REVIEW OF LITERATURE
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HISTORY AND DISCOVERY OF METOCLOPRAMIDE

Vomiting is a common symptom in majority of gastro-intestinal disorders and other diseases. Although a number of drugs are available to give symptomatic relief from vomiting, none is devoid of undesirable effects particularly affecting central and autonomic nervous systems. Phenothiazines, antihistaminics and anticholinergics are popular anti-emetic agents in the current medical knowledge. In addition, local anaesthetics of procaine type are known to possess anti-emetic actions but chlorination of the benzene ring in procainamide leads to a powerful anti-emetic compound (Ortho-chloro-procainamide) without any significant anti-arrhythmic and local anaesthetic effects. This fact attracted the curiosity of a group of French scientists in 1950's. These workers undertook a systematic study of various chlorinated derivatives of para-aminobenzoic and para-aminosalicylic acids to evaluate their anti-emetic and other pharmacological actions. During this search of a new group of anti-emetic agents, metoclopramide (2-methoxy-5-chloro-procainamide) was shown to be the most powerful anti-emetic drug without any central depressant actions which is a common feature of other currently available anti-emetic agents (Justin-Besancon and Laville, 1964 a; 1965 b).
Fig.1(i) shows chemical structure of:

(A) Procaainamide
(B) Metoclopramide
Metoclopramide was synthesized in Belgium and was forgotten without proper evaluation of its therapeutic potentiality. Justin- Besancon, Leveille and Thominet (1964 a; 1965 b) brought this drug to light to apprise the medical community that this new chlorinated procainamide derivative is a powerful anti-emetic drug with novel central and peripheral mechanisms in contrast to any other anti-emetic drug.

PHARMACOLOGICAL STUDY OF METOCLOPRAMIDE

(A) ANIMAL STUDIES

GASTRO-INTESTINAL SYSTEM

It exerts profound effects on gastro-intestinal system. It has been seen that metoclopramide after oral or intravenous administration affects the motility of gastro-intestinal tract. It improves the resting tone of oesophageal sphincter, tone and peristalsis of stomach with accelerated gastric emptying. It increased pyloric activity, caused distension of duodenal bulb and increased peristalsis of duodenum with accelerated transit through duodenum and jejunum. The effects on colonic motor activity are not well marked. The actions of metoclopramide on motility are blocked by atropine. Metoclopramide sensitizes the gut muscle to the actions of acetylcholine.

(1) OESOPHAGUS

In isolated oesophageal smooth muscle preparation from the cat, it has been seen that metoclopramide has stimulant action at low concentration but a depressant action at high concentrations (Marmo et al., 1970 b).
(ii) **STOMACH**

The metoclopramide given intravenously, intramuscularly or orally in the doses of 10-40 mg significantly accelerates gastric emptying and increases frequency and amplitude of gastric contractions. These effects have been shown in anaesthetised and conscious dogs following intravenous doses (Jacoby and Brodie, 1967; Johnson, 1969; 1971a). On the isolated preparation from Guinea-pig and rat-stomach, metoclopramide produced increase in the amplitude of contractions at concentrations of 20 μg/ml (Hay, 1975; Marmo et al., 1970b).

Jacoby and Brodie (1967) have observed that metoclopramide accelerates gastric emptying in rodents and primates. Metoclopramide has no effect on gastric secretion. The experiments on dogs and pylorus-ligated rats have not shown any effect on gastric secretion in the doses which accelerated gastric emptying (Jacoby and Brodie, 1967). But La Barre (1969) has reported that metoclopramide inhibited post-insulinic gastric secretion in the rats in doses of 1 mg/kg.

(iii) **SMALL INTESTINE**

The metoclopramide stimulates contractions of intestinal smooth muscle, so that transit time through it is decreased. Johnson (1971a; 1973a) found that metoclopramide in 2 mg/kg (IV) produces stronger contractions of duodenal smooth muscle but it has little effect in dogs anaesthetised
with sodium pentobarbital (Jacoby and Brodie, 1967). Metoclopramide (1.5mg/kg IV) reduced the mean transit time and volume in anesthetised dog (Tinker and Cox, 1969).

(iv) LARGE INTESTINE

Metoclopramide has little effect on motility in the large intestine. The experimental study on isolated guinea-pig colon has revealed that it affects motility of colon probably by blocking the 5-hydroxy-tryptamine receptors which are involved in the control of gastro-intestinal tone and motility (Beani et al., 1970; Bianchi et al., 1970).

(v) BILIARY TRACT

The studies have shown that metoclopramide does not exert much effect on biliary tract but it stimulates isolated rodent gall bladder (Marmo et al., 1970 b). Johnson (1969; 1971 a) found no effect on gall bladder pressure in anesthetised dogs. Some experiments have revealed that metoclopramide exerts a slight choleretic action and dilates the sphincter of Oddi (Modica et al., 1970).

CENTRAL NERVOUS SYSTEM

Metoclopramide produces anti-emetic effect with varying degree of neuroleptic properties.

(i) ANTI-EMETIC ACTION

Metoclopramide prevents drug induced vomiting in animals. It prevents apomorphine, hydergine, reserpine, tetradotoxin and copper sulphate induced vomiting.
It prevented apomorphine (100 µg/kg E C) and hydergine (90 µg/kg IV) induced vomiting in the dogs (Justin-Besancon and Leaville, 1964a).

It also prevented copper sulphate (10mg/kg orally) induced vomiting (Leaville, 1964).

(ii) NEUROLEPTIC EFFECTS

Metoclopramide has been reported to produce neuroleptic effects in rodents, squirrel and macaque monkeys (Boissier et al., 1964; Marino et al., 1968). Costall and Naylor (1973; 1974) found that metoclopramide could induce dose-dependent cataleptic state with a latency of onset of 12 minutes and a duration of 0.9 hours after an intraperitoneal dose of 5 mg/kg. Metoclopramide induced catalepsy, in contrast to that induced by phenothiazines or butyrophenones, was not potentiated by cholinergic agonists such as arecoline. Neuroleptic property of metoclopramide is reduced or abolished by bilateral lesions of caudate nucleus, putamen, globus pallidus or nucleus accumbens.

