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

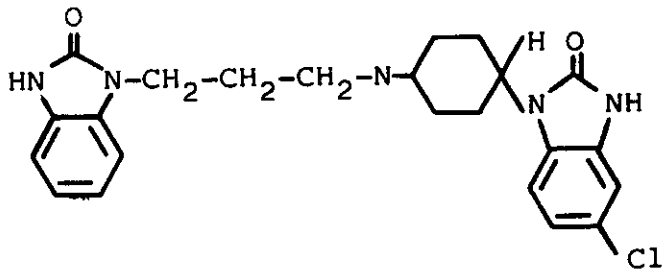
The antiemetic agents currently used are the antihistaminics (Bellville et al., 1960), neuroleptic agents like chlorpromazine and haloperidol (Ingram, 1962; Tornetta, 1972; Barton et al., 1975; Niemegeers and Janssen, 1979) and dopamine receptor blocking agents such as metoclopramide (Peringer et al., 1974).

The antiemetic effect of the antihistamines is properly mediated by the atropine like property of these drugs (Bellville et al., 1960), whereas the neuroleptics possess their antiemetic property due to blockade of dopamine receptors in the chemoreceptor trigger zone (Plotkin, 1973; Christman, 1974; Hollister, 1982; and Sumner, 1982). However, as a result of the non selectivity of the above mentioned drugs their clinical use is rather limited due to the possibility of occurrence of untoward effects. Extrapyramidal manifestation and sedation are frequently observed with the use of neuroleptic drugs (Beckman, 1961; and Meyers et al., 1974). Metoclopramide is an antiemetic drug which shared neuroleptic drugs their site and mechanism of action i.e. blockade of the dopaminergic receptors in the chemoreceptor trigger zone (Peringer et al., 1974; and Pinder

et al., 1976). In addition, metoclopramide possesses a peripheral effect on the gastrointestinal tract (Johnson, 1971). Mild side effects were recorded to occur with the use of metoclopramide. Extrapyramidal manifestations are rare and occur only with relatively high doses of the drug (Borenstien and Bles, 1965; and Robinson, 1973).

However, metoclopramide suffers from disadvantage that it is potent stimulant of prolactin release with consequent galactorrhea (Sousa, 1975).

Domperidone (Motilium) was first synthesized in Janssen research laboratories in 1974 (Niemegeers and Janssen, 1978; and Brugmans, 1981). It is a new synthetic compound which is chemically unrelated to any known antiemetic drug. Domperidone is a benzimidazole derivative with the following chemical structure: 5-chloro-1-[1-[3-(2,3-dihydro-2-oxo-1H-benzimidazole-1-yl)-propyl]-4-piperidnyl]-1,3-dihydro-2H-benzimidazol-2-one - 5-chloro-1-[3-(2-oxo-1-benzimidazol-1-yl)-propyl-4-piperidyl-2-benzimelazolinone]. It has a molecular weight of 425.9 (Reyntgens et al., 1978; and Heykants et al., 1981).



Domperidone

Pharmacological studies have shown that domperidone possessed potent antiemetic and gastrokinetic properties, most probably mediated through blockade of the peripheral dopaminergic receptors (Broekaert, 1979; and Zissis et al., 1979).

Van Neuten et al. (1978) confirmed that domperidone could antagonise the inhibition of gastric movement by sympathetic stimulus, vagal stimulus in the presence of atropine or by dopamine. It has been also reported that domperidone enhanced gastric motility in anaesthetized rabbits and dogs (Fujii et al., 1980; Katsuichi et al., 1980; Hinder and San Garde, 1983).

Furthermore, domperidone was also observed to suppress the delay of gastric emptying induced by dopamine (Katsuichi et al., 1980; and Jacobes et al., 1981) or apomorphine - a well known dopamine agonist (Broekeart, 1979; and Proctor et al., 1981). In addition, domperidone also improved gastroduodenal coordination in

isolated perfused guinea pig and rat stomach (Van Neuten et al., 1978; Katsuichi et al., 1980; Schuurkes and Van Neuten, 1982).

As an antiemetic domperidone has been shown to have antiemetic properties of similar type to metoclopramide and several neuroleptic agents (Van Neuten, and Schuurkes, 1984). However, in contrast to neuroleptic drugs e.g. haloperidol and to metoclopramide it is practically devoid of central effects i.e. it only possessed a peripheral site of action (Niemegeers et al., 1979; and Heykants et al., 1981) as domperidone did not readily cross the blood brain barrier (Brugmans, 1981). Brock-Utne et al. (1980) observed that domperidone did not affect dopaminergic receptors in either the chemoreceptor trigger zone or the basal ganglia of the brain in pregnant female patients. This view was further confirmed by the fact that chemoreceptor trigger zone in man is located beyond the blood brain barrier and consequently it is poorly responsive to domperidone (Brugmans, 1981). However, in contrast to the above mentioned view, Van Neuten and Schuurkes (1984) claimed that in human beings, only part of the C.T.Z. appeared inside the blood brain barrier, but in animals such as dogs,

the C.T.Z. was found to be outside the blood brain barrier (Katsuichi et al., 1980; Brugmans, 1981; Van Neuten and Schuurkes, 1984). This view was further confirmed by the finding that domperidone produced very slight insignificant increase in homovanillic acid (H.V.A.) in rat brain in contrast to metoclopramide which tremendously increased the H.V.A. in the brain of some species. Such finding clearly denotes that domperidone did not readily cross the blood brain barrier (Brugmans, 1981). In conformation with this view, domperidone is relatively devoid of extrapyramidal side effects such as those observed after administration of other antidopaminergic agents such as haloperidol or metoclopramide (Brugmans, 1981; and Dubios et al., 1984). Also, it did not modify the state of vigilance (Dubios et al., 1984).

Consequently domperidone offers a further progress in the treatment of nausea and vomiting (Zissis et al., 1979).

AIM OF THE WORK

The aim of the present study is to screen the pharmacological activity of domperidone and to explore the site and mode of its action on the gastrointestinal tract.

Furthermore, study of the interactions of the domperidone with autonomic neurotransmitter such as acetylcholine and dopamine on intestinal motility of the rabbit both in vivo and in vitro and on the isolated preparation of guinea pig ileum. In addition, interaction of domperidone with direct spasmogenic agents such as barium chloride and local hormones such as histamine and 5-hydroxytryptamine were also screened on the isolated rabbit's intestine, guinea pig ileum and rat fundus strip preparations respectively.