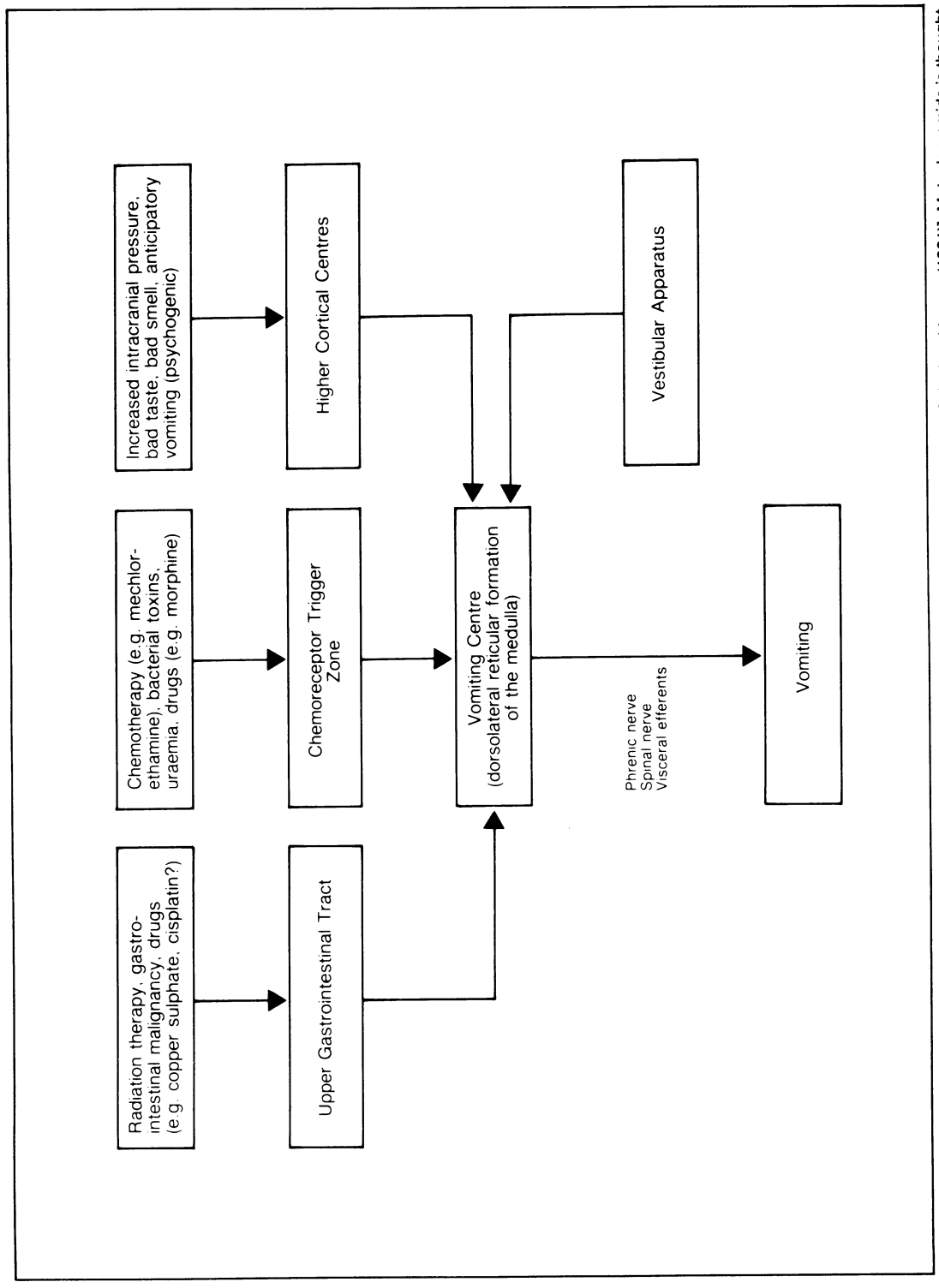

Fig. 4. Diagrammatic presentation of the vomiting reflex pathways [adapted from Frytak and Moertel (1981) and Seigel and Longo (1981)]. Metoclopramide is thought to have antiemetic effects at both peripheral (gastrointestinal) and antral (chemoreceptor trigger zone) sites.

It has been hypothesised that the colonic smooth muscle in these patients is unable to respond to any stimulus. This was confirmed by histological examination which revealed severe fibrosis and atrophy of the colonic muscular wall.

1.1.5 Effects on the Biliary Tract

Although increased contractile activity of muscle strips from human and guinea-pig gallbladder has been shown after exposure to metoclopramide (Schulze-Delrieu, 1979), no consistent effect of the drug on gallbladder contraction in humans or whole animals has been demonstrated (Pinder et al., 1976). Kateuvow (1975) found that intravenous metoclopramide 20mg had no effect on gallbladder size or contraction compared with placebo, in a double-blind study in 45 patients undergoing cholecystography. Metoclopramide had no effect on the release of human cholecystokinin since it did not affect normal gallbladder contraction stimulated by a fatty meal (Kanto and Kateuvow, 1981), leading the authors to suggest the possible usefulness of metoclopramide as an antiemetic in patients with gallstones.

1.1.6 Antiemetic Effects

The physiology of emesis has recently been reviewed (Frytak and Moertel, 1981; Seigel and Longo, 1981). Figure 4 outlines the pathways for the vomiting reflex. When impulses from any of the 4 trigger sites exceed the threshold in the vomiting centre the act of vomiting is initiated. Metoclopramide is thought to have antiemetic effects at both peripheral (gastrointestinal) and central (chemoreceptor trigger zone) sites.

Metoclopramide is effective in preventing apomorphine-induced vomiting in man (Klein et al., 1968), and in animals is a potent antagonist of vomiting induced by apomorphine, hydergine, reserpine, tetrodotoxin and copper sulphate (Pinder et al., 1976).

Following intravenous or intramuscular administration of metoclopramide 0.15 to 0.3 mg/kg to patients with various disorders, it has been shown to be effective in decreasing postoperative vomiting as well as the nausea and vomiting associated with certain drugs (antineoplastic drugs, narcotic analgesics, digitalis, tuberculostatic agents and antibiotics), radiation therapy and pregnancy (see sections 3.2.1, 3.2.2, 3.2.3 and 3.2.4, respectively).

In patients receiving cisplatin, high dose intravenous metoclopramide (2 mg/kg) either prevented nausea and vomiting or reduced the number and duration of emetic episodes and volume of emesis (see section 3.2.2).

1.1.7 Mechanism of Gastrointestinal Effects

Metoclopramide's exact mechanism of action in the gastrointestinal tract remains unclear. However, it is established that metoclopramide-induced oesophageal and gastric contractions are inhibited by anticholinergic agents such as atropine, and potentiated by cholinergic drugs such as carbachol and methacholine. Metoclopramide has no anticholinesterase activity and its actions are not affected by ganglion blocking agents (Pinder et al., 1976). Since vagotomy does not influence metoclopramide's gastrointestinal effects, this suggests that a site of action is located at peripheral nerve endings in gut muscle (Stadaas and Aune, 1971). There are 3 current hypotheses proposed to explain the mechanism of action of metoclopramide on gastrointestinal smooth muscle:

1. Potentiation of cholinergic effects
2. Inhibition of dopaminergic (or tryptaminergic) inhibitory motor neurons
3. Direct action on smooth muscle.

The cholinergic effects of metoclopramide may be due to release of acetylcholine (Hay et al., 1977; Hay and Man, 1979). It may also sensitise muscarinic receptors to acetylcholine in gastrointestinal smooth muscle (Eisner, 1968; Birtley and Baines, 1973; Okwuasoba and Hamilton, 1976) or facilitate cholinergic mechanisms by some other action (Zar et al., 1982). Metoclopramide may therefore activate intramural cholinergic neurons responsible for modifying gastric motility, but not acid secretion, either by direct stimulation or by removal of inhibitory pathways.

Recent experiments have provided evidence that dopamine is an inhibitory neurotransmitter in the oesophagus and stomach of animals and man, and

that metoclopramide acts by antagonising this inhibitory neurotransmitter (Baumann et al., 1976, 1979; Berkowitz and McCallum, 1980; DeCarle and Christensen, 1976). Thus, in a randomised double-blind trial in volunteers, the effects of levodopa and metoclopramide given alone and in combination on lower oesophageal sphincter pressure were measured (Baumann et al., 1979). The increase in lower oesophageal sphincter pressure seen after orally or intravenously administered metoclopramide was inhibited by oral levodopa, and mean lower oesophageal sphincter pressure was significantly less after levodopa administration than after placebo. However, levodopa pretreatment did not inhibit the effect of bethanechol (0.07 mg/kg subcutaneously) on increasing lower oesophageal sphincter pressure. These data are consistent with the hypothesis that the mechanism of action of metoclopramide on the lower oesophageal sphincter is likely to be due to antagonism of dopamine inhibition. However, opposing effects of dopamine and its antagonists on gastrointestinal smooth muscle does not provide proof that dopamine is the inhibitory neurotransmitter in the gut (DeCarle and Christiansen, 1976).

The same investigative group (Berkowitz and McCallum, 1980) used a similar methodology to evaluate the effects of levodopa and metoclopramide on gastric emptying in man. In 7 healthy volunteers receiving levodopa, the mean percentage of radio-labelled solid-liquid meal remaining in the stomach at 90 minutes was significantly greater in those receiving placebo (85% *versus* 55%, respectively). In 4 volunteers given metoclopramide 10mg intramuscularly with levodopa 1000mg and the same test meal, the mean percentage of test meal remaining at 90 minutes was significantly less than when the individuals received levodopa alone (49% *versus* 83%, respectively). The conclusions reached were that levodopa inhibited gastric emptying, metoclopramide antagonised this effect, and that dopaminergic receptors have an inhibitory effect on gastric emptying in man.

Attributing the gastrointestinal effects of metoclopramide to dopamine antagonism is consistent with other known actions of metoclopramide in the central nervous system (see sections 1.1.6, 1.2), endocrine (see section 1.4) and cardiovascular system (see section 1.3).

Cohen and DiMarino (1976) investigated the effect of metoclopramide on the lower oesophageal sphincter muscle of the opossum. Metoclopramide induced a dose-related increase in tension which was not blocked by anticholinergics, hexamethonium, tetradotoxin, phentolamine, propranolol or diphenhydramine. Its effects also were not potentiated by gastrin I, acetylcholine or norepinephrine. From these observations it was suggested that metoclopramide exerted a direct effect on lower oesophageal smooth muscle. However, no dopamine agonist or antagonist substance was tested in this *in vitro* system.

Antiemetic Action

As described in a previous review in the Journal (Pinder et al., 1976), metoclopramide is thought to affect directly the chemoreceptor trigger zone for vomiting, raising its threshold of activity and preventing vomiting by centrally acting emetics. Metoclopramide also decreases the sensitivity of visceral nerves which transmit afferent impulses from the gastrointestinal tract to the emetic centre in the lateral reticular formation.

Since stimulation of the chemoreceptor trigger zone is specific to dopamine-like drugs, antiemetic agents which are believed to block this zone are usually also central dopaminergic antagonists (Cannon, 1975). Metoclopramide has behavioural effects in animals and adverse effects in man which reflect central dopaminergic antagonism (Dolphin et al., 1975; see sections 1.2 and 5.1), and its antiemetic effects are probably mediated, at least partly, by blockade of dopamine receptors in the chemoreceptor trigger zone. In the cat encephale isole, the antiemetic effect of metoclopramide has been related to its selectively suppressive effect on the spontaneous electrically stimulated or apomorphine-induced firing of single neurons in the nucleus tractus solitarii of the brainstem (Takaori et al., 1968). Metoclopramide also had an inhibitory action on the nucleus vestibularis, indicating a possible antivertigo effect (see section 3.3.1).