Neuroleptic effect of metoclopramide is due to blockade of central dopaminergic receptors. The metoclopramide is a potent antagonist of inhibitory responses of dopamine. This property of metoclopramide has been compared with other neuroleptic drugs. The metoclopramide antagonises piribedil, apomorphine and amphetamine-induced stereotypies in rodents though it has little effect on motility following high doses.
of subcutaneous nor-adrenaline (Häckman et al., 1973; Janssen et al., 1967; Poignant et al., 1972). Dolphin et al., (1975) have shown that metoclopramide resembles pimozide having about 1/10th potency of pimozide as a specific dopamine receptor antagonist. Furthermore, association of metoclopramide catal- epsy and that of other neuroleptic drugs with a marked rise in striatal levels of homo-vanillic acid, the peripheral metabolite of dopamine, provides further support for Central dopaminergic blockade by this drug. Ahtee and Buncombe, 1974; Peringer et al., 1975).

Robinson (1979) has shown that metoclopramide is a potent blocker of dopamine receptor but it is a weak inhib- itor of nor-adrenaline receptor coupled with adenylyl-cyclase system in limbic forebrain which is related to the thera-
peutic efficacy of anti-psychotic drugs.

(iii) EXTRAPYRAMIDAL EFFECTS

Metoclopramide produces dyskinesias consisting of torticollis, trismus, facial spasms, opisthotonus and occulogyric crisis (Robinson, 1973 b).

AUTONOMIC NERVOUS SYSTEM

(i) INCREASE OF CHOLINERGIC EFFECT

Metoclopramide increases the resting tone and phasic contractile activity of gastro-intestinal smooth muscle (Eisner, Okwueasaba and Hamilton, 1976). Vagotomy does not
interfere with the actions of metoclopramide but atropine reduces or completely abolishes the effect of metoclopramide. It is believed that metoclopramide acts on those cholinergic neurones that are the part of intestine nerve plexuses of the gut muscle possibly through release of acetylcholine from cholinergic neurones. In addition, metoclopramide also sensitizes the muscarinic receptors on gut smooth muscle to the action of acetylcholine. However, in contrast to betahanechol or pyridostigmine, it does not influence gastro-intestinal secretions (Schulze Delrieu, 1979).

(ii) **ANTAGONISM OF DOPAMINERGIC AND TRYPTAMINERGIC NEUROTRANSMISSION**

Metoclopramide inhibits dopaminergic and tryptaminergic neurotransmission. All effects of metoclopramide on brain stem and on cardiovascular system is due to blockade of dopaminergic receptors (Schulze Delrieu, 1979).

Metoclopramide inhibits gastric relaxation produced by dopamine. This action is antagonised by methysergide. It acts as partial agonist on same receptor as serotonin.

It facilitates peristaltic reflex by acting on nerve fibres. Metoclopramide partially antagonises the inhibitory effect of serotonin on peristalsis.

(iii) **DIRECT SMOOTH MUSCLE EFFECT**

Although metoclopramide acts through cholinergic neurones but it has got direct stimulatory effect on oesopha-
geal sphincter muscle of oppossum (Schulze Deirieu, 1979).

ON CARDIOVASCULAR SYSTEM

In anaesthetised cat or dog, metoclopramide per se has no effect on blood pressure after low intravenous doses (less than 1 mg/kg per minute for 90-100 mts) or oral doses (5 to 10 mg/kg) but higher doses produce transient hypotension (La Barre, 1969; Malmejac and Laville, 1964; Marmo et al., 1969). Metoclopramide (doses upto 10 mg/kg) when administered intravenously did not modify the effects of histamine, adrenaline, nor-adrenaline or acetylcholine on blood pressure. However, depressor responses to dopamine in anaesthetised rat or cat were abolished by intravenous doses of metoclopramide which did not significantly effect pressor responses to nor-adrenaline or isoprenaline (Dey, 1975).

Metoclopramide does not effect cardiac functions in dogs even upto 15 mg/kg doses in electro-cardiographic tracings (Malmejac and Laville, 1964) and rabbits receiving upto 40 mg/kg (Marino et al., 1969). But higher doses led to transient bradycardia with enhancement of R and T waves. Metoclopramide was atleast as effective as procainamide in preventing cardiac arrhythmias in rats and dogs produced by chlorides of barium, calcium, magnesium or potassium and by aconitine, strophanthoside, choloroform—adrenaline and benzene—adrenaline (Bastos, 1968; Marmo et al., 1970 a; Ramos et al., 1967). Since these cardiac effects are evident at a relatively higher doses, its clinical value as an
anti-arrhythmic agent is not convincingly superior to other drugs.

**BIOCHEMICAL AND HAEMATOLOGICAL EFFECTS**

Any abnormal biochemical and haematological changes receiving daily oral doses up to 100 mg/kg of metoclopramide for 3 to 6 months were not observed in limited number of studies conducted (Pinder, Brogden, Phyllis, Sawyer, Speight and Avery, 1976).

(E) **HUMAN STUDIES**

**GASTRO INTESTINAL SYSTEM**

Metoclopramide exerts same effect on human beings as in animals.

(1) **OESOPHAGUS**

Metoclopramide alters oesophageal tone and motility. It increases the lower oesophageal sphincter pressure and amplitude of oesophageal body contraction. Both on oral as well as intravenous administration, metoclopramide produced these changes in normal subjects as well as in patients with reflux oesophagitis. Increase in the lower oesophageal sphincter pressure after oral administration of metoclopramide becomes apparent within 20-30 minutes, and lasts for 90 minutes (Diliwari and Misiewicz, 1972, 1973; Mc Callum et al., 1975). Cohen et al. (1976) also confirmed the efficacy of metoclopramide to relieve lower oesophageal sphincter pressure but at a higher dose.

Behar and Biancani (1976) compared the effects of single doses of metoclopramide (15mg), aluminium hydroxide
(30 ml) and placebo given orally in 15 patients with reflux oesophagitis. In their study metoclopramide was found to be significantly more effective than antacid and placebo therapy in reducing the cumulative duration of reflux oesophagitis following a protein-rich meal.

Most of the studies have also reported an increase in duration and strength of oesophageal contraction (Mc Callum et al., 1975).

(ii) STOMACH

A variety of experimental techniques have established that metoclopramide given intravenously, intramuscularly or orally (10-40 mg) significantly accelerates gastric emptying and increases the amplitude and frequency of gastric contractions. It is not yet clear whether metoclopramide is effective in all post-vagotomy patients but it is effective in patients with abnormally slow rate of gastric emptying.

