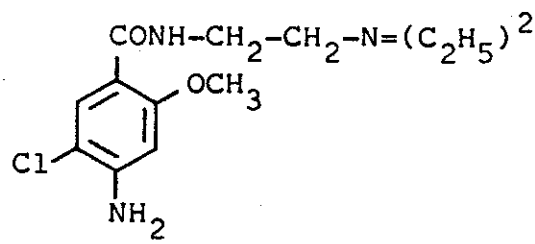
I N T R O D U C T I O N

Despite the availability of so numerous antiemetic drugs, with varying mechanisms of action, there is still an undeniable need for additional drugs with broader effectiveness and fewer untoward effects.

Metoclopramide was first discovered and evaluated as a new antiemetic drug in 1957 by Besancon and others, originating from the synthesis of procainamide, the potent local anaesthetic. The two drugs differ only in the presence of 2-5 aryl substituents in metoclopramide.

Metoclopramide "generic name" has the following formula:

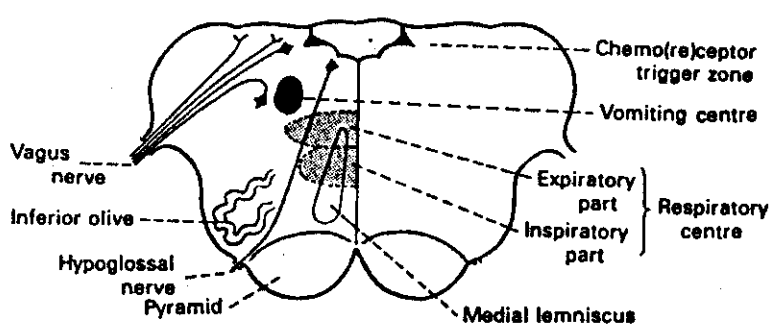


Amino-4-chloro-5-N-(diethylamino-2-ethyl)-methoxy-2-benzamide (dichlorhydrate) (Justin-Besancon and Laville, (1964 a).

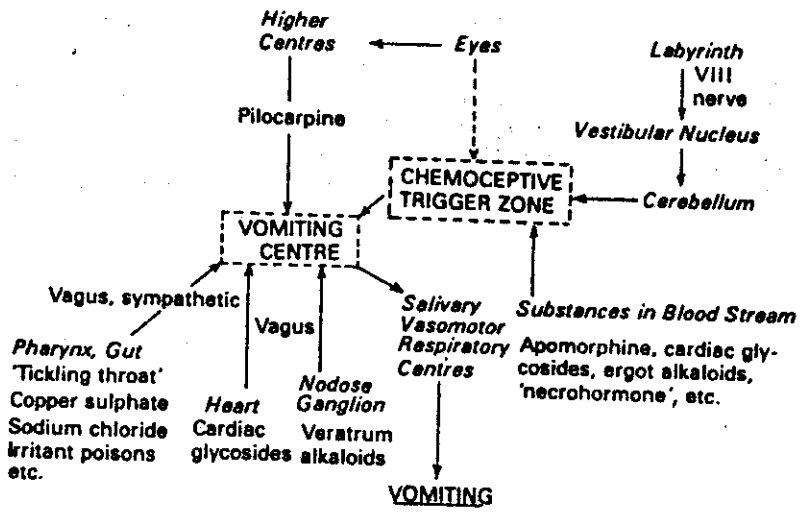
The originality of the formula of metoclopramide explains its unique pharmacological and therapeutic actions with potent antiemetic and profound effects on

the gastrointestinal tract, without any local anaesthetic effect (Pinder et al., 1976).

Metoclopramide is completely unrelated to other antiemetics as belladonna alkaloids, histamine H_1 receptor antagonists, phenothiazines, and butyrophenones. Its pharmacological actions include an inhibition of vomiting probably by a direct central effect at the level of the vomiting center as described by Justin-Besancon and Laville (1964 b) and also a peripheral effect on the gastrointestinal tract as suggested by Jacoby and Brodie (1967).



Section of the Medulla Oblongata



Schematic representation of the chief mechanisms involved in the vomiting reflex (Lewis, 1980; and Meyer's, 1980)

However, in order to study the mechanism of action of antiemetic drugs, the vomiting reflex pathway should be described. The various influences which may promote vomiting are integrated in a small area, the vomiting centre, which is located in the lateral reticular formation of the medulla.

In experimental animals, vomiting is provoked by electrical stimulation of the vomiting centre, while localized destruction of the centre prevents vomiting (Crossland, 1980).

Irritation of the mucosa of the upper gastro-intestinal tract causes vomiting. Impulses are relayed from the mucosa to the vomiting centre over visceral afferent pathways in the sympathetic nerves and vagi. Other afferents presumably reach the vomiting centre from the diencephalon and limbic system. Thus, we speak of "nauseating smells" and "sickening sights" (Ganong, 1983).

Closely associated with the vomiting centre is the chemoceptor, chemoreceptor or chemosensitive, trigger zone. The trigger zone is located in the area postrema of the fourth ventricle. The CTZ contains dopamine receptors on its cells, and since it lies outside the blood brain barrier and has a rich blood supply, it is relatively accessible to drugs. Thus drugs that exert dopamine receptor blocking activity may block these receptors at doses that may not be sufficient to reach other central dopamine receptors (Sumner, 1982), and many substances which cause vomiting after absorption or injection in the blood stream stimulate the trigger zone which then sends impulses to the vomiting centre itself (Meyers et al., 1980).