Metoclopramide probably also has a peripheral mechanism of action, as suggested by its prevention of copper sulphate-induced emesis. Small doses of the drug have been reported to prevent apomorphine-induced emesis without changes in behaviour or autonomic function (Takaori et al., 1967). In addition, metoclopramide markedly increases gastric motor activity and this effect probably prevents the gastric relaxation which precedes the act of vomiting. Ramsbottom and Hunt (1970) showed that metoclopramide prevented apomorphine-induced gastric immobility.

1.2 Central Nervous System Effects

The central nervous system (CNS) effects produced by metoclopramide include those characteristic of neuroleptics in producing catalepsy and reversing the behavioural effects of amphetamine and apomorphine in animals. Antagonism of central dopamine receptors is evidenced by its antiemetic (see section 1.1.6), extrapyramidal and antipsychotic effects (after high doses), and possibly also by the increased prolactin release (see section 1.4.1) that occurs in patients and normal individuals.

The apparent blockade of cerebral dopamine receptors by metoclopramide in animal studies is believed to be a direct central action of the drug itself rather than that of a metabolite (Donaldson et al., 1976; Rotrosen et al., 1981). Costall and Naylor (1973, 1974) have shown metoclopramide-induced catalepsy to be dose-dependent, and similar in some but not all respects to that induced by phenothiazines or butyrophenones.

For example, metoclopramide differs from typical neuroleptic agents in not antagonising hyperactivity induced by dopamine injection into the nucleus accumbens area of the rat mesolimbic system (Costall and Naylor, 1976), and in not antagonising dopamine-stimulated adenylate cyclase *in vitro* or readily displacing radio-labelled ligands (e.g. ^{3}H-spiroperidol) from sites in anterior pituitary tissue (Meltzer et al., 1979). Several hypotheses have been proffered to explain this atypical profile.

There is biochemical and pharmacological evidence of at least 2 distinct categories of dopamine receptors (Kebabian and Calne, 1979). The nomenclature designating the dopamine receptor stimulating adenylate cyclase as the D_1-receptor and the dopamine receptor not enhancing adenylate cyclase activity as the D_2-receptor is now widely accepted (Kebabian et al., 1982). However, the classification of dopamine receptors remains controversial. Most classical neuroleptic agents are antagonists of both D_1- and D_2-receptors. Jenner et al. (1978) determined in rats and mice that substituted benzamide agents, such as metoclopramide, appear to act on cerebral dopamine receptors that are independent of dopamine-sensitive adenylate cyclase and are not balanced by a cholinergic input. Thus, metoclopramide has been classified as selective D_2-receptor antagonist. Although numerous theories have been forwarded, the molecular site and mechanism of action of metoclopramide (and other benzamide derivatives) remains unclear, as the lack of potency which the benzamides display at either D_1- or D_2-receptor sites suggests that neither receptor offers a full explanation for the pharmacological actions of these drugs (Wazer et al., 1982). However, available evidence in rodents suggests that subpopulations of D_1- and D_2-receptors exist, and that a subpopulation of D_2-receptors are functionally important as mediators of metoclopramide's action (Rotrosen et al., 1981).

Metoclopramide has also been observed to worsen extrapyramidal symptoms in Parkinsonian patients (Grimes et al., 1982a) and probably should not be administered to such patients. Prolonged blockade of central dopaminergic receptors can result in receptor hypersensitivity and tardive dyskinesia, an infrequent, though serious, side effect of metoclopramide, thought to involve both D_1- and D_2-receptors (Bateman et al., 1979a; Jenner and Marsden, 1979).

The possible usefulness of high doses (520 to 1000 mg/day) of metoclopramide as an antipsychotic agent (Stanley et al., 1980) further attests to its central activity. Earlier studies which used lower dosages found metoclopramide of little value as an antipsychotic drug (Bornstein and Bleo, 1965;

Nakra et al., 1975). On the basis of *in vivo* effects on dopamine turnover, metoclopramide has been predicted to be equipotent with chlorpromazine as an antipsychotic agent (Stanley and Wuk, 1979).

1.3 Cardiovascular Effects

Although animal studies have not revealed any significant effect of metoclopramide on blood pressure or intracardiac conduction, occasional instances of hypotension during general anaesthesia, hypertensive crisis in a patient with phaeochromocytoma, and cardiac arrhythmias have been reported in man.

As previously reviewed (Pinder et al., 1976), in animals blood pressure responses to acetylcholine, adrenaline, histamine, noradrenaline and nicotine, or to carotid artery occlusion, were not influenced by metoclopramide. In anaesthetised animals, low doses of intravenous (< 1 mg/kg/min for 90 to 100 minutes) or oral (5 to 10 mg/kg) metoclopramide had no effect on blood pressure, whereas higher doses produced transient hypotension (Pinder et al., 1976).

In patients whose blood pressure had been (or still was) decreased during general anaesthesia, intravenous metoclopramide 10mg caused a further clinically significant fall of 17.5mm Hg in mean arterial pressure in one study (Park, 1978) and of 20 to 22% in diastolic and systolic pressure in another (Pegg, 1980).

The aetiology of metoclopramide-induced hypotension is unclear. Park and Pegg attributed the hypotension to peripheral vasodilation and possibly membrane depression because of metoclopramide's structural similarity to procainamide. The hypothesis concerning membrane depression, however, is in conflict with earlier data (Thorburn and Sowton, 1973) in which cardiac output was unchanged after metoclopramide administration.

It is of interest that to date hypotension has not been reported after administration of high dose metoclopramide (1 to 3 mg/kg) for chemotherapy-induced nausea and vomiting.

Hypertensive crisis has occurred in 3 patients with phaeochromocytoma who were given 10mg of metoclopramide intravenously (Agabiti-Rosei et al., 1977; Plouin et al., 1976). A similar reaction has been reported previously with sulpiride, an agent which possesses neuroleptic and central antiemetic effects and is chemically related to metoclopramide. Postoperatively, 1 patient with normal blood pressure and plasma catecholamines was rechallenged, but both parameters remained unchanged (Agabiti-Rosei et al., 1977). Thus, the use of metoclopramide in patients suspected to have phaeochromocytoma is contraindicated because it is believed to cause catecholamine release from the tumour.

As reported in a previous review, electrocardiogram recordings were normal in dogs receiving up to 15 mg/kg of intravenous metoclopramide (Pinder et al., 1976). Also, after intravenous doses of 20mg metoclopramide, 4 patients undergoing His bundle electrocardiograms (conducted to investigate syncopal episodes, extrasystoles or tachycardia) exhibited no changes in intracardiac conduction over a period of 20 minutes. Other haemodynamic parameters (pulmonary artery systolic or diastolic pressures, cardiac output) measured in this study were unchanged after metoclopramide administration (Thorburn and Sowton, 1973).

However, arrhythmias were later reported in 2 patients. Shaklai et al. (1974) observed a female patient in whom 10mg of intramuscular metoclopramide resulted in reproducible multifocal supraventricular extrasystoles. Also, a suspected colitis patient undergoing endoscopy experienced bradycardia and asystole, followed by atrial extrasystoles after 15 to 17mg of intravenous metoclopramide (Schulze and Winkler, 1978). The discrepancy between animal and early human data and the above case reports cannot be easily explained. The phenomenon is rare, not dose-related and possibly could be secondary to a previously undetected cardiac disorder in these patients.

1.4 Endocrine Effects

Metoclopramide is a central dopamine receptor antagonist which stimulates prolactin release, ap-

parently by blocking dopamine-mediated hypothalamic or pituitary (Besser et al., 1980) inhibition of prolactin secretion. Also, metoclopramide causes transient increased secretion of aldosterone either by a direct action on the adrenal cortex or indirectly through dopaminergic or other unknown mechanisms modulating aldosterone secretion.

1.4.1 Effects on Prolactin Release

Metoclopramide has been shown to stimulate the release of prolactin and reduce the amount stored in the pituitary gland in rats (Fang et al., 1977). The exact mechanism involved is not clear however, as high concentrations of metoclopramide, domperidone, haloperidol and chlorpromazine inhibit prolactin release (Besser et al., 1980). The administration of intravenous or oral metoclopramide 2.5 to 10mg in single dose studies and after repeated administration (Graf et al., 1982, Kauppila and Ylikorkala, 1982), has been shown to increase serum prolactin concentration in healthy adults, children, pregnant women and patients with endocrine disorders. After intravenous administration, elevation of serum prolactin is evident within 5 minutes, reaches a peak at 30 minutes and lasts for 2 to 4 hours. After oral administration the increase begins within 15 minutes, is maximal at 90 minutes and lasts for 9 hours (Brandes et al., 1981; Dammacco et al., 1977; McCallum et al., 1975a; Matsumura et al., 1977).

After either oral or intravenous administration, healthy adult volunteers exhibit an average mean increase in serum prolactin of 35.7 ng/ml (13.6 to 95 ng/ml), while children showed a mean increase of 30.5 ng/ml (23.3 to 42.3 ng/ml) and pregnant women 195.4 ng/ml (Brandes et al., 1981; Carey et al., 1979; Dammacco et al., 1977; Ijaiya et al., 1980a,b; McCallum et al., 1975a; Matsumura et al., 1977; Ogihara et al., 1977; Sowers et al., 1977). Although the numerical mean increase in pregnant women is markedly elevated, so also is the basal value. In chronic schizophrenic patients treated with metoclopramide 320 to 1000mg daily for up to 3 weeks, mean plasma prolactin increased from 8.8 to 47.8 ng/ml (Stanley et al., 1980). Thus, there is about a 6-fold increase in all groups of patients.

It has been suggested that the increase in serum prolactin occurs because metoclopramide blocks dopamine-mediated hypothalamic inhibition of prolactin secretion. Although it is well known that dopamine has an inhibitory effect on prolactin secretion, it has recently been postulated that dopamine itself may be the neurohormone prolactin inhibitory factor (PIF) [Mantero et al., 1981]. This is supported to some degree by the finding that metoclopramide-induced prolactin release was inhibited by levodopa (Sowers et al., 1976) and practically abolished by pretreatment with bromocriptine (which acts directly on the pituitary to inhibit prolactin release and synthesis) [Delitala et al., 1975]. Short term corticosteroid administration also suppressed the prolactin response to metoclopramide in healthy volunteers, probably via a direct effect on the anterior pituitary.

It is of interest that domperidone, a potent dopamine antagonist antiemetic which does not readily cross the blood-brain barrier (Brogden et al., 1982), also increases prolactin levels (Brouwers et al., 1980; Solvens et al., 1982). That prolactin was increased at all by domperidone could be attributed to domperidone's effects on the pituitary itself which is outside the blood-brain barrier.

1.4.2 Effects on Aldosterone

Metoclopramide has been shown by Edwards et al. (1980) to directly stimulate aldosterone release in rat zona glomerulosa cells but no direct effect could be demonstrated by Lanella and Bravo (1982) in rabbits. In singe-dose studies, transient increases in plasma aldosterone concentration occur in healthy volunteers without changes in other related biochemical variables, including ACTH, and plasma potassium or renin (Brown et al., 1979; Carey et al., 1979; Mantero et al., 1981; Norbiato et al., 1977). Conflicting data have been presented by Ogihara et al. (1977), who reported that intravenous administration of metoclopramide 5mg to healthy adults resulted in a significant increase in serum prolactin but not in serum aldosterone. The reason for this divergent result (other than the low dose administered) is obscure. However, there was considerable interindividual variation in plasma

aldosterone concentrations in both study and control subjects in this study.

Metoclopramide causes a transient elevation in plasma aldosterone by increasing aldosterone secretion and release; it does not change the metabolic clearance of aldosterone. Measurement of aldosterone secretion rate has revealed a return to baseline values by the fourth day of continuous treatment (Brown et al., 1981). This explains the observation that chronic metoclopramide treatment does not cause hyperaldosteronism.