The effect of metoclopramide on gastric contractions is more pronounced in the antrum in normal subject as well as in patients with dyspeptic symptoms (Banke, 1969; Eisner, 1971; Johnson, 1971 b, 1973). In majority of studies metoclopramide accelerated gastric emptying particularly in subjects with abnormally high gastric emptying times (Kreal et al., 1973; Jacoby and Brodie, 1967). There was complete gastric emptying in 45 minutes (Howells et al., 1971) as compared to normal emptying time of 30-45 minutes.
The gastric emptying is associated with strong entral contractions and the duodenal contractions occur during terminal entral contractions (Weisbrodt et al., 1969). This pattern also prevents reflux of duodenum contents into stomach. Kelly (1973) has shown that metoclopramide converts terminal entral contraction which normally blocks the passage of gastric contents into the duodenum to sequential contraction of high amplitude which propel gastric contents out of stomach.

The metoclopramide is not effective in normal subjects with normal rate of gastric emptying (Hancox et al., 1974). It also increases pyloric sphincter pressure (Valenzuela et al., 1976). However, the effect of metoclopramide in post vagotomy patients are equivocal. Despite its tremendous effect on gastric motility, the metoclopramide does not affect gastric secretions (Connell and George, 1969; McCallum et al., 1975; Meeroff, 1979).

(iii) SMALL INTESTINE

It stimulates contractions of intestinal smooth muscle so that transit time through it is decreased. Such effects are demonstrable in normal subjects and dyspeptic patients. These effects are antagonised by anti-cholinergic drugs (Banke, 1969; Eisner, 1971; James and Hume, 1968).

(iv) LARGE INTESTINE

Metoclopramide has little effect on motility in
large intestine. But Robinson (1973) found that it is effective in the treatment of diarrhoea which could be due to its morphine like action on colon.

(v) **BILIARY TRACT**

Konevuo et al. (1975) found no effects on gall bladder motility but Eisner (1971) has reported biliary colic after parenteral administration of metoclopramide.

**CENTRAL NERVOUS SYSTEM**

(i) **ANTI-EMETIC ACTION**

Metoclopramide prevents drug induced vomiting. It prevented apomorphine induced vomiting in healthy prisoner volunteers in the doses of 0.15 to 0.30 mg/kg (Kelein et al., 1968). Proctor (1978) confirmed the anti-emetic action of metoclopramide in 10 healthy human volunteers against apomorphine induced vomiting.

(ii) **ANALGESIC AND ANTI-PYRETIC EFFECT**

Metoclopramide per se has no analgesic and anti-pyretic effects. However, intramuscular injection of metoclopramide promotes the absorption of salicylates in the patients of migraine attack (Volans, 1975). During acute migraine attack, it is believed that the absorption of salicylates is impaired due to altered gastro-intestinal motility and thereby there is delayed gastric emptying. Improved
gastro-intestinal motility and short gastric emptying time might be the underlying mechanism for better absorption of salicylates.

Lind and Breivik (1970) observed a significantly lower requirement of post-operative pethidine in patients on metoclopramide than in those on perphenazine. However, later on these authors contradicted their findings and found no significant difference between metoclopramide and placebo in influencing pethidine requirements (Breivik and Lind, 1971).

Moreover, it has been shown that metoclopramide also accelerates the absorption of paracetamol but the total excretion of paracetamol in 12 hours with or without metoclopramide was found to be not significant (Nimmo, 1973; Nimmo et al., 1973).

(iii) CARDIOVASCULAR SYSTEM

Metoclopramide has been tried in patients undergoing routine cardiac catheterisation for a variety of conditions, especially mitral stenosis. Intravenous dose of 20 mg metoclopramide did not significantly affect pulmonary artery systolic or diastolic pressures, left ventricular systolic or end diastolic pressures, or cardiac output (Thorburn and Stoward, 1973). There was no change in the travel time of the ball of aortic starr prosthetic valves in some patients in contrast to the 20% reduction produced by intravenous isoprenaline (2.5 μg/kg). This indicates the lack of effect of
metoclopramide on left ventricular functions. There was no change in intracardiac conduction after 20 mg IV doses in 4 patients who were studied during recording of His bundle electrograms conducted for the investigation of syncopal episodes, extrasystole or tachycardias. One patient with an aortic starr valve developed sinus tachycardia of 130 beats /minute immediately after injection of metoclopramide. The heart rate slowed to normal after 3 minutes and there was no change in left ventricular function. It showed modest and transient anti-arrhythmie action lasting for five minutes in one patient who was having frequent extrasystole.

On the whole, metoclopramide has anti-dopaminergic action on cardiovascular system. It causes transient hypotension in relatively larger doses and anti-arrhythmic action which has no clinical significance (Pinder et al., 1976).

(IV) OTHER CLINICAL PHARMACOLOGICAL STUDIES WITH METOCLOPRAMIDE

In controlled trials, metoclopramide has been studied as an anti-emetic, has been used in treatment of vertigo, migraine, dyspepsia, gastro-oesophageal reflux and gastric and duodenal ulcers. It has been used as preanaesthetic medication to promote gastric emptying (Pinder et al., 1976).

ANTI-EMETIC STUDY

(a) POST-OPERATIVE EMESIS

Boisson and Albot (1966) have shown that 10 to
60 mg doses of metoclopramide (I V or I M) reduces or eliminates post-operative nausea and vomiting in 90% of patients. Some studies have demonstrated that it is superior to placebo (Clark and Storrs, 1969; Handley, 1967; Tornetta, 1969). While others have demonstrated that it is not superior to placebo (Breivik and Lind, 1971; Dobkin et al., 1968; Dundee and Clarke, 1973; Ellis and Spence, 1970; Shah and Wilson, 1972). The 20 mg I V or I M doses of metoclopramide compared well with trimethobenzamide (300 mg) (Dobkin et al., 1968) but was slightly superior to the prochlorperazine in 10 mg dose (Tornetta, 1969). Metoclopramide (10 mg I M) was found to be superior to 5 mg perphenazine (Lind and Breivik, 1970) but in other study it was found to be equi-effective with perphenazine (Handley, 1967).

Tornetta (1969) found metoclopramide (20mg) superior to the 10 mg prochlorperazine or placebo while study of Lind and Breivik (1970) showed that metoclopramide is better than perphenazine in cases of gynaecological laparotomies.