Antiemetics:

1) Belladonna alkaloids: (Atropine and Hyoscine)

The use of belladonna alkaloids for the treatment of seasickness was proposed as long ago as "1869" and their effectiveness as antiemetic agents is soundly established. Hyoscine (scopolamine), which has central depressant properties, is more effective than atropine for motion sickness in voyages of short duration. Although the belladonna alkaloids inhibit movement of the gastrointestinal tract, this action is not the major cause of their effectiveness as antiemetic drugs. Relaxation of the gastrointestinal tract may be of some benefit, since it will reduce the intensity of the afferent discharge from the mucosa, but the antiemetic effect of atropine and hyoscine is largely a consequence of their central action. In recent years, the therapeutic use of belladonna alkaloids in motion sickness has declined because of their side effects mainly vertigo, dry mouth, drowsiness, blurred vision, and altered pulse rate (Crossland, 1980).

2) The antihistaminics (H_1 antagonists):

In 1947, antihistamine drugs were appearing in large number in the treatment of motion sickness in

general. The most effective are buclizine, cyclizine, chlorcyclizine, dimenhydrinate, meclazine and promethazine. Cyclizine is the shortest acting of these compounds. Meclazine has the longest duration of actions. Antihistaminics have also a place in the therapy of Menière syndrome. It has been suggested that antihistamines owe their antiemetic activity to the sedative action commonly seen with this group of compounds. However, their antiemetic effect is out of proportion to their sedative action and some of the antihistamines, which commonly cause sedation, are of no value as antiemetics. It is possible that antihistamines and the belladonna alkaloids share a common mechanism of antiemetic action, since some of the effective antihistamines antagonize acetylcholine in vitro. However, meclizine and cyclizine, which show no antiacetylcholine activity in vitro, are as effective in this respect as are those antiemetic antihistamines that do have atropine-like actions on isolated preparations (Crossland, 1980).

3) Phenothiazine Derivatives:

Courvoiser and his colleagues (1953), who introduced chlorpromazine as the prototype of phenothiazine

derivatives, reported central antiemetic action of the drug by virtue of its action within the chemotrigger zone of the medulla. Chlorpromazine was much more effective than either hyoscine or the antihistamines in the treatment of vomiting due to drugs, pregnancy, uraemia and systemic infection. It was, however, found to be quite ineffective against motion sickness in man and dog. This was surprising, in view of the evidence that the trigger zone is concerned in the production of motion sickness. Moreover, chlorpromazine has both antiacetylcholine and antihistamine actions and these might have been expected to add to its value as a motion sickness remedy. Some of the newer phenothiazine derivatives, particularly those carrying a piperazine ring on the side chain, are more powerful antiemetics than chlorpromazine itself. They include trifluopromazine, perphenazine, prochlorperazine and triethylperazine. Their tranquillizing properties probably contribute to their antiemetic action though triethylperazine is devoid of significant tranquillizing activity.

All phenothiazines are likely to produce side effects, especially on the extrapyramidal system. They

may also cause hypotension and agranulocytosis. They have, therefore, to be used with caution and avoided in children. When vomiting occurs in pregnancy, it does so in the early months when the foetus is most vulnerable to teratogenic influences (Beckman, 1961; and Meyers et al., 1974).

The phenothiazines have been shown to block the central actions of dopamine, and this action may play a role in their ability to depress the usual response of the CTZ to stimuli (Hollister, 1982; and Sumner, 1982).

Promethazine is chemically a phenothiazine derivative, but functionally, it is an antihistamine, Like the other antihistamines, and unlike the phenothiazine derivatives mentioned previously, it does not depress the trigger zone and it is effective against motion sickness.

4) Butyrophenones:

Butyrophenones have phenothiazine-like properties, also their chemical structure shows little resemblance to phenothiazine. However, the pharmacological properties of these agents are similar to those of piperazine phenothiazine. Thus, haloperidol and droperidol

are potent and effective antiemetics and also block dopamine receptors in CTZ. They are often given with fentanyl to produce a state of neuroleptanalgesia often employed in anaesthetic practices to minimise nausea and vomiting. However, droperidol is faster than haloperidol with a shorter duration and less toxic. Haloperidol has also peripheral anticholinergic properties (Closanti, 1982; Howie and Smith, 1982).

5) Metoclopramide:

Metoclopramide is considered as one of the most interesting drugs to come our way in a long while, and its ultimate spectrum of utility is only beginning to be appreciated not only as a potent antiemetic, chiefly because it antagonises dopamine at the chemotrigger zone (Peringer et al., 1974; and Pinder et al., 1976), also partially because of a peripheral action on the gastrointestinal musculature promoting peristalsis, gastric emptying is accelerated and small intestinal motility is increased. The drug finds clinical application as an antiemetic in prevention of post operative vomiting, in treatment of radiation sickness, pregnancy vomiting and in association with cancer chemotherapy. The drug has

been also used to facilitate gastrointestinal intubation procedures, and by radiologists to hasten the passage of barium through the small intestine (Heading, 1979). Also Snape et al. (1983) found that metoclopramide could be used to treat gastroparesis due to diabetes mellitus.

The general conclusion is that the metoclopramide is useful and safe drug. However, few adverse reactions are observed when given in the usual therapeutic doses, and fortunately a mild, transient, reversible by withdrawal of metoclopramide. The most common side effects are lassitude, drowsiness and may be bowel disturbances (Robinson, 1973). Extrapyramidal side effects are rare and occur only with high doses of metoclopramide (Borenstein and Bles, 1965). Perhaps the most annoying side effect is that metoclopramide is a potent stimulant of prolactin release with galactorrhea in both sexes (Sousa, 1975).