Norbiato et al. (1979) found intravenous metoclopramide to produce a greater absolute change in plasma aldosterone concentrations in patients with idiopathic oedema than in controls. Plasma renin activity after metoclopramide was also consistently high in patients. Combination levodopa-carbidopa administration led to reduced plasma renin activity and reduced aldosterone levels suggesting decreased dopaminergic activity as a cause for this oedema.

Dopamine infusion has been shown to inhibit metoclopramide-induced increases in plasma aldosterone and prolactin concentrations in normal volunteers. The dopamine agonist, bromocriptine, suppressed metoclopramide-stimulated prolactin release; however, it did not suppress metoclopramide-stimulated aldosterone release (Carey et al., 1980). Since bromocriptine did not inhibit the metoclopramide-induced aldosterone response, the speculation of distinct dopamine receptors being involved in aldosterone and prolactin secretion is raised.

1.4.3 Other Effects

The effect of metoclopramide on growth hormone release is somewhat controversial. Metoclopramide has been shown not to stimulate growth hormone release in animals (Fang et al., 1977) or normal adults (Healy and Burger, 1978; Judd et al., 1976; Masala et al., 1978). After administration of metoclopramide to 8 children of short stature, Ijaiya et al. (1980b) also observed no growth hormone response. However, Cohen et al. (1979) have demonstrated that metoclopramide stimulated the release of growth hormone in 29 of 35 adolescent

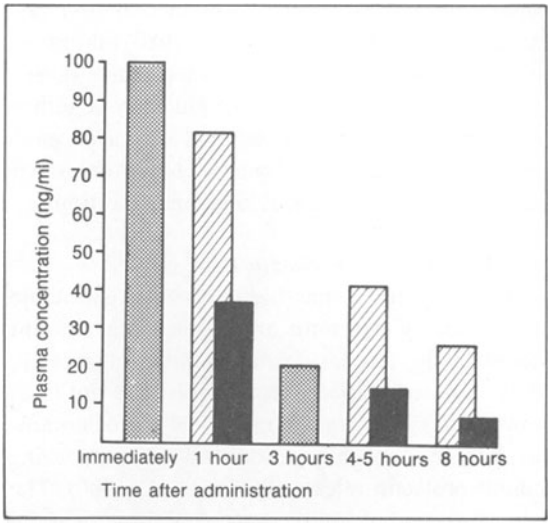

Fig. 5. Mean plasma metoclopramide concentration after intravenous administration of 10mg (▨) over 30 minutes and oral administration of 10mg (■) and 20mg (▨) [data from Bateman et al., 1980].

males with short stature, and in 10 hypogonadal adult males. It is possible that this response may be dependent upon the sex hormone status of the individuals (Ijaiya et al., 1980b), and until clarified, metoclopramide administration cannot be recommended as a reliable test for growth hormone deficiency in children.

Metoclopramide has been reported to decrease ACTH-stimulated growth hormone secretion (Pinto et al., 1977). It also diminishes the prolactin response to thyrotrophin releasing hormone (TRH) in normal women (Healy and Burger, 1978). Metoclopramide suppresses TRH-stimulated parathormone secretion (Bernheim et al., 1979).

Metoclopramide also stimulates human pancreatic polypeptide release and atropine has been shown to abolish this pancreatic response to metoclopramide (Spitz et al., 1978). However, any clinical relevance of this observation is not yet apparent.

1.5 Effects on the Urinary Tract

It has been suggested that dopamine, serotonin (5-hydroxytryptamine) and prostaglandins may

have receptor site activity in vesicourethral physiology and function. Schelin (1979) hypothesised that metoclopramide could promote ureteral peristalsis and reported increased ureteral peristalsis and symptomatic improvement in a series of 4 patients with dilated hypomotile ureters who were given metoclopramide 20mg intravenously.

Metoclopramide 20mg intravenously produced no change in detrusor reflux activity or in peak urethral pressures (cystometric evaluation) in 10 patients with neurogenic bladder dysfunction (Vaidyanathan et al., 1980a), whereas haloperidol decreased peak urethral pressure (Vaidyanathan et al., 1980b). The difference in effect on urethral pressure between the drugs may be related to differing effects at dopamine receptors (section 1.2).

2. *Pharmacokinetic Studies*

Early pharmacokinetic studies in man were hampered by analytical methods of insufficient sensitivity to detect concentrations of metoclopramide in the nanogram range (Pinder et al., 1976). Other assay techniques are now available (Graffner et al., 1979; Ross-Lee et al., 1980; Tam and Axelson, 1978; Teng et al., 1977) and several single-dose pharmacokinetic studies in healthy volunteers have been completed (Bateman et al., 1978b, 1979b, 1980; Graffner et al., 1979; Ross-Lee et al., 1981).

2.1 Absorption

Metoclopramide is rapidly absorbed after oral administration, reaching peak plasma concentrations in a mean time of 0.93 hours (Ross-Lee et al., 1981). Representative mean plasma metoclopramide levels after 10 and 20mg oral and 10mg intravenous bolus doses can be found in figure 5. Peak plasma concentrations (table I) after oral administration may show considerable interindividual variation due to variable 'first-pass' metabolism (Bateman et al., 1979b; Ross-Lee et al., 1981). It has been suggested that toxic effects (dyskinesia, akathisia), or lack of consistent pharmacological effects between individuals, may be related to this variability in first-pass metabolism (Bateman et al., 1979b; Bateman and Davies, 1979; Bateman et al., 1980).

Systemic availability after a 10mg oral dose (tablet) was shown to vary between 32 and 97% (Bateman et al., 1980). The properties of a solid oral dose form have an effect on the absorption of the drug. A significant correlation between bioavailability and the urine ratio of free to conjugated metoclopramide existed, suggesting that first-pass conjugation (sulphation) is a major influence on bioavailability.

Graffner et al. (1979) administered metoclopramide as a slow-release tablet and demonstrated flat concentration-time curves, with plasma concentrations 75% higher at 10 hours after drug administration than with conventional tablets. This suggests that metoclopramide is absorbed throughout a large segment of the gastrointestinal tract. After rectal administration of metoclopramide, absorption is protracted and incomplete (Block et al., 1981), with peak plasma concentrations being attained after 1 to 3 hours, with a second peak in the plasma profile curve between 4 and 8 hours.

Table I. Peak plasma metoclopramide concentration (ng/ml) in healthy subjects after orally administered drug at 2 dose levels (10mg and 20mg). Adapted from Bateman et al. (1979b)

Subject	Peak plasma metoclopramide levels (ng/ml)	
	10mg orally	20mg orally
1	14.5	70
2	54	120[a]
3	42	138[a]
4	140[a]	131[a]
5	28.5	88
6	17	40

a Denotes presence of akathisia.

Table II. Pharmacokinetic parameters following single 10mg intravenous and 10mg oral doses of metoclopramide to healthy volunteers

Reference	Elimination half-life (h)	AUC (μg/L • h)	Volume of distribution (L/kg)	Total body clearance (ml/min/kg)	Peak plasma concentration (μg/L)	Time to peak concentration (min)
Oral dose 10mg						
Ross-Lee et al. (1981)	5.17	262.6	4.00	8.83	54.3	55.8
Intravenous dose 10mg						
Ross-Lee et al. (1981)	4.55	346.9	3.43	8.83		
Bateman et al. (1978b)	2.76		2.19	10.89		
Graffner et al. (1979)	5.4	1108[a]	2.9	477[b]		
Bateman et al. (1980)	2.61		2.22	11.61		

a nmol/L • h.
b ml/minute.

Peak plasma concentrations were lower after 40mg rectally than after 26.7mg orally in the same subjects. Similarly, mean bioavailability was lower after rectal (53%) than after oral administration (76 to 79%).

2.2 Distribution

A 2-compartment model has been found to adequately describe the disposition of intravenous metoclopramide (Bateman et al., 1980). After a 10mg intravenous dose, there is an initial rapid fall in plasma concentration (table II), reflecting metoclopramide's rapid distribution in the body as expected with a lipid-soluble, basic drug. The mean volume of distribution at steady-state is relatively high (2.2 to 3.4 L/kg), indicative of extensive extravascular distribution.

Data regarding distribution into specific organ systems in man are few. In mice, highest concentrations after intragastric or intramuscular administration were in the intestinal mucosa, the liver and biliary tracts, and the salivary glands. Lesser amounts were present in the central nervous system, heart, thymus, and suprarenal glands, and in fat and bone marrow. In the central nervous system metoclopramide was localised in the area postrema, which contains the chemoreceptor trigger zone for vomiting in man (Pinder et al., 1976).

Metoclopramide appears to readily enter into breast milk (Lewis et al., 1980). 10 mothers who were breast feeding their infants (for 7 to 10 days after delivery) were given a 10mg oral dose of metoclopramide. Two hours after administration mean plasma and milk concentrations were 68.5 ng/ml and 125.7 ng/ml, respectively.

Metoclopramide is known to be weakly bound to plasma proteins in animals and men; (Denisoff and Moller, 1978; Pinder et al., 1976), but is more weakly bound to human than to bovine serum albumin, and appears to bind at only 1 site (Denisoff and Moller, 1978).

2.3 Elimination

2.3.1 Metabolism and Excretion

Within 24 hours after administration of 10 to 20mg doses of oral metoclopramide in healthy volunteers, about 80% of a dose is excreted in the urine either as unchanged drug (up to 25%), 2 me-

tabolites, or as sulphate and glucuronide conjugates of non-metabolised drug (Bateman et al., 1980; Teng et al., 1977). A major metabolite is the N-4-sulphate of metoclopramide which accounts for 32% and 40% of the dose recovered after intravenous and oral administration, respectively (Bateman et al., 1980).

Total body plasma clearance approximates liver plasma flow (11.61 ml/min/kg). Renal clearance accounts for 20% of total body clearance (2.6 ml/min/kg) [Bateman et al., 1980]. Since renal clearance is about 2.6 ml/min/kg, and total body plasma clearance about 11.61 ml/min/kg (approximating predicted values of liver plasma flow), this suggests that its clearance is probably limited by liver blood flow rather than liver metabolic capacity.

Half-life

The elimination half-life of metoclopramide after oral administration of 10mg is 4.2 to 5.1 hours (table II) and after intravenous and intramuscular administration of the same dose is 2.6 to 4.6 hours and 3.6 hours, respectively (Bateman et al., 1979b; Graffner et al., 1979) in studies in which blood sampling was not done longer than 12 hours after administration. With more sensitive analytical methods and incorporation of longer sampling times an elimination half-life of 5.1 to 6 hours has been recorded (data on file, Robins).

Single-dose studies have suggested dose-dependent elimination (Bateman et al., 1979b), but more recent studies (data on file, Robins) have failed to demonstrate dose-dependent pharmacokinetics with oral doses of up to 100mg.

2.4 Effect of Disease States on Pharmacokinetics

Although renal clearance accounts for only about 20% of total body clearance of metoclopramide, side effects (extrapyramidal reactions) appear to occur more commonly in patients with renal failure (Bateman and Davies, 1979; Bateman and Gokal, 1980; Caralps, 1979). In 6 patients with chronic renal failure (creatinine clearance less than 14 ml/min) the average elimination half-life after single 10mg oral and intravenous doses was approximately 14 hours. Total body clearance was 16.7 L/hour (normals 52.5 L/hour) [Bateman et al., 1981]. The change in total body clearance cannot be entirely explained by reduced renal clearance since the renal route accounts for only 20% of total clearance in normals. This suggests that renal metabolism and/or an enterohepatic circulation of the sulphate conjugate may also occur in renal failure. A reduction in dose of at least 50% is recommended in patients with severe renal failure (Bateman et al., 1981).

In rats with hepatic failure a 3-fold increase in half-life and decrease in body clearance was observed (Tam et al., 1981). No human pharmacokinetic studies have been conducted to date in patients with hepatic failure.