Dobkin et al. (1968) have compared the anti-emetic activities of metoclopramide, trimethobenzamide and placebo. The drugs were given intravenously 30 minutes before the end of operation. The drug did not show any advantage over other drugs. Dundee and Clarke (1973) gave metoclopramide for premedication and also found no advantage
over either placebo or diazepam. The metoclopramide definitely reduces the pre-and post-operative vomiting in patients given pethidine (Assat et al., 1974a; Dundee and Clarke, 1973; Dundee et al., 1974; Tornetta, 1969).

The type of anaesthetic may also influence the efficacy of metoclopramide. Shah and Wilson (1972) demonstrated that metoclopramide is ineffective in halothane anaesthesia while Breivik and Lind (1971), Handley (1967) and Lind and Breivik (1970) showed significant advantage of metoclopramide in halothane anaesthesia. Tornetta (1969) used different anaesthetics and demonstrated more effectiveness of metoclopramide over placebo.

Preanaesthetic medication with atropine like drugs has no effect on anti-emetic potency of metoclopramide.

(b) DRUG-INDUCED EMESIS

Boisson and Albot (1966) demonstrated that metoclopramide prevents vomiting induced by various types of drugs like analgesics, digitalis, tuberculostatic and cytostatic agents, antibiotics and anti-parkinsonian drugs.

(i) ANALGESICS

It prevented analgesic induced vomiting used pre- or post-operatively. Clarke and Sterrs (1969) and Handley (1967) demonstrated advantage over placebo in morphine induced vomiting while Ellis and Spence (1970) and Shah and Wilson (1972) showed that it has no advantage.
Lind and Breivik (1970) observed a lower requirement of pethidine in cases in which metoclopramide was given while perphenazine did not reduce the requirement of post-operative pethidine. Later Breivik and Lind, (1971) found no significant difference between metoclopramide and placebo in pethidine requirements.

Some studies have shown that metoclopramide is more effective than placebo and superior to perphenazine or prochlorperazine in preventing emesis due to pethidine or morphine. The drug was effective when given together with pethidine both in post-operative patients (Lind and Breivik, 1970) and in women during labour (Mc Garry, 1971).

From the above study it is clear that metoclopramide prevented pre-or post-operative emesis of pethidine. It was also very much effective when given with pethidine during labour and it does not produce any harm to either mother or baby.

(ii) IODIPAMIDE

Iodipamide meglumate is used for intravenous cholangiography which normally produces nausea which is not prevented by metoclopramide (20 mg) or chlorpromazine (James and Hume, 1968).

(iii) CYTOSTATIC DRUGS

Metoclopramide does not prevent cytostatic drugs induced vomiting (Moertel and Reitemeier, 1969).
(iv) **MISCELLANEOUS DRUGS**

Nausea and vomiting induced by levodopa in the treatment of parkinsonism was prevented by 30-80 mg dose of metoclopramide without any effect on response to levodopa (Fischer et al., 1973; Tersey et al., 1975).

(c) **RADIATION SICKNESS**

Boisson and Albot (1966) showed 6% success rate of metoclopramide in radiation sickness. Since metoclopramide releases prolactin which promotes growth of breast cancer, therefore use is limited in radiation sickness in breast cancer.

Ward (1973) has done a comparative study of prochlorperazine and metoclopramide in radiation sickness. He showed 61% success rate in case of prochlorperazine while 53% in case of metoclopramide.

(d) **EMESIS OF PREGNANCY**

Metoclopramide is effective in treating the vomiting of pregnancy without any adverse effects either on mother or fetus. No dysmorphogenic effects have been reported in animals even in first trimester of pregnancy.

Singh and Lean (1970) studied and compared the metoclopramide, prochlorperazine and placebo in cases of hyperemesis gravidarum. They obtained better results and lesser side effects with metoclopramide as compared to
prochlorperazine or placebo. No congenital malformation was observed.

(e) NAUSEA AND VOMITING

Metoclopramide successfully prevented nausea and vomiting in a variety of disorders (Boisson and Albot, 1966; Robinson, 1973 a). It prevented the vomiting of gastritis, gastroenteritis, gastric carcinoma, hepatic and biliary disorders, renal insufficiency, cardiac disease and alcoholism.

Trafford et al. (1967) have studied metoclopramide in patients with chronic nausea and vomiting or dyspepsia. They showed a success rate of 64%. Jones (1968) has demonstrated that metoclopramide successfully prevents the vomiting of emotional origin and chronic renal failure.

Metoclopramide also prevents vomiting of post gastrectomy syndromes, peptic ulcer, cholecystitis, pancreatitis, cardiac failure, cirrhosis, hepatitis and renal failure (Trafford et al., 1967).

VERTIGO AND ASSOCIATED DISORDERS

The role of metoclopramide in vertigo is uncertain but studies have been done by different workers and they showed different results. Marshall (1970) compared metoclopramide
(10 mg t.d.s.) and prochlorperazine (5 mg t.d.s.) and found that metoclopramide was superior to prochlorperazine in cases of vertigo but equal in patients with Meniere's syndromes. It was as effective as prochlorperazine in controlling the nausea and vomiting of labyrinthine origin.

Metoclopramide controls the nausea and vomiting of vestibular and labyrinthine origin but is ineffective in other associated symptoms of vertigo like dizziness (Boisson and Albot, 1966). Robinson (1973a) reported good response of the drug against emetic and postural symptoms. Sales (1967) also studied this drug in various types of labyrinthine vertigo and found that this drug considerably relieved paroxysmal attacks of vertigo but it did not relieve tinnitus and hearing loss. However, Stewart and Maran (1973) found no beneficial effects by metoclopramide in labyrinthine vertigo.

Probably it has no role in the sea sickness. Mc Murray (1973) found some advantage over placebo with 10 mg oral doses but better results were obtained with 10 mg I M doses.

**MIGRAINE**

Clinical studies have shown that metoclopramide prevents nausea and vomiting of migraine and it also relieves other symptoms of migraine. But the clear cut role of this drug is yet to be established. Boisson and Albot (1966) and (Robinson, 1973a) have found that it does not lessen the
frequency of migraine attacks but relieves ophthalmological symptoms. Flavell Metts (1974) has done a double blind study and showed that it did not affect the frequency of migraine attacks but relieves nausea and vomiting. Further, it is more useful to give metoclopramide with analgesics because it accelerates and enhances their absorption from gut (Mimmo et al., 1973; Volans, 1975).

