The treatment of ulcers has 2 aims: to remove or correct the aetiologial factors which cause ulcers and, failing that primary objective, to alter the clinical course of ulcer disease empirically with a view to relieving symptoms and preventing complications. This review examines how 2 different types of antiulcer drugs - the histamine H₂-receptor antagonists and the prostaglandin derivatives - meet these objectives.

Unfortunately, the causes of gastric and duodenal ulcers have not been defined. It seems likely that environmental factors, including infectious and chemical ulcerogens, are aetiologically important (Wormsley 1988), although none has yet been proven to be a cause of ulcers.

At present the treatment of ulcers cannot be causal, and must therefore be empirical. Three criteria have been found to correlate well with the ability of antiulcer drugs to relieve symptoms and heal ulcers: the removal of intraluminal ‘aggressive’ factors, especially gastric juice; the stimulation of ‘defensive’ factors which, it is supposed, protect the mucosa of the upper alimentary tract against ‘corrosive’ injury and maintain mucosal integrity; and the promotion of mucosal repair.

Many features of the gastric inhibitory and mucosal protective effects of the histamine H₂-receptor antagonists and prostaglandin derivatives have been defined, and since these effects seem to be therapeutically relevant both in preventing ulcer formation and in the healing of the ulcers, the subsequent sections briefly outline these aspects of the 2 types of antiulcer drug. It must be kept in mind, however, that the actions of the histamine H₂-receptor antagonists and prostaglandins on acid and alkaline secretions merely indicate that they are exerting pharmacological effects, without necessarily defining the mechanisms of the antiulcer effects of these drugs.

1. Pharmacological Effects of the Antiulcer Drugs

1.1 Effects on Gastric Secretion

1.1.1 Histamine H₂-Receptor Antagonists

The histamine H₂-receptor antagonists inhibit acid secretion by blocking histamine H₂-receptors (Black et al. 1972; Soll 1986) and therefore interfere with the processes which activate gastric parietal cells (Malinowska & Sachs 1984). The interaction with the H₂-receptors is competitive in the case of cimetidine (Black et al. 1985), ranitidine (Daly et al. 1981; Reeves & Stables 1987; Sewing & Hannemann 1986), nizatidine (Lin et al. 1986), and roxatidine (Sewing et al. 1988); either competitive (Reeves & Stables 1987) or non-competitive (Bertaccini et al. 1986; Sewing & Hannemann 1986) with famotidine; and non-competitive with the newer and more powerful H₂-receptor antagonists such as loxitidine (Brittain et al. 1985; Reeves & Stables 1987).
As a consequence of the blocking of the H₂-receptors, both stimulated and 'spontaneous' (basal and nocturnal) gastric secretion are inhibited to a variable extent (Jones et al. 1987; Pounder 1984), ranging from approximately 60% with cimetidine, rather more with ranitidine and famotidine, to almost complete inhibition with the more powerful inhibitors like loxidine (Boyd & Wormsley 1984; Brogden et al. 1978; Campoli-Richards & Clissold 1986; Daly & Price 1983; Price & Brogden 1988; Scholtholt et al. 1988).

The H₂-receptor antagonists also inhibit the secretion of pepsin (Pounder 1984), although the mechanisms have not been defined.

1.1.2 Prostaglandins

Prostaglandins of the E, I and A series inhibit the gastric secretion of acid (Cohen 1987a,b) and pepsin (Cohen 1987b). The mechanisms of the effects of prostaglandins on acid secretion are apparently different from the effects of the H₂-receptor antagonists, being exerted intracellularly via an interference with the histamine-induced activation of adenylate cyclase (Soll 1986, 1987). Whatever the mechanisms of gastric secretory inhibition, the prostaglandin derivatives are relatively weak inhibitors, even when given in reasonably large doses.

It has been suggested that some of the inhibition of acid secretion by prostaglandins might be 'spurious' and result from a topically damaging effect of the drugs on the gastric mucosa, resulting in an increased permeability of the mucosa to intraluminal hydrogen ions (Bolton & Cohen 1979; O'Brien & Carter 1975). While the matter has not been studied extensively, it seems that at least some of the prostaglandins in current therapeutic use do not adversely influence gastric mucosal permeability (Penston et al. 1986a,b).

1.2 Effects on 'Mucosal Protective Factors'

1.2.1 Secretion of Bicarbonate

Prostaglandins have been shown to increase the secretion of bicarbonate by the gastric (Cohen 1987a,b; Flemstrom 1986; Miller 1983) and duodenal (Isenberg et al. 1986; Flemstrom 1986; Miller 1983) mucosa in a dose-dependent manner.

While there is still some controversy, it seems that H₂-receptor antagonists do not stimulate mucosal secretion of bicarbonate (Guslandi 1985).

1.2.2 Synthesis and Secretion of Mucus

Prostaglandins have been shown to increase the synthesis and secretion of mucus by the gastric and duodenal mucosa (Jentjens et al. 1984; Lee et al. 1987; Miller 1983; Svendsen et al. 1987; Waterbury et al. 1986). Similarly, cimetidine stimulates synthesis of gastric mucus (Kakei et al. 1986).

1.2.3 Mucosal Blood Flow

Gastric mucosal blood flow is involved in maintaining the integrity of the gastric and duodenal mucosa and in the healing of ulcers. It may therefore be relevant that exogenous prostaglandins usually increase gastric mucosal blood flow in animals (Miller 1983). On the other hand, some prostaglandin derivatives reduce gastric mucosal blood flow but nevertheless retain the capacity to 'protect' the gastric mucosa against injury (Leung et al. 1985). It seems that the beneficial effects of the prostaglandin derivatives are exerted principally on the microcirculation of the gastric mucosa (Gaskill et al. 1984; Guth et al. 1984; O'Brien et al. 1986). Cimetidine, however, does not appear to influence gastric blood flow (Delaney et al. 1978).

It is necessary to emphasise that the relevance to ulcerogenesis and ulcer healing of the effects of prostaglandins on the secretion of bicarbonate and mucus and on the regulation of the gastric microcirculation has not been established.

1.3 Effects on Mucosal Repair

1.3.1 Cellular Kinetics

It has been proposed that prostaglandins preserve the cells of the mucosal proliferative zone which are important in the recovery from mucosal injury (Lacy 1985; Morris 1986). In addition, some prostaglandins exert a growth-promoting effect on the gastric mucosa (Arakawa et al. 1987; Halter et al. 1984).