2.5 Plasma Concentrations and Clinical Effects

An apparent correlation between plasma metoclopramide concentrations and gastric emptying of ethanol (70 ml/kg), as evidenced by the decreased time to peak ethanol plasma concentration and the degree of ethanol-induced sedation, has been demonstrated after intravenous administration of 10mg of metoclopramide to healthy volunteers (Bateman et al., 1978b). A linear relationship between plasma concentrations of metoclopramide and prolactin was also observed after intravenous administration. However, no association between plasma metoclopramide concentrations and gastric emptying was found after oral administration of 10 or 20mg doses (Bateman et al., 1979b). Although it has been suggested that metoclopramide-induced tremor in Parkinsonian patients may be related to dose and plasma concentration (Bateman et al., 1978a), dystonic reactions in children do not appear to be related to plasma concentrations of metoclopramide (Bateman et al., 1983).

As suggested by the authors it is possible that rapid delivery of high concentrations of the drug to the brain (as is obtained with intravenous dos-

ing) is required to produce an effect on the stomach. Subsequent decline of drug effect may then be unrelated to the plasma concentration.

3. Therapeutic Trials

Since the previous review of metoclopramide in the Journal (Pinder et al., 1976), the results of adequately controlled trials have documented the usefulness of metoclopramide in alleviating the symptoms of several gastrointestinal disorders other than vomiting. However, objective improvement in the presumed underlying pathophysiological defect has not been consistently demonstrable. Some apparent differences may be due to the various methods of measuring the end-point (e.g. use of solid *versus* liquid meal to monitor gastric emptying). Metoclopramide reduces the symptoms of gastro-oesophageal reflux disease (section 3.1.1) and functional gastrointestinal disorders (section 3.1.5). The role of metoclopramide in dyspepsia established by earlier controlled trials remains intact (section 3.1.3). There is additional evidence in recent controlled trials to support earlier observations of successful management of gastric stasis associated with gastric resection and vagotomy or diabetes mellitus (section 3.1.2) with metoclopramide. Larger patient populations are needed however, to confirm its apparent efficacy in diabetic gastroparesis. The optimum dose for management of gastric stasis has yet to be established and may in part explain the controversial results. Recent trials have failed to confirm that metoclopramide enhances healing or alleviates the symptoms of peptic ulceration (section 3.1.3).

The antiemetic efficacy of metoclopramide in postoperative patients (section 3.2.1), narcotic-induced vomiting (3.2.2), radiation sickness (3.2.3), vomiting of pregnancy (3.2.4) was established at the time of the earlier review (Pinder et al., 1976). Despite preliminary reports to the contrary, a major new role for metoclopramide has emerged in the management of cisplatin-induced emesis (section 3.2.2). The positive outcome of recent studies may be partially attributed to rigorous methodology which includes the use of high dose parenteral metoclopramide, controlled hospital environment throughout the observation period, patients previously unexposed to cisplatin (*versus* those rendered refractory during earlier courses), and a uniform emetogenic stimulus in all patients. Additional trials are needed to determine the efficacy of metoclopramide in controlling emesis due to other antineoplastic drugs, in maintaining control during subsequent courses, and in treating previously exposed patients.

Metoclopramide has recently been evaluated in disorders not traditionally managed with gastrointestinally active drugs. Additional uncontrolled trials support earlier reports of activity in migraine headache (3.3.1). New evidence suggests that the therapeutic effect may be due to correction of the delayed absorption accompanying migraine which compromised the oral bioavailability of analgesics. Controlled studies are needed to determine the significance of recent small trials in which metoclopramide improved defective lactation and corrected low serum prolactin (section 3.3.2), corrected orthostatic hypotension associated with Parkinson's disease (3.3.4), and alleviated the symptoms of tardive dyskinesia (3.3.5).

3.1 Gastrointestinal Disorders Other than Vomiting

3.1.1 Gastro-Oesophageal Reflux

The symptoms of gastro-oesophageal reflux disease (heartburn and regurgitation of sour fluids) are due at least in part to incompetency of the lower oesophageal sphincter. There is also evidence of slow gastric emptying of solid food (Albibi and McCallum, 1983). Regurgitation of gastrointestinal secretions into the oesophagus results in local mucosal damage (Behar, 1976). On the basis of its pharmacodynamic activity (section 1.1.1), metoclopramide would appear to correct the underlying defects. However, controlled and uncontrolled studies have produced inconsistent results (Pinder et al., 1976) [table III]. With 1 exception (Johnson, 1971), initial double-blind studies demonstrated no

Table III. Summary of double-blind trials of metoclopramide in patients with oesophageal reflux disease

Reference	No. of patients	Daily dose (mg)	Results[a]		
			heartburn	LESP	oesophageal erosion
Johnson (1971)	47	30	MCP > P	ND	ND
Venables et al. (1973)	15	30	MCP = P		
Paull and Grant (1974)	31	40	MCP = P		
McCallum et al. (1977)	31	40	MCP > P	MCP = P	ND
Bright-Asare and El-Bassoussi (1980)	50	40	MCP = CIM > P	MCP = CIM = P	MCP = CIM = P
Winnan et al. (1980)	19	40	MCP > PA	MCP > PA	ND
Cohen (Unpubl.)	33	60	MCP > P	MCP > P	MCP > P

Abbreviations: MCP = metoclopramide; CIM = cimetidine; P = placebo; PA = placebo plus antacid; ND = not done or not reported; LESP = lower oesophageal sphincter pressure.

a > indicates significant difference ($p < 0.05$); = indicates insignificant difference.

difference between metoclopramide and placebo in the symptomatic relief of gastro-oesophageal reflux (Paull and Grant, 1974; Venables et al., 1973). Daily oral doses (30 to 40mg) and duration of therapy (6 to 8 weeks) were similar in each of these trials. The outstanding feature in the positive report (Johnson, 1971) was the lack of documentation of gastro-oesophageal reflux. Thus, patients may have been included with heartburn not caused by incompetency of the lower oesophageal sphincter.

In 2 subsequent studies, metoclopramide significantly decreased heartburn in comparison with placebo, but there was no significant effect on lower oesophageal sphincter pressure as measured by manometry after completion of treatment (Bright-Asare and El-Bassoussi, 1980; McCallum et al., 1977). The lack of correlation between subjective relief and objective improvement was attributed to a decreased response to metoclopramide in patients with severe basal sphincter incompetency (Behar and Biancani, 1976; McCallum et al., 1977). Winnan et al. (1980) were able to document increased gastric emptying and a significant decrease in heartburn and simultaneous increase in lower oesophageal sphincter pressure determined within 90 minutes of a 10mg oral dose of metoclopramide.

On the basis of a dose-response relationship seen between metoclopramide and lower oesophageal sphincter pressure (Behar and Biancani, 1976), Cohen (unpublished data on file, Robins) chose a dose of 15mg 4 times daily in a randomised placebo controlled study. After 12 weeks of treatment, metoclopramide alleviated symptoms, raised lower oesophageal sphincter pressure, and improved the endoscopic appearance of oesophageal erosions. The additional 4 weeks of treatment in this study may have contributed to the endoscopic improvement not achieved in previous trials. The higher dose was well tolerated except for drowsiness which occurred in 75 and 33% of patients in the metoclopramide and control groups, respectively.

Thus, although metoclopramide has been shown to alleviate symptoms of gastro-oesophageal reflux, and in some instances to also increase lower oesophageal sphincter pressure at usual therapeutic dosages, it has yet to be demonstrated adequately that relief of symptoms is accompanied by endoscopic healing.

Recent documentation of the ability of parenteral metoclopramide to raise lower oesophageal sphincter pressure in pregnant women (see section 1.1.1) suggests a role for the drug in reflux oesophagitis associated with pregnancy. Although the

response to a single intravenous dose was limited to 4 of 10 women in a double-blind study, 16 of 17 pregnant women (94%) responded to oral metoclopramide within 2 or 3 days. Hey and Ostick (1978) proposed that the effect may be cumulative. However, these uncontrolled observations require further confirmation to determine the place of metoclopramide in the chronic management of reflux oesophagitis associated with pregnancy.

3.1.2 Delayed Gastric Emptying

Gastroparesis is frequently associated with diabetes or vagotomy and gastric resection (Malagelada, 1980). On fluoroscopic examination, the hypomotility present in diabetics and after truncal vagotomy is indistinguishable (Fox and Behar, 1980). Symptoms of gastric stasis commonly include early satiety, nausea, vomiting, bloating, weight loss and anorexia (Longstreth et al., 1977). Abdominal pain is less frequently seen and may suggest alternative diagnoses. Results of pharmacodynamic studies suggest a role for metoclopramide in the treatment of gastroparesis (see section 1.1.2).

In uncontrolled observations, dramatic relief of symptoms was reported in 10 of 21 patients with gastric stasis following vagotomy and gastric resection during treatment with metoclopramide 30mg daily (Davidson et al., 1977; Wright and MacGregor, 1979). These results were confirmed in double-blind trials (table IV), although patient numbers were likely too few to detect any statistically significant difference between metoclopramide and placebo in some studies. Follow-up was 4 weeks or less in all trials.

Case reports of 5 patients with diabetic gastroparesis refractory to standard medical therapy revealed correction of symptoms after metoclopramide 30 to 60mg daily. Gastric emptying was improved (Braverman and Bogoch, 1978) and control was maintained for 5 or 6 months in 2 cases (Hartong et al., 1977; Longstreth et al., 1977). Double-blind trials of metoclopramide in diabetic gastroparesis generally contain insufficient numbers of subjects to demonstrate statistical significance. 'Improvement' was noted in 25 patients who received metoclopramide in controlled environments (Berkowitz et al., 1976; Millar et al., 1980; Perkel et al., 1980; Snape et al., 1982). In a multi-

Table IV. Summary of double-blind trials comparing metoclopramide (MCP) and placebo (P) in patients with gastroparesis of varying aetiology

Reference	No. of patients	Metoclopramide dose and route	Aetiology	Effect on symptoms[a,b]	Effect on gastric emptying[a,b]
Berkowitz et al. (1976)	4	40 mg/day po	Diabetes	'Improved'	MCP > P
	4	40 mg/day po	Postop	'Improved'	...
	4	40 mg/day po	Pseudo-obstr.	MCP = P	...
Metzger et al. (1976)	6	40mg im	Vagotomy	'Improved'	MCP > P
Millar et al. (1980)	6	Not stated po	Diabetes	'Improved'	MCP = P
Perkel et al. (1980)	5	40mg po	Diabetes	MCP = P	...
	21	40mg po	Vagotomy	MCP > P	...
	29	40mg po	Idiopathic	MCP > P	...
Snape et al. (1982)	10	40mg po	Diabetes	'Improved'	MCP > P
Behar et al. (Unpubl)	40	40mg po	Diabetes	MCP > P	...

a ... = not done or not reported.

b > indicates a significant difference ($p < 0.05$); = indicates no significant difference.

centre trial, 40 patients were randomised to receive either metoclopramide or placebo for 3 weeks. Nausea, early satiety, feeling of fullness and meal intolerance were reduced ($p < 0.05$) in the treatment group, but there was no difference in anorexia or vomiting (Behar et al., unpublished data on file, Robins).

An improvement in symptoms after treatment of diabetic gastroparesis with metoclopramide has not consistently been accompanied by increased gastric emptying (isotope-labelled solid and/or liquid meal) in either controlled (Millar et al., 1980; Snape et al., 1982) or uncontrolled trials (Battle et al., 1979). Thus, the central antiemetic effect of metoclopramide assumes an important role in such conditions (McCallum, personal communication). In post-vagotomy patients however, symptomatic relief was accompanied by increased gastric motility (Metzger et al., 1976).

Metoclopramide also produced a greater increase in gastric motor activity in surgical than in diabetic patients with gastric stasis in an experimental study conducted by Malagelada et al. (1980). The variation in findings may be related to the different pathophysiology, the mechanism of symptomatic relief (Snape et al., 1982), the route of administration or drug dosage.

In intestinal pseudo-obstruction, a form of gastroparesis (Malagelada et al., 1980), there was no response to metoclopramide in a child refractory to surgery (Telander et al., 1978), or in 1 patient included in a double-blind study (Berkowitz et al., 1976).