**HICCUPS**

The role of metoclopramide in treatment of hiccup is uncertain. It has been tried in cases of hiccups of uraemic origin (Boisson and Albot, 1975; Middleton, 1973) but is not superior to haloperidol or chlorpromazine (Korczyn, 1971).

**GASTRO-INTESTINAL DISORDERS**

(a) **DYSPESIA**

Metoclopramide provides symptomatic relief in cases of dyspepsia (Boisson and Albot, 1966; Robinson, 1973 a; Trafford et al., 1967).

Various double blind studies have revealed that metoclopramide is superior to placebo in relieving dyspeptic symptoms (Uzeta Mejia, 1971; Johnson, 1971 c). Johnson (1973 b) found that metoclopramide is effective in relieving nausea and vomiting, epigastric burning, heart burn, regurgitation of sour fluid but is not successful in relieving flatulent symptoms of belching, bloating and distension.
Natale (1975) has compared the effectiveness of metoclopramide and anti-cholinergic drug—pipenzolate bromide in relieving dyspeptic symptoms. He combined both the drugs with medazepam either in tablet or suppository and found that combination of metoclopramide was superior to the combination of pipenzolate bromide in relieving dyspepsia. Marshall (1970) showed in his study that metoclopramide was better than prochlorperazine in dyspepsia.

(b) GASTRO- OESOPHAGEAL REFLUX

The studies by different workers have shown that metoclopramide increases both oesophageal motility and lower oesophageal sphincter pressure in normal subjects and in patients with gastro-oesophageal reflux. Its effectiveness in the treatment of gastro-oesophageal reflux is variable. Different workers have given different opinions (Pinder et al., 1976).

Johnson (1971 c : 1973 b) showed that it relieves heart burn. McCullum et al. (1976) demonstrated in double blind study in patients of chronic heart burn and reflux that metoclopramide produced improvement and reduced severity, frequency and antacid requirement. Paul and Kerr Grant (1974) showed that metoclopramide is not so much effective in reflux oesophagitis. No significant difference was observed between metoclopramide and placebo. Walls (1972) and Venables et al. (1973) studied and showed no significant effect of
drug on reflux oesophagitis.

(c) **GASTRIC EMPTYING**

Metoclopramide accelerates gastric emptying. Since it also prevents vomiting, therefore, it is specially useful in emergency anaesthesia during labour. It is beneficial where rapid clearance of gastric contents is required (Pinder et al., 1976). Double blind study has shown that 20 mg I V dose produces complete gastric emptying within 1½ hour. Davies and Howells (1973) and Armstrong (1973) have recommended its use in emergency anaesthesia.

Howard and Sharp (1973) showed beneficial effects of 10 mg I M metoclopramide during labour as there is no danger of vomiting due to delayed gastric emptying.

Howells et al. (1971) confirmed the efficacy and advantage of metoclopramide during anaesthesia by making water load in patients. He allowed unrestricted drinking in one group, 1 litre water in other group, no water and unrestricted water with metoclopramide. Results have shown that group receiving metoclopramide behaved in a similar manner as total fasting.

Fry (1974) also observed that 10 mg I M dose of metoclopramide given 2 hours before operation and 1 hour after premedication reduced the incidence of nausea and thirst.

Stadass and Aune (1972) have shown that metoclopramide may be useful in the treatment of postvagotomy stasis. It may also be used in symptomatic gastric retention
of diabetes mellitus, termed as gastroparesis diabeticorum (Brownlee and Kroopf, 1974).

(d) **PEPTIC ULCER**

The efficacy of metoclopramide in healing of gastric and duodenal ulcers has not been determined with certainty. Different workers have given different results with their studies.

In uncontrolled studies it has been shown that metoclopramide (30-60 mg P.O) may be effective in promotion of healing of gastric and duodenal ulcers (Boisson and Albot, 1966; Kocian and Kociánova, 1975; Mur Lineres and Llorca, 1968, Robinson, 1973 a, Schutz, 1976). Hoskins (1973) compared metoclopramide (30 mg daily) with carbenoxolone (300 mg daily) and observed better results with metoclopramide than carbenoxolone in healing of ulcers. Kennedy (1973 b) tried metoclopramide in gastric ulcer patients in a double blind study and found improvement or remission. Moshal (1973) demonstrated in his double blind study that metoclopramide was significantly superior to placebo in preventing relapse in duodenal ulcer patients.

Kocian and Kociánova (1975) indicated the superiority of metoclopramide to placebo in both gastric and duodenal patients in terms of symptomatic improvement but no radiological or other details were given.

(e) **FUNCTIONAL GASTRO-INTESTINAL DISORDERS**

Metoclopramide has been used in various gastro-
intestinal disorders but its efficacy has not been compared with current treatment of choice. Kocian and Kocianova (1975) have shown that metoclopramide (10 mg t.d.s.) was significantly superior to placebo in relieving the symptoms of various functional disorders. De Vris (1969) compared the effects of metoclopramide (10 mg t.d.s.) with those of a mixture of haloperidol and isopropamide iodide (0.3 mg and 2 mg t.d.s.) known to be useful in the treatment of functional disorders. Metoclopramide showed superiority over placebo but there was no difference in the effect of metoclopramide and combination of haloperidol and isopropamide iodide.

Mikaye et al. (1972) demonstrated in their double blind study that metoclopramide was certainly superior to placebo in improving the symptoms of gastritis and gastroptosis, loss of appetite, gastric fullness and epigastric pain but there was no difference between metoclopramide and placebo in patients with gastric neurosis.

Metoclopramide has been used to conservatively treat complete pyloric obstruction due to duodenal ulcer in order to avoid emergency operation. Zer and Dintsman (1975) gave I V metoclopramide (10 mg t.d.s.) followed by oral doses (30 to 40 mg daily) in patients of acute pyloric obstruction. The treatment with metoclopramide was also combined with usual therapy of gastric decompression, fluid and electrolytes. This therapy showed improvement in 80% patients. Metoclopramide
should not be used in pyloric stenosis due to carcinoma or severe fibrosis.

**USE IN GASTRO-INTESTINAL DIAGNOSTICS**

It has been used in diagnostic radiology and has been given before barium meal which provides excellent conditions for the diagnosis of lesions in the duodenum, jejunum and ileum. Metoclopramide also facilitates and accelerates the introduction of tubes or biopsy capsule in the small intestine (Pinder et al., 1976).

