DISCUSSION
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Metoclopramide is a newly introduced antiemetic drug. The drug has been reported to have certain pharmacological effects which are peculiar to it and other antiemetic agents do not possess them. This drug is known to possess various central and peripheral effects and has many advantages over other clinically used antiemetic drugs. Despite a large number of studies conducted to pinpoint its mechanism of action and its position in the pharmacological (antiemetic) classification, it has yet not been possible because this drug has got many other actions on the body besides being an antiemetic.

An attempt has been made, in the present study, to investigate certain pharmacological effects with special emphasis on central nervous and cardiovascular systems. Further, since the drug may be used for prolonged periods in some patients, the effects on haematological and biochemical parameters of blood were also examined to preclude any adverse effects. This study was carried out both in experimental animals as well as in healthy human volunteers.

In the present study, the analgesic effect of metoclopramide was studied in albino rats and mice by different methods. The results show that metoclopramide per se did not possess any analgesic effect even up to 100 mg/kg (oral) dose (Tables 1-3). Volans (1975) used metoclopramide in patients of migraine and in his study the
drug per se did not exhibit any analgesic effect; however, the intramuscular injection of metoclopramide was found to potentiate the effect of salicylates in these patients. In patients of migraine, the absorption of salicylates is hampered due to impaired gastro-intestinal motility. The metoclopramide, by improving gastro-intestinal motility, promotes the absorption of salicylates and, thus, indirectly potentiates its analgesic effect. Metoclopramide definitely potentiated the analgesic effect of morphine in this investigation as judged by increase in reaction time in tail flick method in rats, it was observed that peak potentiation occurred at half an hour and persisted up to 1 hour of drug administration. The potentiation of morphine analgesia by metoclopramide was statistically significant (see Table 4 and Fig. 1). The present experimental study can be compared to some extent with the clinical study of Lind and Preivik (1970) about post-operative requirement of pethidine in patients. These authors observed that pretreatment with metoclopramide in post-operative cases lowers the requirement of pethidine to alleviate pain. Absence of any literature about mechanism of this effect requires pharmacokinetic studies for further elucidation.

Metoclopramide per se did not produce any antipyretic effect as judged on TBE vaccine induced pyrexia in rabbits (see Table 5 and Fig. 2). The clinical studies of Nimmo and Nimmo et al. (1973) show that metoclopramide per se has no antipyretic effect but accelerates the absorption of
paracetamol to some extent and thus it enhances antipyretic effect of paracetamol.

The anticonvulsant effect of metoclopramide was studied by electroshock method. The results show that metoclopramide did not produce anticonvulsant effect ($p > .05$) even up to 100mg/kg oral dose (Table 6). Though the higher doses protected slightly against the extensor phase but there was no clear cut anticonvulsant effect.

The experiments conducted to investigate the antiemetic activity of metoclopramide yielded interesting results. Metoclopramide prevented copper sulphate induced vomiting in dogs. Copper sulphate (10 mg/kg) induced retching and vomiting in 90% of dogs within 15-30 min of oral administration. Metoclopramide given half an hour before the copper sulphate significantly prevented vomiting in all the dogs ($p < 0.001$). Metoclopramide treated group did not exhibit salivation, retching and vomiting (Table 7). The data of present study is in agreement with the study of Leville (1964) but in his study, metoclopramide was administered subcutaneously. Furthermore, it has been demonstrated by Pinder et al. (1976) that metoclopramide decreases the sensitivity of peripheral visceral nerves which transmit afferent impulses from the gastrointestinal tract to the emetic centre in the lateral reticular formation. Thus, the antiemetic action of metoclopramide against copper sul-
-phate induced vomiting appears to be mainly a peripheral action and thus it differs from other conventional antiemetic drugs which act only centrally.

In this study, metoclopramide produced a dose dependent tranquillising effect in albino rats (see Table 8). The tranquillising effect was observed after half an hour of the treatment and the effect was maximal at one hour. The tranquillising potency was compared with chlorpromazine; the effect of oral metoclopramide (20 mg/kg) was almost equipotent to chlorpromazine (10 mg/kg P.O.). The results of present study show that the maximum tranquillising effect was observed with 50 mg/kg oral dose of metoclopramide (see Fig. 3). The tranquillising effect of metoclopramide observed in the present study was almost comparable with the study of Boissier et al. (1964); Marino et al. (1968) and Costall and Naylor (1973; 1974). In their study, metoclopramide produced typical neuroleptic effect in rodents, squirrel, macaque monkeys and rats. They also observed a marked dose dependent cataleptic state following administration of metoclopramide. The cataleptic state was abolished by bilateral lesions of caudate putamen, globus pallidus or nucleus accumbens.

The cardiovascular effects of metoclopramide were studied in albino rats, frogs and healthy human volunteers. In the rats, intravenous administration of metoclopramide
produced a dose-dependent hypotensive effect for a transient period. With the doses 3 mg, 4 mg and 5 mg, significant lowering of the blood pressure for a transient period was observed (Table 9 and Fig. 4). Oral administration of metoclopramide in rats produced a slight fall in blood pressure which was not significant (see Table 10 and Fig. 5). The findings of the present study are in agreement with those of Laberre (1969); Malmejac and Laville (1964) and Marmo et al. (1969) who observed in anaesthetised cat or dog that lower intravenous doses (less than 1 mg/kg) or oral doses (5 to 10 mg/kg) had no effect on blood pressure while higher doses produced transient hypotension. Kulsreshtha et al. (1980) also showed similar cardiovascular effects of metoclopramide in albino rats.

