INTRODUCTION
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Peptic ulcer disease represents a major health problem. Research advances during the last few years offered new insights in the therapy and prevention of gastroduodenal ulceration, by measures directed towards strengthening of the mucosal defence mechanism along with attenuation of the aggressive acid-pepsin factors responsible for the genesis of ulcers.

The discovery of calcium channel blockers has fostered considerable research effort in basic and applied health disciplines to reexamine both the normal and abnormal calcium dependent cellular processes. Since last decade, calcium has been considered as a serious contender for the development of ulcers. The role of calcium in both the secretory and electrical parameters of the gastric oxyntic cells (acid secreting cells) has been well established (Kasbekar and Chugani, 1976; Kirkegaard et al., 1982). Calcium influx seems to play an essential role in the stimulation-secretion coupling in mammalian oxyntic cells. This response of calcium influx is well inhibited by calcium channel blockers (Soll, 1981; Kirkegaard et al., 1982; Sewing and Hannemann, 1983). Indeed, in vitro studies support the importance of transmembrane Ca\(^{2+}\) transport for gastric acid secretion (Berglindh, 1980; Soll, 1981; Kirkegaard et al., 1982) and gastrin release (Fiddian-Green et al., 1983).
Calcium channel blockers are reported to have an inhibitory effect on histamine, gastrin, carbachol and cAMP-induced stimulation of gastric acid secretion. Increased gastric acid secretion is strongly implicated in the causation of gastric ulcers by anti-inflammatory drugs (Rainsford, 1984). Clinically also the relationship between Ca$^{2+}$, gastric acid secretion and gastric ulcer formation is best represented in patients with primary hyperparathyroidism. The elevated serum calcium levels found in such patients are thought to account for the high incidence of peptic ulcer disease due to hypersecretion of gastric acid (Hellstrom, 1958). Calcium channel blockers can inhibit the contractility of gastric muscle as well as basal and stimulated gastric secretion (American College of Gastroenterology's Committee Report, 1984). However, sufficient information is not available to suggest the use of calcium channel blockers in patients with hypersecretory states. In spite of this, there are evidences suggesting a possible role of calcium in the pathogenesis of gastric ulcers.

There are a few reports on gastric anti-secretory action of verapamil (Ogle et al., 1985; Brage et al., 1985). Verapamil, an organic calcium channel blocker (Kohlhardt et al., 1972) has been shown to inhibit mast cell degranulation (Ogle et al., 1985), suppress acid secretion (Kirkegaard et al., 1982; Ogle et al., 1985) and decrease gastric motility (Ochillo and Tsai, 1982; Koo et al., 1985). The anti-ulcer property of verapamil
may, therefore, be wholly or partly due to these actions. Koo et al. (1986) reported that the anti-ulcer action of verapamil in stress ulcer model is significantly associated with the prevention of stomach wall mucus loss.

In a preliminary study of Sainath and coworkers, verapamil orally in a dose of 15 mg/kg protected rats against duodenal ulceration induced by cysteamine. In in vitro studies, it reduced histamine and pentagastrin stimulated secretions from guinea-pig duodenal mucosa (Kirkegaard et al., 1982) and isolated whole stomach of mouse (Szelenyi, 1980). However, effect of verapamil on histamine or pentagastrin stimulated acid secretion is controversial. Clinical reports are equally controversial. Verapamil has been found to reduce gastrin or pentagastrin-stimulated secretion in man (Kirkegaard et al., 1982; Sonnenberg et al., 1984). However, other workers could not find any effect of verapamil on acid secretion stimulated by histamine (Sonnenberg, 1984) or pentagastrin (Aadland and Berstad, 1983) or by bethanechol (Sonnenberg et al., 1984). Histamine is a critical component of gastric function as well as in disease states such as gastroduodenal ulcers. Koo et al. (1986) noted that verapamil inhibits gastric acid accumulation in pylorus-ligated rats but only at low doses. However, using the rat isolated perfused stomach, Canfield et al. (1985) found that verapamil did not affect gastric secretion. Wait et al. (1985) confirmed the anti-stress ulcer effect of verapamil.
and also noted that this compound decreased plasma gastrin levels in stressed rats. Glavin (1988), reported that verapamil significantly decreased basal, conscious gastric acid secretion in the chronic gastric fistula in rat and that another calcium channel antagonist nifedipine, exerts significant anti-secretory and anti-ulcer properties.

As far as the cytoprotective action of verapamil and other calcium channel blockers is concerned, the reports are found to be controversial. Koo et al. (1986b) reported that verapamil worsens the ethanol induced gastric ulcers in rats. Ghanayem et al. (1987) reported protective effect of calcium channel blockers such as verapamil and diltiazem against ethanol and indomethacin induced gastric lesions in rats. Recently Ulak et al. (1991) reported gastroprotective effect of nitrendipine on stress-induced gastric lesions in rats. There is one a clinical report on the effect of nifedipine in attenuating gastric secretion in man (Caldara et al., 1985).

In the stomach, motility and acid secretion have been shown to be dependent to some extent on Ca\(^{2+}\) and are likely to be modified by calcium channel blockers (Castell, 1985). However, at present there is no experimental evidence available to show a major effect of calcium channel blockers on gastric motility and reports about their influence on gastric acid secretion are scarce and controversial (Kirkegaard et al., 1982; Levine et al., 1983; Im et al., 1984; Sonnenberg et al.,
Brage et al. (1986) showed that pretreatment with calcium channel blockers like verapamil, diltiazem and cinnarizine delayed gastric emptying in rats. They also observed that verapamil and diltiazem inhibit gastric acid secretion in the pylorus ligated rats without affecting pepsin output. Recent studies (Ogle et al., 1985a; Koo et al., 1986a) indicate that verapamil may antagonize stress ulceration chiefly through its ability to reduce gastric smooth muscle contractions and to permit the mucus layer to remain intact. Fukuda and coworkers (1991) showed protection of gastric surface epithelial cells against ethanol injury only by phenylalkylamine calcium channel blocker e.g. verapamil. They also worked with nifedipine and diltiazem like drugs but these drugs were not found to be effective. On the contrary, nifedipine treatment aggravated the damage of gastric surface epithelial cells.

In the light of above reports, it was considered worthwhile to undertake a detailed study on the anti-ulcer activity of calcium channel blockers and elucidate their possible mechanism of action.