**RADIOLOGY**

Metoclopramide is indicated in those patients who, on standard barium meal examination, show gastric stasis, pylorospasm or pyloric stenosis and spasm of duodenal bulb (Kreel, 1973; Margieson and Williams, 1968; Trafford et al., 1967). It controls the nausea or regurgitation of barium that occurs in some patients. It also markedly shortens the time needed for small bowel examination.

**INTRAVENOUS METOCLOPRAMIDE**

James and Melrose (1969) demonstrated that IV metoclopramide (20 mg) also facilitates the barium meal X-ray (Howarth et al., 1969).

**ORAL METOCLOPRAMIDE**

This also facilitates radiological examination and there was no difference in the effect among oral, IM or IV
metoclopramide (Kreel, 1970; Pearson et al., 1973).

INTUBATION AND BIOPSY

Metoclopramide facilitates duodenal intubation and also facilitates rapid and successful biopsy of small intestine as demonstrated both in controlled and uncontrolled trials (Moshal, 1972; Mitchell and Perkins, 1969; Tarpila and Wiljasalo, 1966; Bolin, 1969; Arvanitakis et al., 1975; Kocian and Kocinova, 1975; Pirola, 1967; Harris et al., 1968; Hradsky and Stockbugger, 1974).

EMERGENCY ENDOSCOPY

Metoclopramide has been employed to clear blood out of stomach for assessment and diagnosis of upper gastro-intestinal haemorrhage (Bader, 1973; Moshal, 1973). Emergency endoscopy has been facilitated by 10 mg IV metoclopramide but it may be possible that further haemorrhage may occur due to acceleration of stomach activity.

PROLACTIN RELEASE

Metoclopramide stimulates prolactin release in both the sexes. Galactorrhea has been reported on prolonged administration of drug (Mc Neilly et al., 1974). Increased lactation has been reported in nursing mothers without any side effects (Sousa, 1975). In some cases cardiac arrhythmias have been reported which may be due to prolactin
release (Shaklai et al., 1974).

**PHARMACOKINETICS OF METOCLOPRAMIDE**

Little is known of pharmacokinetic behaviour of metoclopramide particularly in human beings. Studies in animals have shown that it is well absorbed and rapidly excreted with a short half life and only partial metabolism by o-demethylation, N-deethylation and amide hydrolysis (Pinder et al., 1976).

**ABSORPTION**

Metoclopramide is rapidly absorbed from human gastro intestinal tract with maximum blood level of about 40 ng/ml occurring within 2 hours after a dose of 10 mg P.O. Doubling the dose doubles the blood level (Schulze Delriou, 1979). The rectal administration of 40 mg increases motor activity of duodenum within 20 minutes. Hacker et al. (1966) have shown that after intramuscular administration of 40 mg of metoclopramide, no drug was detected in the plasma after 1 hour but levels of 0.02 to 0.2 µg/ml were observed at 2-3 hours. However, accurate measurement of plasma level is not possible due to lack of suitable analytical methods.

It is well and rapidly absorbed from gastro-intestinal tract in mouse. This has been confirmed by the widespread distribution of radio-activity when animals were sacrificed 1 hour after intragastric doses or 5 minutes after intramuscular doses (Ingrand and Boulu, 1970). In rabbits,
oral doses of 200 mg/kg gave average plasma level of 90 
µg/ml 30-120 minutes after administration and completely 
disappeared by 5 hours (Kumada, 1965). Intravenous adminis-
tration (20 mg/kg) gave similar levels immediately. Metoc-
oclopramide was well absorbed when given rectally to dog 
(Hucker et al., 1966).

PLASMA HALF LIFE

The plasma half life of metoclopramide appears 
to be about 60-90 minutes in the rat and dog (Hucker et al., 
1966) and approximately 2 hours in the rabbit (Kumada, 
1965). After intravenous administration, it has short half 
life (Bakke and Segura, 1976) and high apparent volumes of 
distribution (1.1 L/kg) in rats, rabbits and dogs. No 
data are available for man.

DISTRIBUTION

After intragastric or intramuscular administration 
, metoclopramide was found in the intestinal mucosa, the liver 
and biliary tracts and the salivary glands. Lesser amounts 
were found in central nervous system, heart, thymus, supra-
renal glands, fat and bone marrow of mice as observed on 
autoradiography (Ingrand and Boulu, 1970). This pattern of 
distribution has been established at 5 minutes after intra-
muscular and 1 hour after intragastric doses. The radioactivity 
was absent from autoradiogram after 24 hours. It is significant 
from the point of view of its anti-emetic action that
the drug was localised in the central nervous system at the area postrema which contains chemo-receptor trigger zone for vomiting in man.

**Plasma Protein Binding**

Hucker et al. (1966) stated that metoclopramide was moderately bound to human plasma protein. In vitro studies with plasma protein from cows, dogs, rabbits and rats showed that metoclopramide was bound most strongly to albumin followed by alpha-globulins, beta-globulins and fibrinogen (Pagnini and Di-Carlo, 1972). However, the binding was weak.

**Metabolism and Excretion**

The metabolism of metoclopramide in man is not clearly known, but urinary excretion studies indicated that 24% of the dose was excreted unchanged in the first 24 hours following an intramuscular dose of 40 mg (Hucker et al., 1966). After oral doses of 10 mg, about 50% of the dose was excreted unchanged in the urine over 8 hours (Kumada, 1965). Metoclopramide is eliminated slowly after oral administration in rats, rabbits and dogs, with the liver playing a major role in reducing its systemic availability (Eakke and Segura, 1976). 10% of oral dose of drug reached in systemic circulation as unchanged drug. Metoclopramide is excreted mainly in urine, 50% of the total dose of the drug is excreted unchanged while the remainder is metabolised mainly by N-deethylation and partly by O-demethylation with
some acidic and basic metabolites (Bakke and Segura, 1976; Hucker et al., 1966).

In the rabbit, Kumada (1965) found that oral or intravenous doses of 20 mg/kg gave about 50% excretion in the urine, mainly as N-acetyl derivatives after 8 or 48 hours respectively. Other studies (Arita et al., 1970 a,b,c) have found no evidence for the presence of N-acetyl derivatives but have identified the major components of urinary excretion in rabbits as metoclopramide and its N-glucuronide and N-sulfonate. There were also minor amounts of the products of N-deethylation or oxidation namely 4-amino-5-chloro-B-(2-ethylaminoethyl) -2-methoxy benzamide and 4-amino-5-chloro-2 Methoxybenzoic acid. Faecal excretion has not been examined, but distribution studies suggest that some tritiated material was excreted by this route in the mouse(Ingrand and Boulu, 1970).