In the present study, intravenous administration of metoclopramide (3mg/kg, 4mg/kg and 5 mg/kg) produced a dose-dependent bradycrotic effect in rats. With 3mg/kg it decreased heart rate 15.4 ± 1.21 (p < .001) whereas the decrease with 4mg/kg and 5mg/kg doses was 22.60 ± 1.16 (p < .001) and 26.80 ± 1.53 (p < .001) respectively. Malmejac and Laville (1964), in their study, did not notice such effect even with the dose of 15 mg/kg (IV) of metoclopramide. The higher doses i.e. more than 15 mg/kg (IV) produced transient bradycardia with enhancement of R and T waves. In this study, an attempt has been made to explain the mechanism of action of metoclopramide. Intravenous administration of
metoclopramide did not modify the vascular effects of acetylcholine, noradrenaline, adrenaline, histamine, isoprenaline, bilateral carotid artery occlusion response and dopamine (Table 11). This study suggests that metoclopramide does not produce hypotension through peripheral vascular alpha and beta receptors blockade or central mechanism. In addition, it seems clear that metoclopramide does not possess any anticholinergic, antihistaminic or antidopaminergic effects on vascular smooth muscles. In this study, since it is well known that central effects of metoclopramide are dopamine mediated, the vasodepressive effect of metoclopramide was also thought to be due to vascular dopamine receptors blockade but dopamine showed vasopressor effects in rats which was not blocked by both haloperidol or metoclopramide. All the effects of our study were comparable with the study of Day (1975) except the effect of dopamine. Day (1975) has shown the vasodepressive response of dopamine which was blocked by metoclopramide. However, in our study dopamine produced vasopressor effect which was not blocked by both metoclopramide and haloperidol; in higher doses dopamine does stimulate alpha-adrenergic receptors (Goodman Gilman, A; Goodman, LS and Gilman, A, 1980).

The present study on cardiovascular effects in rats has also shown that the vasodepressive response of metoclopramide was not blocked by atropine, mepyramine and propranolol (see Table 12 and Fig. 6). Since the transient hypotensive effect of metoclopramide is not blocked by anticholinergic,
antihistaminics and beta-blocker, it can be assumed that the drug does not act through these vascular receptors. Therefore, it may be concluded that the effect of metoclopramide is direct either through cardiac depression or vasodilation. Further studies in frogs confirm that in all probability hypotensive effect of metoclopramide is by cardiac depression.

The study in isolated frog heart has shown that metoclopramide has depressant action on heart which was not blocked by atropine (Fig. 7). The blood vessel perfusion experiment on frogs demonstrated the vasoconstrictor effect of metoclopramide and this vasoconstricting effect was blocked by alpha blocking agent. However, atropine could not block the vasoconstricting effects of acetylcholine and metoclopramide (Table 13). This study indicates that vasoconstricting effect of both acetylcholine and metoclopramide might be alpha receptor mediated. It is to be noted that acetylcholine produces vasoconstriction in frogs (Gambhir et al., 1970). Although, metoclopramide produces vasoconstriction in isolated frog vessel, it produces vasodilatation and fall of blood pressure in intact experiments and human beings. Day (1975) and Dougan et al. (1974) have also shown the cardiac depressant action on the beating heart of the mollusc Tapes waterlingi which they assumed to be dopamine mediated.

In healthy human volunteers, metoclopramide (10 mg P.O)
produced slight but significant fall of blood pressure. Both systolic and diastolic pressure in both postures were recorded after one hour of treatment and this lowering of blood pressure continued up to 2 hours (Table 14). Our results are not in agreement with those obtained by Thorburn and Sowton (1973) as they did not notice any significant change in blood pressure or cardiac output with intravenous metoclopramide (20mg) administration in the patients undergoing routine cardiac catheterization. The discrepancy might be due to different routes of administration employed.

From the present study and existing literature, though it is difficult to suggest the exact mechanism of action of metoclopramide on cardiovascular system, it appears that the hypotensive effect is probably direct.

In isolated preparation of frog rectus abdominis muscle, the acetylcholine produced a dose-dependent response. Metoclopramide was found to potentiate this effect of acetylcholine (Fig.8). Similar findings were obtained by Eisner (1976) and Okwuasaba and Hamilton (1976). They studied the effect on gut smooth muscle and found that metoclopramide potentiated the action of acetylcholine. From the foregoing, it appears that metoclopramide sensitises the receptors to the action of acetylcholine. Although it has anti-cholinesterase activity but the cardiovascular effects of metoclopramide are not antagonised by anticholinergic agents.
The biochemical effects were studied in animals as well as in human volunteers. In rabbits, metoclopramide did not influence the blood sugar level and serum uric acid level (Table 15 and 19, Fig. 9 and 13) but significantly lowered serum cholesterol level ($p \leq 0.001$) after one hour and 2 hours of drug treatment (Table 17 and Fig. 11). But in double blind human experiments, metoclopramide did not produce any change in blood glucose and serum cholesterol levels (Table 16 and 18, Fig. 10 and 12). This study indicates that metoclopramide in therapeutic doses does not produce significant biochemical alterations.

Our results on haematological parameters showed that metoclopramide in animals as well as in healthy human volunteers did not exhibit any significant changes on Hb content, total erythrocyte count, total leucocyte count, differential leucocyte count, clotting time and platelet count even after one week of treatment (Table 20 and 21). But in rabbits, a slight but significant increase in fibrinogen content (Fig. 14) as well as in E.L.T (Fig. 15) was observed. Increase in E.L.T indicates higher anti-fibrinolytic action of a drug. Thus, metoclopramide exhibited anti-fibrinolytic action in addition to increased plasma fibrinogen level. From our study, it may be concluded that metoclopramide is devoid of any marked haematological effects in animals as well as in human beings. The data of present study is almost comparable with the study of Pinder et al. (1976); they could not observe any significant effects on haematological parameters on chronic administration of drug even upto three months.