Symptoms of anorexia nervosa (postprandial discomfort, bloating, early satiety, regurgitation of sour fluid, heartburn, nausea and vomiting) are not unlike those of other diseases associated with delayed gastric emptying. Preliminary clinical experience suggests that metoclopramide may have an ancillary role in the treatment of this disease. In an open study, metoclopramide 10mg 4 times daily resulted in symptomatic improvement, weight gain and increased gastric emptying in 5 of 7 patients (Saleh and Lebwohl, 1980), whilst under double-blind conditions 30mg daily provided 'dramatic' relief in 3 of 5 patients (Moldofsky et al., 1977). Severe mental depression necessitated withdrawal of treatment in 2 patients.

Several double-blind trials adequately document the usefulness of metoclopramide in facilitating clearance of gastrointestinal contents, thus enabling earlier induction of anaesthesia in emergency situations including during labour (Brock-Utne et al., 1978; Hey and Ostick, 1978; Hey et al., 1981; Olsson and Hallen, 1982).

3.1.3 Peptic Ulcer

While initial uncontrolled observations suggested that metoclopramide accelerates the healing of gastric ulcers, controlled studies have failed to confirm this (Pinder et al., 1976).

In a more recent double-blind study of 48 patients with gastric ulcer, there was no difference between the effects of metoclopramide 40mg daily and placebo in promoting healing. The 4-week observation period was minimal. Uncontrolled evaluation of 30 patients with duodenal ulcer treated with high dose metoclopramide (60mg daily) and antacids revealed normalisation of duodenal mucosa within 52 days. Pain relief was reported in all patients, usually within 3 to 8 days (Schütz, 1976). Further well designed therapeutic trials comparing metoclopramide with drugs shown to be effective in promoting healing of gastric and duodenal ulcer are necessary to determine its usefulness in peptic ulceration.

3.1.4 Dyspepsia

The successful treatment of flatulent dyspepsia of varying origin with metoclopramide has been confirmed in double-blind trials. Standard doses of metoclopramide were superior to placebo, the anticholinergic drug pipenzolate bromide (15mg daily), and prochlorperazine 15mg daily (Pinder et al., 1976). In a recent randomised evaluation of 69 patients, metoclopramide was as effective as antacid in alleviating symptoms of dyspepsia (de Almeida et al., 1980).

In a 6-week pilot study conducted to test the potential of metoclopramide for improving tolerance to various non-steroidal anti-inflammatory agents, 4 of 7 patients experienced complete relief

of dyspepsia when metoclopramide 10mg was administered 30 minutes prior to the analgesic. Mean serum salicyclate concentrations increased from 0.48 mmol/L to 1.26 mmol/L (therapeutic range > 1.1 to 1.8 mmol/L) [Awerbuch et al., 1981].

3.1.5 Functional Gastrointestinal Disorders

Metoclopramide has been used in a variety of functional gastrointestinal disorders, but data from well designed studies are lacking and additional controlled trials comparing metoclopramide with standard medical therapy are required before its role can be clearly defined. In small double-blind studies of patients with disorders such as irritable bowel syndrome, functional vomiting and diarrhoea, or spastic constipation, metoclopramide, 30mg daily, was superior to placebo and equivalent to a combination of haloperidol and isopropamide (0.3mg and 2mg, respectively, thrice daily) [Pinder et al., 1976].

In a double-blind multicentre study of 232 patients with irritable colon syndrome, patients were randomised to a 2-week treatment with either metoclopramide, 10 or 20mg thrice daily, or to placebo. Pretreatment symptoms of abnormal bowel movement, diffuse abdominal pain, and flatulence were reduced by 74.8% in the experimental group and 63.2% in the control group ($p < 0.05$) [Kjaerulff and Tøjner, 1977]. This remarkably high placebo response has also been noted in other evaluations of irritable bowel syndrome (Longstreth et al., 1981). Both dosages of metoclopramide were well tolerated.

3.2 Vomiting

3.2.1 Postoperative Vomiting

Despite initial uncontrolled observations of the reduction or elimination of postoperative nausea and vomiting in about 90% of patients who received metoclopramide, the results of controlled studies were not uniform. While some trials failed to detect a difference between the antiemetic effects of metoclopramide and placebo, others demonstrated that the drug was superior to placebo and either equivalent to or superior to standard antiemetic therapy (Pinder et al., 1976). Factors which may contribute to the variation in results between the studies include the interval between drug administration and induction of anaesthesia, the anaesthetic drugs, the postoperative use of narcotic analgesics in some studies but not in others, and the different surgical procedures.

Thus, in a recent study in which antiemetics were administered immediately prior to the induction of anaesthesia, intravenous metoclopramide 10mg was superior to placebo and equivalent to intravenous domperidone 4mg in the reduction of vomiting following caesarean section (Cooke et al., 1979). However, when antiemetic administration preceded anaesthesia by 2 to 10 minutes in outpatient abortions, there was no difference between intravenous metoclopramide 10mg and placebo (Cohen et al., 1981). Droperidol, which has a more prolonged duration of action, reduced ($p < 0.05$) the incidence of nausea and vomiting in the same clinic population.

The type of anaesthetic agent used may also influence antiemetic efficacy (Pinder et al., 1976). In the double-blind evaluation of antiemetics administered to patients undergoing various gynaecological procedures, the reduction of nausea and vomiting in the halothane-treated group did not achieve statistical significance; whereas the subset of patients undergoing caesarean section with neuroleptanaesthesia appeared to benefit ($p < 0.05$) from metoclopramide or domperidone (Cooke et al., 1979). The lower overall incidence of vomiting in the halothane-treated group (30%) compared with in the other group (42%) may have decreased the likelihood of demonstrating a significant difference between active drug and placebo in the small numbers of patients.

A similar situation may have been responsible for intergroup differences in over 200 patients given a single 20mg oral dose of metoclopramide or placebo 2 hours prior to surgery. The decrease in nausea and vomiting was significant ($p < 0.05$) during the first half of the 6-hour observation period, but was more impressive in the subset of patients who received hydromorphone for pain during recovery. Narcotic analgesia may have con-

tributed to the nearly 100% greater frequency of nausea and vomiting observed in this subset in comparison with patients who were denied opiates, and thus the greater difference between metoclopramide and placebo (Diamond and Keeri-Szanto, 1980).

In a preliminary study designed to evaluate the ability of metoclopramide to prevent postoperative ileus, patients were randomised to receive either metoclopramide, 10mg before meals, or placebo. The treatment was begun the evening before abdominal surgery and continued until symptoms of ileus abated. Overall, there was less nausea in metoclopramide patients ($p < 0.05$). A decrease ($p < 0.05$) in vomiting was observed in the subset of patients whose gastrointestinal tracts remained intact (Davidson et al., 1979).

3.2.2 Drug-induced Vomiting

Whereas most initial trials of the antiemetic effect of metoclopramide have been in postoperative vomiting (Pinder et al., 1976), a number of recent studies have examined the efficacy of metoclopramide in preventing emesis due to antineoplastic therapy.

Cytotoxic Drugs

In contrast with the encouraging reports from uncontrolled observations, early double-blind trials (Pinder et al., 1976) as well as more recent studies failed to demonstrate significant antiemetic efficacy of 'usual doses' of metoclopramide in the treatment of cancer chemotherapy-induced vomiting. Thus, Arnold et al. (1980) found that neither metoclopramide 20mg nor prochlorperazine 25mg (administered 30 minutes before and 3 hours after chemotherapy) were effective in decreasing vomiting in patients treated with cisplatin. In a similar trial, the reduction in vomiting following oral metoclopramide 20mg was superior to that of prochlorperazine 10mg ($p < 0.05$), but neither treatment was considered satisfactory as the incidence of vomiting exceeded 70% (Frytak et al., 1981). These findings are in contrast to positive results with single oral 20mg doses of metoclopramide in an open study (Kahn et al., 1978).

Table V. Summary of double-blind trials comparing metoclopramide (MCP) with placebo (P), prochlorperazine (PCP), thiethylperazine (TEP) and tetrahydrocannabinol (THC) in patients with cytotoxic-induced vomiting

Reference	No. of patients	Cytostatic drug(s)	Dose and route of metoclopramide	Dose interval (h)	No. of doses	Antiemetic effects[a]	Major responses[b] (%)
Colls et al. (1980)	35	Various	5 mg/m² iv	4	3	MCP = THC = TEP	
Arnold et al. (1980)	8	Cisplatin (not stated)	20mg po	4	2	MCP = PCP	
Frytak et al. (1981)	100	Cisplatin (40-120 mg/m²)	20mg po	8	3	MCP > PCP	26
Gralla et al. (1981)	41	Cisplatin (120 mg/m²)	2 mg/kg iv	2	5	MCP > P or PCP	60
Gralla et al. (1982)	27	Cisplatin (120 mg/m²)	2 mg/kg iv	2	5	MCP > THC	86
Homesley et al. (1982)	21	Cisplatin (50-100 mg/m²)	1 mg/kg iv	2-3	6	MCP > P	55[c]

a > indicates significant difference ($p < 0.05$); = indicates insignificant difference ($p > 0.05$).
b 0 to 2 emetic episodes.
c In this study, percentage indicates protections instead of major responses.

The lack of benefit in these trials may be due to the postulated effect of hepatic metabolism upon oral bioavailability of metoclopramide (section 2.1).

However, more recent double-blind studies have shown high dose intravenous metoclopramide to effectively decrease vomiting caused by cisplatin and other antineoplastic drugs (table V).

Thus, in carefully designed trials in patients receiving the same high dose of cisplatin (120 mg/m^2 intravenously over 20 minutes) who had not received prior antineoplastic drugs, high dose intravenous metoclopramide (2 mg/kg) was effective in decreasing vomiting and superior to placebo, intramuscular prochlorperazine 10mg (Gralla et al., 1981) and oral tetrahydrocannabinol 10 mg/m^2 (Gralla et al., 1982) [table V]. Drugs were administered 30 minutes before and 1.5, 3.5, 5.5 and 8.5 hours after beginning chemotherapy. The high success rate (median number of episodes per patients = 1) in the metoclopramide group might not be achieved in patients previously exposed to chemotherapy (Gralla et al., 1981), as the effect of 'anticipatory nausea and vomiting' in such patients is expected to compromise antiemetic efficacy (Morrow et al., 1982). Nevertheless, continued control of vomiting episodes was documented in 18 metoclopramide responders during the non-blind observation of subsequent cisplatin administration (Gralla et al., 1982).

In 2 uncontrolled trials (Goslin and Garnick, 1981; Strum et al., 1982) and 1 double-blind study (Homesley et al., 1982) the dose of metoclopramide was reduced to 1 mg/kg and a sixth dose was added at 12.5 hours after cisplatin. In a combined total of 67 previously unexposed patients treated with cisplatin, generally in doses lower than those used by Gralla (20 to 120 mg/m^2), nausea and vomiting was prevented in 55% of patients and the median number of episodes was similar to that reported by Gralla et al. (1981).

There was a trend towards a more satisfactory response to metoclopramide in the patients who received lower doses of cisplatin (50 mg/m^2 or less) [Homesley et al., 1982; Strum et al., 1982]. An increase in metoclopramide dose to 2 mg/kg improved the response in 2 patients receiving cisplatin doses in excess of 100 mg/m^2.

In a multicentre, crossover trial, patients receiving various antineoplastic regimens were treated with parenteral metoclopramide at the relatively low dose of 5 mg/m^2, oral thiethylperazine, or oral tetrahydrocannabinol. There was no significant difference in the mean number of vomiting episodes with any of the 3 drugs. However, tetrahydrocannabinol caused the most neuropsychiatric reactions ($p < 0.01$) [Colls et al., 1980].