The vitro studies showed that metoclopramide was transformed into 8 metabolites (Beckett and Huizing, 1975). Six of these were products of amide cleavage, 4 showed evidence of rupture of amino-ethyl q band, and one was a product of N-oxidation. Two were positively identified as the mono- and di-deallylated derivatives.

TOXICITY OF METOCLOPRAMIDE

(i) ACUTE TOXICITY

The toxicity of metoclopramide in man is not well
defined. Robinson (1973 b) reported two instances of overdosage in which subjects took 360 and 800 mg respectively of metoclopramide without fatal outcome. In adults, deliberate or accidental overdosages are very rare but children and infants received overdosages. The signs of overdosages are muscle hypertonia, irritability and agitation. These signs of overdosages disappeared with withdrawal of drug but in severe cases anti-cholinergic agent like benztrpine may be required.

Galletti et al. (1974) reported accidental poisoning in infants. The toxic signs consisted of generalised convulsions in some cases and methaemoglobinemia in one case and these effects were reversible.

The overdosage may cause neurological complications. In animals, acute toxicity by oral route is very low but intravenous metoclopramide is more toxic. Prior treatment with monoamine oxidase inhibitors such as phenelzine increases the acute toxicity of drug (Pinder et al., 1976).

(ii) Sub-Acute Toxicity

80 mg/kg dose given for 5 days in a week over 16 weeks showed marked behavioural changes like fine tremors, subdued behaviour, anorexia and miosis (Pinder et al., 1976). These signs disappeared after withdrawal of drug.

Animals showed signs of fine tremors, hypoactivity, miosis, panting and bizarre positions following I.V or I.M
doses of metoclopramide up to 20 mg/kg for 4 to 5 weeks (Watanabe et al., 1968a; Pinder et al., 1976). These signs appeared and disappeared more rapidly with IV than IM administration.

(iii) **CHRONIC TOXICITY**

There were no abnormal haematological, biochemical or histopathological changes in rats receiving daily oral doses of metoclopramide up to 40 mg/kg (Pinder et al., 1976) or 100 mg/kg for 3 to 6 weeks but 300 mg/kg slowed growth and weight gain in animals while 600 mg/kg resulted in the death of the majority of animals (Watanabe et al., 1968a). There were no significant alterations in liver, renal or cardiovascular functions.

(iv) **SIDE EFFECTS**

In therapeutic doses, metoclopramide produces few adverse reactions which are mild, transient and reversible on withdrawal of drug. Extrapyramidal reactions can occur in some patients. The total incidence of side effects are about 11% (Robinson, 1973b). The side effects include lassitude and drowsiness, bowel disturbances like constipation and diarrhoea. In some patients, it may cause urticarial or maculo-papular rashes, tongue or peri-orbital oedema, dry mouth, transient feeling of anxiety or agitation, stimulation of lactation and methaemoglobinemia. Metoclopramide does not produce any cardiovascular side effects when given
preoperatively (Dobkin et al., 1968; Ellis and Spence, 1970; Lind and Breivik, 1970; Shah and Wilson, 1972; Torentta, 1969).

There were no side effects with oral doses of 20 mg metoclopramide given 4 times daily for 10 days (Scarzella et al., 1968). Clarke and Dundee (1971) found that with 10 mg I M doses, there was only dryness of mouth. Metoclopramide has no adverse effects on the fetus during labour (Mc Garry, 1971).

(v) EXTRAPYRAMIDAL REACTIONS

This side effect usually does not occur with therapeutic dose of metoclopramide but sometimes transient agitation and motor restlessness is seen commonly after intravenous administration. Dystonic reactions occur in about 1% of patients. These dyskinesias begin acutely after drug administration particularly in young patients and consists of trismus, torticollis, facial spasms, opisthotonous and oculogyric crisis (Borenstein and Bles, 1965; Casteelsvan Daele et al., 1970; De Silva et al., 1973; Giger, 1975; Sicard et al., 1973). They occur within 36 hours of starting of treatment and usually disappear within 24 hours of withdrawal of metoclopramide. They respond to classical anti-parkinsonian drugs like intramuscular benztropine or diazepam. Women are more affected than men. This reaction may occur in all age group.

Metoclopramide induced dyskinesias are similar to
tetanic spasm of neck, back and facial muscles in nature (Cochlin, 1974). These dyskinesias are identical with dyskinesias produced by phenothiazines or butyrophenones but incidence with later group is much higher (Giger, 1975). The dystonic reactions are due to the ability of metoclopramide to block central dopaminergic receptors which are responsible for motor functions (Tarsey et al., 1975). Parkinsonian symptoms like tremor, rigidity, akinesia are very rare with metoclopramide except sometimes with overdosage. These symptoms do not occur during chronic administration (Bozenstem and Bles, 1965; Tarsey et al., 1975). In cases of laevodopa induced dyskinesias, 30 mg of metoclopramide daily for 8 weeks neither increased Parkinsonian symptoms nor altered the severity of laevodopa dyskinesias (Tarsey et al., 1975).

MODE OF ACTION OF METOCLOPRAMIDE

(i) GASTROINTESTINAL SYSTEM

On gastro-intestinal system, it has following mechanism of actions:-

(a) Release of acetylcholine from post-ganglionic nerve endings.

Metoclopramide releases acetylcholine from post-ganglionic nerve endings and most of the effects on gastro-intestinal system come through this action (Hay, 1977; Bury et al., 1976).

(b) Sensitizing smooth muscle receptors

Metoclopramide sensitizes the smooth muscle
receptors on gut, thus, it potentiates the effect of acetylcholine and histamine on gut smooth muscle (Eisner, 1976; Okwuasaba and Hamilton, 1976).

(c) **Decrease of tryptaminergic and dopaminergic effects:**

It inhibits dopaminergic and tryptaminergic neurotransmission on gut smooth muscle. (Okwuasaba and Hamilton, 1976; Dougan et al., 1974; Valenzuela, 1978).

**ON OESOPHAGUS**

The metoclopramide acts on oesophagus by dopaminergic mechanism (Baumann et al., 1976).

