CONCLUSION
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Metoclopramide is a newly introduced antiemetic drug. Inspite of a number of drugs currently available to treat the vomiting, not a single agent meets the requirements of an ideal antiemetic. This is particularly due to involvement of central and autonomic nervous systems in the complex act of vomiting. Introduction for general use of an ideal drug is the ultimate goal of the medical scientists. Metoclopramide was synthesized in the year 1950s and was forgotten for a long time. This drug is an ortho-chlorinated derivative of procainamide, a potent anti-arrhythmic agent. Procaine is a potent local anaesthetic but has a weak antiemetic effect but chlorinated compounds of procaine were found to be better antiemetic than local anaesthetic agent. With this aim in view Justin, Leville and Thominet, the French group of scientists, re-examined the long forgotten ortho-chloroprocainamide (metoclopramide) in 1964 for its antiemetic effect. It was found that this agent possessed a potent antiemetic effect with various other pharmacological properties not similar to commonly and popularly employed antiemetic drugs. Subsequently, this drug stimulated a large number of scientists throughout the world to further investigate the pharmacological properties, therapeutic utility and toxicity of metoclopramide. The diverse effects produced by metoclopramide and its peculiar pharmacological profile made it difficult to
put it in the conventional classification of antiemetic drugs.

In the present study, it was decided to further investigate the pharmacological properties and undesirable effects of metoclopramide in animal experiments and human volunteers. The study was conducted in albino rats, mice, rabbits and healthy human volunteers. Neuropharmacological studies included analgesic, antipyretic, anticonvulsant, tranquillising and antiemetic activities in suitable animal experimental models. Cardiovascular studies were conducted in isolated as well as in intact preparations in rats and frogs. The cardiovascular effects of drug were mainly studied in anaesthetised rats after cannulating the left common carotid artery and connecting it to a pressure transducer for recording on polygraph. Heart rate was counted by using ECG channel of polygraph. Cardiovascular effects of the drug were also studied in human volunteers with the help of sphygmomanometer and counting cardiac beats with a stethoscope; the blood pressure was recorded both in sitting and standing postures to observe any possibility of orthostatic hypotension. Most of the drugs by affecting autonomic nervous system and endocrines influence the carbohydrate, protein and fat metabolism and produce biochemical alterations in blood to varying extent. Such effects are of great clinical significance when the drug is used in diseases with metabolic disorders and also if used in
combination with other drugs likely to affect the body metabolism. In this study an attempt has been made to see the effect metoclopramide after acute administration and after treatment for a week on blood sugar, serum cholesterol and serum uric acid levels. Similarly, the drug was also evaluated for its effect on the haemopoietic system. Study of haematological profile was undertaken to see the effect of metoclopramide on various cellular counts, coagulation time, fibrinogen content and E L T both in animals and human volunteers.

In the present study, metoclopramide did not exhibit any significant analgesic, antipyretic and anti-convulsant effects in animal studies. However, metoclopramide potentiated analgesic effect of morphine. The mechanism of potentiation though not clear but it can be assumed from our study and previous studies in human beings that the mechanism is through central opiate receptors, it is pertinent to note that metoclopramide lowers the requirement of pethidine also. These findings seem to be of great clinical significance as they warrant caution in prescribing metoclopramide and narcotic analgesics together. Metoclopramide was also observed to be a good tranquilliser and antiemetic agent in animal experiments.

In anaesthetised rats, metoclopramide produced a dose dependent hypotensive effect after intravenous administration and a slight hypotension after oral administration.
The vasodepressor effect was always associated with cardiac depressant responses as judged from bradycardia. The cardiovascular effects could not be prevented by anti-cholinergic, antihistaminics and beta-blocking agents and metoclopramide could not modify the pressor responses to noradrenaline, adrenaline and bilateral carotid occlusion. It is well known that metoclopramide possesses certain degree of anticholinesterase action, though in our study cholinesterase has not been estimated, but it potentiated the action of acetylcholine on frog rectus abdominis muscle preparation. However, metoclopramide induced cardiovascular effects were direct and were not histaminergic or anti-adrenergic in nature. Furthermore, on gastrointestinal system the effect is antagonised by anticholinergics (Jacoby and Prodie, 1967; Johnson, 1971a) and may be through its anticholinesterase action. It is yet not clear why such selectivity in action on different systems was observed. The direct cardiac depressant action of metoclopramide was confirmed on frog heart preparation.

On the other hand, no significant effect on blood pressure and heart rate was observed after metoclopramide treatment in human volunteers. Although the drug produces vasodepressor and bradycrotic effects in rats. In the human beings, the drug seems to be devoid of any undesirable cardiovascular effects in therapeutic doses.

In this study, metoclopramide did not markedly
influence blood sugar level and serum uric acid level in rabbits as well as in human volunteers; it slightly but significantly reduced serum cholesterol level in rabbits without any effect in human volunteers. Similarly, metoclopramide did not produce any significant change in blood haemoglobin content, total erythrocyte count, total leucocyte count, and platelet count in both animals and human beings but a slight increase in fibrinogen content and E L T was observed in rabbits without any change in coagulation time.

This study indicates that metoclopramide is comparatively safer drug without much systemic undesirable effects on cardiovascular system, haematological system and body metabolism.