Analgesics

There have been few studies published since the earlier review in the Journal (Pinder et al., 1976), which concluded that metoclopramide 10mg is superior to placebo in the reduction of nausea due to pethidine 50 to 100mg or morphine 15mg, and appears to be equivalent or superior to standard antiemetics including prochlorperazine 10mg and perphenazine 5mg. Recently the superiority of oral metoclopramide 20mg over placebo in the prevention of postoperative nausea and vomiting has been reported in patients receiving hydromorphone for pain (see also section 3.1.1). The observed difference achieved significance during the first postoperative hour ($p < 0.05$) and again between 1 and 3 hours ($p < 0.01$). The lack of difference between 3 and 6 hours was not suprising because of the relatively short duration of action of metoclopramide (Diamond and Keeri-Szanto, 1980).

Another observation was the limitation of antiemetic benefit to the subset of male patients undergoing orthopaedic surgery ($p < 0.001$). There was no difference between treated and control patients in a group of females undergoing abdominal hysterectomy. Diamond and Keeri-Szanto (1980) proposed that a sex-dependent difference in pharmacokinetic handling of metoclopramide may account for this disparity.

Although the superiority of metoclopramide over standard antiemetics has not been conclusively demonstrated (Pinder et al., 1976), there is a theoretical advantage which requires further clinical evaluation. In contrast with other antiemetic and anticholinergic drugs, metoclopramide normalises the reduced lower oesophageal sphincter barrier

pressure associated with pethidine administration (see section 1). This difference may be important in patients predisposed to aspiration, such as trauma victims requiring analgesia prior to the induction of general anaesthesia for emergency surgery (Hey et al., 1981).

Miscellaneous Drugs

Because nausea and vomiting are often dose-limiting side effects of levodopa, the antiemetic effect of metoclopramide has been evaluated in the medical management of Parkinson's disease. In uncontrolled observations, daily doses of 30 to 80mg appeared to reduce nausea and vomiting of Parkinson's disease (Pinder et al., 1976), but is probably best avoided in such patients (section 1.2). Apomorphine is also a potent stimulant of dopamine, but its usefulness is limited by emetic activity. In a double-blind, crossover study of normal volunteers, metoclopramide 10mg, sulpiride 10 and 100mg, and haloperidol 2mg prevented vomiting due to parenteral apomorphine. In patients with Parkinson's disease, the combination of apomorphine plus metoclopramide or sulpiride improved neurological symptoms without emesis, whereas haloperidol blocked both the therapeutic and emetic activity of apomorphine (Corsini et al., 1976). Additional trials are needed to determine the role of metoclopramide in the long term management of drug-induced nausea and vomiting in patients with Parkinson's disease. The effect of metoclopramide on neurological status in these patients requires further evaluation since Bateman et al. (1978a) reported that metoclopramide 60mg daily was associated with a significant increase in the incidence of tremor in patients with Parkinson's disease.

Patients who received an oral electrolyte solution in preparation for colonoscopy were randomised to either metoclopramide 10mg orally or placebo 30 minutes prior to the electrolyte solution. Metoclopramide significantly reduced bloating ($p < 0.005$) and nausea ($p < 0.025$), but the observed decrease in cramps and vomiting did not achieve statistical significance (Rhodes et al., 1978).

Metoclopramide also appears to control nausea and vomiting associated with digitalis, tuberculostatic agents, and antibiotics. It is not effective as an antiemetic following iodipamide for intravenous cholangiography (Pinder et al., 1976).

3.2.3 Radiation Sickness

In uncontrolled observations, metoclopramide alleviated nausea and vomiting associated with radiation sickness in 86% of patients. Metoclopramide appeared to be as effective as prochlorperazine in reducing nausea and vomiting due to radiation therapy in a double-blind, crossover study (Pinder et al., 1976).

3.2.4 Vomiting of Pregnancy

The antiemetic effect of metoclopramide has been confirmed in a double-blind trial of 120 pregnant women with hyperemesis gravidarum. Metoclopramide, 10mg 3 times daily and prochlorperazine 5mg 3 times daily were similarly beneficial and superior to placebo. The 14% incidence of side effects after metoclopramide (drowsiness, diarrhoea, glossitis, oculogyric crisis) compared favourably with the 36% incidence noted after prochlorperazine (drowsiness, opisthotonus) [Singh and Lean, 1970]. At the time of this study, there were no reports of congenital malformations (Pinder et al., 1976); none have been noted subsequently, either in laboratory models or in the clinical literature.

3.2.5 Nonspecific Nausea and Vomiting

Early uncontrolled observations of metoclopramide for the relief of nausea and vomiting associated with a variety of conditions revealed efficacy in about 80 to 90% of patients. Disease states included recurrent gastritis, gastroenteritis, gastric carcinoma, hepatic and biliary disorders, chronic renal failure, cardiac disease, and alcoholism (Pinder et al., 1976). With the exception of 2 double-blind studies (Jones, 1968; Trafford et al., 1967), in which metoclopramide was superior to placebo in a total of 78 patients, these impressions have not been further confirmed. The efficacy of metoclopramide in functional gastrointestinal disorders is reviewed in section 3.1.

3.3 Miscellaneous Trials

3.3.1 Migraine

Metoclopramide was originally administered in migraine for the treatment of associated nausea and vomiting. In uncontrolled observations, it appeared that the combination of metoclopramide plus non-narcotic analgesia promoted more rapid resolution of headache (Hughes, 1977; Jones and Harrop, 1980; Olesen et al., 1979). Further investigation revealed that metoclopramide corrected the delayed absorption caused by poor gastric emptying during migraine attacks enabling more rapid attainment of therapeutic serum concentrations of orally administered analgesic (Ross-Lee et al., 1982; Wainscott et al., 1976; see also section 9). Metoclopramide appears not to decrease the frequency of migraine attacks.

In a double-blind crossover study, 33 patients were given either metoclopramide 10mg or placebo to take at the onset of migraine attacks during a 4-week period. Ergotamine and analgesic use was quantitated but not controlled. In 27 evaluable patients the incidence of nausea was reduced ($p < 0.03$), and there was a trend towards less vomiting ($p < 0.07$). The single dose of metoclopramide did not alter the amount of analgesics consumed, the duration or intensity of migraine, or frequency of diarrhoea. Slettnes and Sjaastad (1977) proposed that a higher response rate may be seen with an increased dose(s) of metoclopramide.

In 2 large outpatient clinics, the standard protocol for the management of migrainous headache includes metoclopramide 10mg orally or intramuscularly, followed by aspirin or paracetamol 1Hg with or without diazepam 5mg. Between the 2 institutions, 950 cases of migrain were evaluated retrospectively. Approximately 92% of patients were discharged symptom-free or with minimum residual headache after a median hospitalisation time of 4 hours. Ergotamine was rarely indicated and narcotics were unnecessary (Olesen et al., 1979; Wilkinson et al., 1978). Uncontrolled observation of 36 employees with migraine headache who were treated with a similar protocol revealed that 97% were able to return to work within 1 hour. Retrospective analysis of 111 similar incidents treated with regimens not containing metoclopramide, revealed that they lasted 2 to 12 hours and necessitated 2.53 days absenteeism per attack (Jones and Harrop, 1980). Drug therapy was well tolerated with few side effects in all reports.

The concomitant administration of oral or intramuscular metoclopramide and aspirin to patients with migraine headache resulted in a recovery time of less than 2 hours in all instances (Ross-Lee et al., 1982; Volans, 1975). Although this study was not placebo controlled, this result is comparable to that in a similar study in which aspirin plus intramuscular thiethylperazine alleviated migraine headache within 2 hours in 9 of 16 patients (Wainscott et al., 1976). However, there are to date no adequate controlled studies confirming that oral metoclopramide increases the efficacy of orally administered analgesics in patients with delayed gastric emptying. The positive effect of metoclopramide may have been due to enhanced absorption of aspirin, although there was no correlation between plasma salicylate concentration and recovery time (Wainscott et al., 1976).

3.3.2 Defective Lactation

The observation that metoclopramide stimulates prolactin release (see section 1.6.1) provides a basis for the evaluation of metoclopramide in promoting lactation. In 2 of 3 double-blind trials, metoclopramide 20 to 45mg daily improved breast milk yield and corrected depressed serum prolactin concentrations in women. In the studies with positive findings, patients either had a history of defective lactation following previous delivery or had a new diagnosis of defective lactation within 2 months of delivery. (Guzman et al., 1979; Kaupilla et al., 1981). In the study with negative findings (Lewis et al., 1980), eligibility was determined on the basis of caesarean section without evidence of defective lactation. An unusually high placebo response in this study also minimised the possibility of detecting a difference between treatments. Furthermore, Lewis et al. (1980) restricted metoclopramide administration to the first week of the 3-month observation period, whereas metoclopra-

mide was continued throughout the 2- or 4-week observation period in the other trials (Guzman et al., 1979; Kaupilla et al., 1981).

3.3.3 Functional Urinary Tract Disorders

Case reports of the effect of metoclopramide suggest a potential role for the drug in patients with hypomotile ureter. A single 20mg intravenous dose of metoclopramide alleviated pain and promoted micturition in all 4 patients with ureteral dysfunction associated with recurrent pyelonephritis, renal stones or stenosis (Schelin, 1979).

In an evaluation of 10 patients with neurogenic bladder dysfunction, intravenous metoclopramide 20mg did not affect either bladder detrussor reflex activity or urethral pressure (Vaidyanathan et al., 1980b). Additional studies are needed to assess the effect of metoclopramide on the symptoms of neurogenic bladder dysfunction and ureteral dysfunction.

3.3.4 Orthostatic Hypotension

The observation of elevated urine dopamine excretion in patients with severe orthostatic hypotension led to the study of metoclopramide in such patients (Kuchel et al., 1980). In a 64-year-old female who developed severe orthostatic hypotension after sympathectomy for Raynaud's disease (urine dopamine was reported as 3 times normal), metoclopramide 10mg thrice daily eliminated symptoms of orthostatic hypotension, and upright blood pressure became normal. The response was maintained for 2 years without adverse effects at the time of publication. Response to previously administered dopamine antagonists had been transient.

In a double-blind study of 11 patients with Parkinson's disease treated with levodopa, metoclopramide 10mg thrice daily raised supine (98 to 104mm Hg) and standing (85 to 97mm Hg) mean arterial blood pressure in 5 of 9 patients with orthostatic hypotension. A positive response occurred only in patients who had a postural fall in systolic blood pressure of greater than 15mm Hg and was not evident with a dose of 60mg daily. There was no significant change in the group as a whole. The reasons for the inverse dose dependency and lack of effect in patients with mild orthostatic hypotension are not understood. It is possible that mild and severe orthostatic hypotension do not share the same aetiology (Bateman et al., 1978a).

3.3.5 Tardive Dyskinesia

Symptoms of tardive dyskinesias associated with neuroleptic therapy often respond temporarily to increased doses of the causative agent or other antidopaminergic drugs. In a double-blind evaluation of single intravenous doses, metoclopramide 40mg ($p < 0.02$), and haloperidol 5mg ($p < 0.01$) and 10mg ($p < 0.01$) reduced the symptoms of tardive dyskinesia in 8 patients. There was a trend towards improvement after metoclopramide 20mg, but with neither this dose nor 10mg was the improvement statistically significant ($p > 0.05$). Although a dose-related response is suggested, frequency of extrapyramidal side effects associated with the dose of metoclopramide required to alleviate symptoms may preclude its therapeutic usefulness (Bateman et al., 1979a) [see section 5.1].

Karp et al. (1981) reported that all 5 patients with tardive dyskinesia refractory to standard therapy 'improved' (2 of 5: complete response; 3 of 5: 50% response) after treatment with metoclopramide. The mean daily dose was 54mg (range 20 to 80mg). The response was maintained during an 8-month follow-up period. It is likely that metoclopramide masked the symptoms of tardive dyskinesia (Shader and Greenblatt, 1982).