**ON STOMACH**

The gastric contractions induced by metoclopramide are blocked by anti-cholinergic drugs such as atropine and potentiated by cholinergic agonists like carbachol and methacholine (Jacoby and Brodie, 1967; Johnson, 1971a).

Metoclopramide has no action per se on isolated preparation of human smooth muscle from stomach but sensitizes the smooth muscle to the action of acetylcholine, this effect is partially antagonised by atropine (Eisner, 1968). Metoclopramide activates intramural cholinergic neurones which are responsible for modifying gastric motility either by direct stimulation or by removal of inhibitory pathways but it does not affect acid secretion (Hey, 1975). Metoclopramide induced stimulation is blocked by hyoscine but not by tetrodotoxin or hexamethonium. However, the sensitization to acetylcholine
is prevented by tetrodotoxin and hexamethonium (Pinder et al., 1976).

**ON SMALL INTESTINE**

The stimulatory action of metoclopramide on motility of small intestine is blocked by anti-cholinergic drugs (Jacoby and Brodie, 1967; Schmid and Ritter, 1972). The duodenal stimulatory effects of pancreozymin which are potentiated by metoclopramide are abolished by atropine (Johnson, 1971a).

Metoclopramide sensitizes the preparation to the action of acetylcholine and produces contractions per se (Eisner, 1968). However, in higher concentration, it has been observed that it inhibits contractions (Birdley and Baines, 1973; Forthine and Reese, 1972; Marmo et al., 1970b). The metoclopramide does not antagonise the actions of isoprenaline or 5-hydroxytryptamine on human smooth muscle preparation but metoclopramide antagonises the 5-hydroxytryptamine induced contractions in animal experiments (Eisner, 1968).

**ON LARGE INTESTINE**

Metoclopramide has similar mechanism of action as above on large intestine (Eisner, 1968). It blocks the 5-hydroxytryptamine receptors which controls tone and motility of gastro-intestinal tract (Beani et al., 1970; Bianchi et al., 1970). Low concentration of metoclopramide did not change acetylcholine release on large intestine but increased response to exogenous acetylcholine and to pelvic nerve stimulation, these effects were blocked by atropine, tetrodotoxin and
morphine but not by hexamethonium. Metoclopramide enhanced cholinergic responses to nicotine but abolished the effects of 5-hydroxytryptamine (Pinder et al., 1976).

(ii) **MECHANISM OF ANTI-EMETIC ACTION**

Metoclopramide is believed to exert anti-emetic effects partly by central and partly by peripheral actions. Possibly it raises the threshold of chemo-receptor trigger zone (CTZ) and, thus, prevents vomiting by central action. In addition, it decreases the sensitivity of visceral nerves which transmit afferent impulses from the gastro-intestinal tract to the emetic centre in the lateral reticular formation (Pinder et al., 1976).

Stimulation of CTZ is specific to dopamine like drugs and anti-emetic agents which are believed to block the CTZ are in general also block central dopaminergic receptor (Cannon, 1975). Since, metoclopramide produces behavioural effects in animals, therefore, it indicates that it has also central dopaminergic antagonism (Dolphin et al., 1975). It seems that the anti-emetic effect of metoclopramide is mediated partly by blockade of CTZ dopamine receptors. Metoclopramide prevented retching and vomiting in the cat 'encephale Isole' preparation induced by electrical stimulation of the nucleus tractus, Solitarii of the brain stem (Takaori et al., 1968). Spontaneous discharges from single neurone in this area were significantly increased by intravenous apomorphine (1mg/kg), a known dopamine receptor agonist. However, this
increase could be abolished by intravenous metoclopramide (3mg/kg) treatment. Thus, metoclopramide has selectively suppressive effect on the firing of single neurone in the nucleus tractus solitarii. This has also inhibitory influence on the nucleus vestibularis suggesting a possible anti-vertigo action. The metoclopramide prevents copper sulphate induced vomiting suggesting thereby that the drug also has peripheral action. Takgori et al. (1976) reported that small doses of metoclopramide prevented apomorphine induced retching and vomiting without any apparent changes in behaviour and autonomic functions. Metoclopramide markedly increases gastric motor activity in both men (Bhaduri and Bradley, 1969) and animals (Hukuhara et al., 1966; Jacoby and Brodie, 1967) and this effect probably prevents the gastric immobility which precedes the act of vomiting.

**METOCLOPRAMIDE AND OTHER ANTI-EMETIC DRUGS**

Phenothiazines are the commonly used anti-emetic drugs. Since metoclopramide is basically an anti-emetic drug, it will be worthwhile to compare this drug with other commonly used anti-emetic agents.

Metoclopramide is not superior to chlorpromazine in relieving hiccups (Korczyn, 1971) but both the drugs were not able to prevent the iodipamide induced nausea and vomiting (James and Hume, 1968). Nausea and vomiting induced by levodopa in the treatment of parkinsonism was successfully prevented by metoclopramide without any harmful effects.
on parkinsonian symptoms while chlorpromazine was not superior to metoclopramide and also aggravated the symptoms (Fischer et al., 1973; Tarssey et al., 1975).

Metoclopramide has been used in preventing nausea and vomiting in post-operative cases and it has been found slightly superior to prochlorperazine. Metoclopramide has also been found to be superior to prochlorperazine in preventing emesis due to pethidine or morphine (Lind and Breivik, 1970; McGarry, 1971). But prochlorperazine was found to be superior in radiation sickness (Ward, 1973). Singh and Lean (1970) compared the metoclopramide and prochlorperazine in cases of hyperemesis gravidarum and found better results with metoclopramide. Moreover, they also showed that side effects with metoclopramide were lesser than prochlorperazine. Metoclopramide was found to be superior to prochlorperazine in relieving vertigo but was equipotent in cases of Menier's syndrome, it was equieffective with prochlorperazine in controlling nausea and vomiting of labyrinthine origin (Marshall, 1977). Marshall (1977) showed better results with metoclopramide than prochlorperazine in flatulent dyspepsia.

In post-operative nausea and vomiting due to pethidine or morphine, metoclopramide was superior to perphenazine (Lind and Breivik, 1970).

Natalae (1975) has compared the effectiveness of
of metoclopramide and anti-cholinergic drugs—pipenzolate bromide in relieving dyspeptic symptoms. He combined both the drugs with medazepam and found that combination of medazepam and metoclopramide was superior to the combination of medazepam and pipenzolate bromide.