3.3.6 Vertigo and Associated Disorders

There are few controlled trials that assess the efficacy of metoclopramide in alleviating the symptoms of vertigo. In a typical open study, the combination of metoclopramide 20mg, dimenhydrinate 50mg and pyridoxine 100mg was judged to yield 'satisfactory results' in the treatment of vertigo of varying aetiology (González et al., 1977). On the basis of a small (14 patients) double-blind study and uncontrolled observations, it appears that metoclopramide may be effective in reducing nausea and vomiting associated with vertigo. How-

ever, larger studies are needed to determine the role of metoclopramide in treating other symptoms of vertigo. Likewise, there are insufficient data to support the routine use of metoclopramide for seasickness (Pinder et al., 1976).

4. Use in Gastrointestinal Diagnosis

At the time of the previous review in the Journal (Pinder et al., 1976), adequately controlled trials documented the usefulness of metoclopramide in small bowel examination (section 4.1) and in intubation and biopsy of the small intestine (section 4.2). Intravenous metoclopramide clearly reduces barium transit time through the small intestine, but the question of whether oral administration compromises examination sensitivity remains unanswered. Poor coating of the small intestine during the new double-contrast examinations has been attributed to delayed emptying. Metoclopramide failed to improve the quality of films from the double-contrast examinations, but the significant reduction in transit time was considered beneficial. Additional studies are needed to define the effect of metoclopramide upon film quality. The facilitation of intubation, successful biopsy, and reduction in fluoroscopic radiation exposure attributed to metoclopramide in earlier controlled studies has gained additional support.

There are 3 potential indications for metoclopramide in gastrointestinal diagnosis. Metoclopramide has been administered prior to barium contrast examination to improve quality and to reduce total radiation exposure (see section 4.1), to facilitate and accelerate introduction of a multipurpose biopsy tube or capsule into the small intestines (see section 4.2), and to remove gastric contents from the visual field before emergency endoscopy (see section 4.3).

4.1 Radiology

Parenteral metoclopramide facilitates the passage of barium through the gastrointestinal tract thereby reducing the time required for examination, minimising patient exposure to radiation and limiting the number of films needed. Controlled trials have demonstrated the superiority of metoclopramide 10 or 20mg over placebo in increasing stomach peristalsis, relaxing the pyloric canal, dilating the duodenal cap, accelerating duodenal filling, and reducing overall transit time. Quality of radiological examination is not compromised.

The intravenous administration of metoclopramide to patients undergoing double-contrast examination of the small bowel has been proposed as a means to improve the quality of visualisation. Metoclopramide is thought to correct poor barium coating of the mucosa due either to inadequate gastric cleansing (Gopichandran et al., 1980) and/or to physical changes in barium associated with prolonged contact time (Ho et al., 1978). Pajewski et al. (1975) tested the effect of intravenous metoclopramide 20mg in 40 patients undergoing double-contrast examinations. In comparison with previous conventional techniques, visualisation was described as excellent. However, in 1 large historically controlled study, and in another double-blind study, metoclopramide did not alter mucosal coating or the quality of the visualisation (Ho et al., 1978; Skucas and House, 1978), respectively. Nevertheless, the reduced transit time and the ability to differentiate spasm from stricture in patients with peripyloric narrowing were deemed beneficial.

In controlled trials, the use of oral metoclopramide in double-contrast radiology has produced mixed results (Pinder et al., 1976). Most recently, Gopichandran et al. (1980) assigned at random 135 patients to either oral metoclopramide 20mg or placebo to assess the effect on examination quality. There was no difference in barium coating or in quality of visualisation. The lack of response may have been due to inadequate dose or to inability to improve upon gastric conditions induced by a 6-hour starvation prior to radiological evaluation.

4.2 Intubation and Biopsy

Recent trials confirm the usefulness of metoclopramide in facilitating intubation. In double-blind

assessments in normal volunteers (Christie and Ament, 1976), and in patients referred for jejunal biopsy (Arvantikas et al., 1976), metoclopramide 10mg intravenously halved overall intubation time. Shorter exposure to fluoroscopic radiation (1.4 minutes compared with 2.5 minutes) and greater operator preference ($p < 0.001$) were also noted in the experimental group, whereas patient tolerance was unchanged (Arvantikas et al., 1976). In patients with a history of pylorospasm during previous endoscopy, intravenous metoclopramide 10mg elicited pyloric relaxation relative to placebo (Hradsky and Furugard, 1978). Metoclopramide appears to be particularly useful in decreasing the time required for biopsy capsules to reach the ligament of Treitz (Christie and Ament, 1976).

4.3 Emergency Endoscopy

Metoclopramide has been administered to remove blood from the stomach prior to endoscopic evaluation of upper gastrointestinal haemorrhage (Pinder et al., 1976). The controlled trials required to assess any potential deleterious effect of metoclopramide on haemorrhage remain to be conducted.

5. Side Effects

Metoclopramide causes few adverse drug reactions when administered in the usual therapeutic doses (30 to 40mg daily). Side effects are normally mild, transient, and reversible upon discontinuation of therapy. Alarming extrapyramidal reactions have been reported occasionally at therapeutic doses. The overall incidence of side effects was approximately 11% in large surveys (Pinder et al., 1976); however it may be as high as 34% in double-blind studies in which daily dosages are between 30 and 80mg (Perkel et al., 1980; see table VI).

Drowsiness and restlessness are the most common side effects and occur in up to 10% of patients (Pinder et al., 1976), although a 76% incidence of mild sedation was noted in cancer patients who received high dose (2 mg/kg) metoclopramide, (Gralla et al., 1981; see section 5.4). Bowel disturbances include constipation and diarrhoea and are seen in 1 to 3% of patients. Extrapyramidal reactions have been reported in up to 9% of patients (see section 5.1). Other side effects noted infrequently include rash (Arndt and Jick, 1976), tongue or peri-orbital oedema, dry mouth, depression, and methaemoglobinaemia (in premature newborn infants) [Pinder et al., 1976]. There are no reports of positive antinuclear antibodies (McCallum et al., 1977). Cardiovascular (see section 5.2) and endocrine effects (see section 5.3) are unusual. In surgical patients, there is no evidence to suggest prolonged recovery from anaesthesia due to metoclopramide (Cohen et al., 1981; Cooke et al., 1979; Pinder et al., 1976).

Despite seemingly appropriate dose adjustment, children are at increased risk of developing unwanted neurological effects due to metoclopramide. Children and young adults are particularly prone to the acute dystonic type of extrapyramidal reactions which manifest as neck pain and rigidity, trismus, and oculogyric crises (Goslin and Garnick, 1981; Pinder et al., 1976; Reynolds, 1978). It is not known whether this increased susceptibility is due to a true neurological hypersensitivity. There is also 1 case report of a young child who developed symptoms of acute intermittent porphyria immediately after an intramuscular dose of metoclopramide. Urinary porphyrin levels confirmed the diagnosis. The patient had a known history of acute intermittent porphyria exacerbated by various drugs (Doss et al., 1981).

5.1 Extrapyramidal Reactions

Akathisia or motor restlessness is the most common extrapyramidal reaction associated with metoclopramide (see table VI). It usually occurs shortly after initiation of therapy (Goslin and Garnick, 1981) and may or may not necessitate discontinuation of therapy (Bright-Asare and El-Bassoussi, 1980). Akathisia is reversible upon cessation of metoclopramide.

Table VI. Reported frequency of side effects (%) in patients receiving metoclopramide or placebo in double-blind trials[a]

Side effect	Metoclopramide				Placebo	
	30-80 mg/day po	10-20 mg/day iv/im	1 mg/kg 6 doses	2 mg/kg 5 doses	po	iv/im
CNS	24	12	18	81	11	9
drowsiness	9	8	none	76	4	7
dizziness	3	3	none	none	3	2
anxiety	2	none	none	none	none	none
EPR	9	1	18	5	3	none
akathisia	8	1	18	none	2	none
dystonia	1	none	none	5	1	none
GIT	2	0.4	9	43	none	none
nausea	1	0.4	none	none	none	none
diarrhoea	1	none	9	43	none	none
Other						
depression	2	0.4	none	none	none	none
malaise	none	none	none	none	0.3	none
gynaecomastia	0.3	none	none	none	none	none
tachycardia	none	0.4	none	none	none	none
Discontinue therapy	6	none	none	none	1	none
Overall % SE	34	14	27	81	19	12
Total no. patients	312	236	11	21	314	215

a Percentage of side effects as reported in double-blind trials in sections 3 and 4.

Abbreviations: CNS = central nervous system; EPR = extrapyramidal reactions (any type); GIT = gastrointestinal tract; SE = side effects.

Dystonias, including trismus, torticollis, facial spasms, opisthotonos, and oculogyric crisis, occur most frequently in young patients and less frequently than akathisia. These reactions are also noted shortly after initiation of therapy and are usually responsive to antihistamines or anticholinergic drugs (Bright-Asare and El-Bassoussi, 1980; Goslin and Garnick, 1981). Patients sometimes refuse subsequent doses of metoclopramide (Goslin and Garnick, 1981). However, therapy has been successfully continued in patients experiencing such reactions initially without recurrence (Gralla et al., 1981). Diphenhydramine has been used prophylactically in some patients. There is 1 case report of 2 young adults whose dystonias were accompanied by fevers of 38°C. Extrapyramidal reactions responded to anticholinergic therapy, and the fevers subsided within 24 hours (Wandless et al., 1980).

Parkinsonism with typical tremor, rigidity, and akinesia is a significant risk of long term metoclopramide therapy. The incidence is higher in older patients. In a survey of recent experience in a movement disorders clinic, the average time to onset of metoclopramide-induced Parkinson's disease was 8.7 months and the mean daily dose was 29.5mg. Symptoms were reversible upon discontinuation of metoclopramide (Grimes, 1981).

Until recently (Lavy et al., 1978), there were no reports of tardive dyskinesia secondary to metoclopramide. However, recent reports suggest that potentially irreversible tardive dyskinesia may result from long term metoclopramide therapy. The onset of tardive dyskinesia usually occurs after at

least 1 year of continuous treatment. Symptoms have been reported to still be present up to 3 years after cessation of metoclopramide (Grimes et al., 1982b; Häggström, 1981).

5.2 Cardiovascular Reactions

Although metoclopramide does not usually produce cardiovascular reactions (Pinder et al., 1976), several case reports merit scrutiny. Three patients with phaeochromocytoma developed hypertensive crisis immediately after administration of metoclopramide 10mg intravenously. Pretreatment blood pressures ranging from 290/120mm Hg to 140/95mm Hg rose to a maximum of 340mm Hg systolic. All patients responded promptly to phentolamine and were not rechallenged (Agabiti-Rosei et al., 1977; Plouin et al., 1976). Elevation of blood pressure from 170/110mm Hg to 270/140mm Hg was reported in another patient with Parkinson's disease. Concomitant drugs included amitriptyline, digoxin and cyclopenthiazide. Hypertension began 24 hours after initiation of metoclopramide 10mg, levodopa 50mg, and carbidopa 5mg (all given 3 times daily), and it declined when therapy was discontinued. Phaeochromocytoma was ruled out, and the patient was not rechallenged (Rampton, 1977).

Following hypotensive anaesthesia for neurosurgical procedures, intravenous metoclopramide 10mg was administered 10 to 20 minutes prior to completion of surgery. Acute hypotension was noted in 20 patients, blood pressure decreasing to a minimum arterial pressure of 50mm Hg. Various anaesthetic agents with and without ganglionic blocking agents were used. The incidence and mechanism of this reaction are unknown (Park, 1978; Pegg, 1980).

There is 1 report of severe bradycardia occurring immediately after metoclopramide 15 to 17mg intravenously. There was no history of cardiac disease nor exposure to other causative drugs. A tonic-clonic seizure was reported, and the patient recovered without treatment (Schulze and Winkler, 1978).

5.3 Endocrine Reactions

Metoclopramide stimulates prolactin release in males and females (Pinder et al., 1976). Galactorrhoea associated with elevated serum prolactin has been reported after daily doses of metoclopramide 15 to 30mg. Mean time to onset of symptoms was 23 days, and recovery occurred within a mean of 57 days after withdrawal of the drug (Aono et al., 1978). Reversible amenorrhoea and increased serum prolactin have also been noted with usual therapeutic doses of metoclopramide (Anderson et al., 1981).

Gynaecomastia has been reported in a male during therapy with metoclopramide 10mg 4 times daily for 8 weeks (McCallum et al., 1977).

5.4 'High Dose' Metoclopramide

A dose-related increase in sedation is evident after metoclopramide 2 mg/kg for control of cisplatin-induced vomiting (table VI). Trismus was reported in only 1 patient, and subsequent doses were administered without recurrence. Diarrhoea occurred in 44% of all patients, but this incidence was not significantly different ($p > 0.05$) from that in a similar group of patients treated with placebo (Gralla et al., 1981). Transient hypertension following administration of 2 mg/kg metoclopramide for control of cisplatin-induced vomiting has also been reported in 2 patients by Sheridan et al. (1982); neither patient had any clinical evidence of phaeochromocytoma.

Intermediate-dose metoclopramide (1 mg/kg) [Homesley et al., 1982] appears to be associated with fewer adverse reactions overall than high dose (2 mg/kg) in double-blind trials. However, the use of 11 of 21 cases, respectively, as a basis for comparison limits the credibility of this conclusion. Inclusion of data from 2 uncontrolled studies (Goslin and Garnick, 1981; Strum et al., 1982) raises the overall incidence of side effects to intermediate-dose metoclopramide (sedation 60%, restlessness 18%, dystonia 5%, diarrhoea 13%) to a level similar to that caused by high dose metoclopramide (Gralla et al., 1981). It is noteworthy that diarrhoea oc-

curred most frequently in patients receiving the highest doses of cisplatin, a drug that causes diarrhoea (Gralla, personal communication). Additional experience is needed to clearly determine rates of adverse effects at high and intermediate doses of metoclopramide, particularly in children and young adults (Bui et al., 1982; Goslin and Garnick, 1981).

6. *Overdosage*

Reports of deliberate or accidental overdosage with metoclopramide in adults are rare. Inadvertent administration of adult doses to children provides the majority of overdosage information. The usual signs of muscle hypertonia, irritability and agitation readily respond to discontinuation of metoclopramide and institution of anticholinergic therapy (Pinder et al., 1976).

In a classic case, a 6-year-old female received 4 doses of metoclopramide totalling 70mg within a 24-hour period. The child presented with rolled up eyes (oculogyric crises), blurred vision, painful contractions of the neck musculature with the head rotated to the left (torticollis), and severe agitation. Several recurrences lasting approximately 2 minutes were observed before complete resolution of symptoms (Fumiani et al., 1975).

7. *Dosage and Administration*

The usual oral dose (tablets or syrup) in adults is 10mg, 3 or 4 times daily, given 30 minutes prior to meals and at bedtime or before symptoms are likely to occur. Young adults may receive 5 to 10mg, 2 to 3 times daily. In children under 14, the dose is 0.1 mg/kg per dose, the total daily dose not to exceed 0.5 mg/kg/day. Intramuscular or intravenous administration of up to 10mg may be used where necessary.

For diagnostic procedures in adults, a single dose of metoclopramide 10mg is administered intravenously over a 1- to 2-minute period 10 minutes prior to examination. Children aged under 14 may receive 1 to 5mg according to age and bodyweight.

For the prevention of cisplatin-induced emesis in adults, metoclopramide should be diluted in 50ml of an intravenous solution and infused over a period of 15 minutes of more. Administration should be initiated 30 minutes prior to cisplatin and repeated every 2 hours for 2 doses, then every 3 hours for 3 doses. The initial doses should be 2 mg/kg. If vomiting is controlled, subsequent doses may be reduced to 1 mg/kg, and the sixth dose (at 12.5 hours) may be omitted. Children and young adults are known to be susceptible to the development of extrapyramidal reactions at this dosage schedule; the optimum dosing recommendations for these patients remains to be established.

Metoclopramide should not be administered in combination with drugs of the phenothiazine, butyrophenone or thioxanthene types, since potentiation of extrapyramidal effects may occur.

Metoclopramide is contraindicated in patients with known or suspected phaeochromocytoma because it has been reported to induce hypertensive crisis in this patient population (Agabiti-Rosei et al., 1977; Plouin et al., 1976).

Metoclopramide should not be used when enhanced gastrointestinal motility may be hazardous to the patient (e.g. obstruction or perforation).

8. *The Place of Metoclopramide in Therapy*

Vomiting associated with narcotic analgesics, radiation therapy, or pregnancy responds to metoclopramide as well as or better than to phenothiazine antiemetics. Postoperative vomiting is controlled by metoclopramide when the drug is administered towards the end of surgery. Recent well designed studies indicate that high dose metoclopramide reduces the debilitating emesis of cisplatin to a more tolerable level. Additional trials are required to determine the most suitable dosage and frequency of administration and efficacy in emesis caused by other antineoplastic drugs.

Metoclopramide is superior to placebo in a variety of gastrointestinal disorders associated with

Table VII. Effect of metoclopramide on the gastrointestinal absorption of concomitantly administered drugs in patients or volunteers

Drug	Reference[a]	No. of subjects	Daily dose (mg) and route of metoclopramide	Effect on time to peak concentration[b]	Effect on peak drug concentration	Comment
Aspirin	Pinder et al. (1976)	20	10 im	↓	↑	Migraine
	Ross-Lee et al. (1982)	30	10 im	↔	↑	Migraine
			10 po	↔	↔	
Atenolol	Regardh et al. (1981)	6	25 po	↔	↔	
Cimetidine	Gugler et al. (1981)	8	14 po	↔	↔	Trend ↓ AUC
	Kanto et al. (1981)	8	20 po	↔	↔	↓ AUC
Diazepam	Gamble et al. (1976)	10	10 iv	↓	↑	
Digoxin[d]	Pinder et al. (1976)	11	30 po			↓ AUC
	Johnson et al. (1978)	10	10 po			↓ AUC
Ethanol	Pinder et al. (1976)	7	20 iv + po	↓	↑	
Levodopa	Pinder et al. (1976)	13	10 iv or 20 po	↓	↑	
Lorazepam	Diamond (1978)	10	20 po	↔	↔	
Mexiletine	Wing et al. (1980)		10 iv	↓	↔	
Paracetamol	Pinder et al. (1976)	5	10 iv	↓	↑	Slow absorbers
	Crome et al. (1981)	12	10 po	↓	↔	Normal subject
Pivampicillin	Pinder et al. (1976)	6	10 po	↓	↔	
Propranolol	Charles et al. (1981)	12	30 po	↔	↔	
Tetracycline	Pinder et al. (1976)	10	10 + 20 po	↓	↔	
Theophylline	Steeves et al. (1982)	8	10 po	↔	↔	Healthy subjects
Tolfenamic acid	Tokola and Neuvonen (1982)	6	20 r	↓	↔	Migraine
				↓	↔	Migraine-free

Abbreviations: iv = intravenous; im = intramuscular; po = oral; r = rectal; AUC = area under the curve.

a Data reviewed by Pinder et al. (1976) presented as compilation.

b ↑ indicates a significant increase, ↓ a significant decrease and ↔ no significant change.

c Slow release formulation.

d Large particle size and slow release formulations used in these studies.

delayed gastric emptying. 'Traditional' daily doses (40mg) alleviate symptoms of gastro-oesophageal reflux and limited studies suggest that higher doses (60mg daily) facilitate healing of local inflammation. In gastric stasis following vagotomy, metoclopramide reduces symptoms and improves gastric emptying. However, objective improvement in diabetic gastroparesis is difficult to demonstrate and in most instances improvement is limited to symptomatic relief. Metoclopramide is equivalent or superior to 'standard' therapy (e.g. anticholinergics, phenothiazine antiemetics, antacids) in the treatment of dyspepsia. There is no evidence that metoclopramide promotes healing of peptic ulcer.

Enhancement of peristalsis and relaxation of the pylorus with metoclopramide are beneficial in radiological procedures. Accelerated passage of barium through the gastrointestinal tract reduces the number of films required and the total radiation exposure for the patient. Intubation and bi-

opsy are facilitated. Metoclopramide also promotes removal of gastric contents from the visual field prior to endoscopy.

A limited number of studies suggest that metoclopramide may be useful in the treatment of migraine headache, defective lactation, hypomotile ureter, and orthostatic hypotension, but further adequately designed studies are necessary to determine its likely role in these conditions.

9. Drug Interactions

The small intestine is the predominant site of absorption for most drugs which are absorbed as un-ionised molecules by passive diffusion. Even for easily diffusible low molecular weight compounds (e.g. ethanol and weakly acidic drugs like acetylsalicylic acid), absorption from the stomach is slower than from the small intestine. Therefore, the time required for orally administered drugs to reach the small intestine often becomes the rate-limiting step in drug absorption. It is not surprising that metoclopramide, which enhances gastric emptying, alters the absorption of some other drugs (table VII). There is no evidence that metoclopramide affects urinary or biliary excretion of other drugs (Pinder et al., 1976).

Parenteral metoclopramide corrected the delayed and diminished absorption of aspirin in patients with migraine and of paracetamol in subjects with delayed gastric emptying (Pinder et al., 1976; Ross-Lee et al., 1982). Oral metoclopramide shortened the time to peak paracetamol serum concentrations in normal volunteers but had no effect on peak or total (cumulative) serum concentrations (Crome et al., 1981). Likewise, the time to peak antibiotic concentrations was shortened in volunteers receiving metoclopramide plus either tetracycline or pivampicillin, but there was no effect on peak serum concentrations (Pinder et al., 1976).

In 2 evaluations of the effect of metoclopramide upon benzodiazepine absorption, outcome may have been determined by the primary site of drug absorption. Metoclopramide reduced the time to achieve peak serum concentration of diazepam and increased the peak drug level (Gamble et al., 1976), however there was no effect on the pharmacokinetics of lorazepam. Like most drugs, diazepam is absorbed primarily in the small intestine so that metoclopramide would be expected to facilitate absorption. In contrast, lorazepam is absorbed from both the stomach and small intestine so improved gastric emptying would not have as great an impact upon drug absorption (Diamond, 1978). These discrepancies underscore the need for additional studies to confirm or refute generalisations regarding the mechanism of metoclopramide-induced alterations in drug absorption.

Metoclopramide has a favourable effect on the absorption of drugs in which this is subject to wide interindividual variation. In volunteers, and in 1 patient with Parkinson's disease, metoclopramide decreased the time to peak concentration and increased both the peak and overall (cumulative) drug concentration of levodopa (Pinder et al., 1976). Similarly, metoclopramide corrected the delayed appearance of peak mexiletine levels, but had no effect upon either the peak or the total (cumulative) drug concentration in volunteers (Wing et al., 1980).

Slow-release formulations may be carried beyond the site of absorption before passive diffusion is completed. Total (cumulative) digoxin concentrations may be compromised by coadministration of metoclopramide (Johnson et al., 1978; Pinder et al., 1976) but this has been shown only with the now obsolete large-particle formulation. The second peak of cimetidine absorption, which is thought to represent more distal small intestinal absorption, was abolished by metoclopramide. Increased motility which may have propelled unabsorbed drug beyond the second site would be compatible with this observation (Kanto et al., 1981). However, oral metoclopramide 10mg did not influence the absorption of slow-release theophylline (Steeves et al., 1982). Additional studies are required to confirm these observations and to determine the clinical significance of metoclopramide-induced changes in drug absorption.

In a study in 10 volunteers, the combination of

atropine 0.6mg plus metoclopramide 10mg abolished the increase in lower oesophageal pressure demonstrated with metoclopramide alone (Brock-Utne et al., 1976).

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