Enhancing mucosal defence and repair mechanisms

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INTRODUCTION

Inhibition of gastric acid secretion has proved to be an extremely effective pharmacological approach in the management of human peptic ulcer disease. This is reflected by the success of cimetidine and ranitidine, which have become the world’s two top selling drugs, and by the plethora of other antisecretory agents which have entered clinical trials over recent years. Efficacy of antisecretory therapy largely reflects retardation of wound healing by the acidic environment which prevails in the upper gastrointestinal tract. Hyperacidity does not, however, provide an aetiologic basis for the disease since gastric and most duodenal ulcer patients secrete normal or less than normal amounts of acid. Two possible causes of ulceration are failure of mechanisms which normally enable gastroduodenal mucosa to resist intraluminal acid and pepsin, or failure of mechanisms which normally enable the epithelium to rapidly repair superficial damage. Potentially, therefore, drugs which seek to enhance either mucosal protection or repair represent attractive alternatives to inhibiting acid secretion, particularly in view of concerns over the consequences of long-term therapy with antisecretory drugs. Thus, a number of potent, long-acting inhibitors of acid secretion have induced tumours in the stomachs of laboratory animals during toxicological evaluation, while diseases associated with hypochlorhydria such as pernicious anaemia, or surgery aimed at reducing intraluminal acidity increase susceptibility to gastric cancer.

The ability of gastric and duodenal mucosa to resist autodigestion has been
a source of intrigue for more than two centuries but, despite intensification of basic research effort, the underlying mechanisms are not fully understood\(^4,5\). Lack of a unifying hypothesis of mucosal protection has hampered the search for drugs which act by mechanisms other than inhibiting acid secretion and the majority of protective drugs in current use were developed with little knowledge of their mode of action. Prostaglandins represent the most recent attempt to introduce a new class of antiulcer drug which combine antisecretory and protective actions. However, these agents have proved somewhat disappointing clinically and it would appear that efficacy can be explained solely on the basis of antisecretory activity\(^6\). In comparison with the study of acid secretion and even mucosal protection, mechanisms of healing of gastric and duodenal mucosal lesions have received much less attention. Recent descriptions of rapid re-epithelialization of the stomach following superficial injury have served to focus attention on one aspect of mucosal repair (see Chapter 8). While this process is clearly distinct from the repair of a chronic ulcer, it is possible that ulcers develop as a result of failure of superficial repair mechanisms.

The aims of this chapter are broadly two-fold: firstly, to review the actions of current protective drugs since it is only by understanding their activity that rational improvements in design can be contemplated and secondly, to describe proposed mechanisms of protection and repair in order that an appreciation can be gained of the prospects of developing novel antiulcer drugs.

**PROTECTIVE DRUGS**

These agents may be considered to act by enhancing protective mechanisms owing to a specific pharmacological action or by reducing the autolytic activity of luminal contents due to adsorption of HCl, proteolytic enzymes and bile acids within the lumen or at the mucosal surface. Adherence of insoluble particles to the mucosa may also induce liberation of biologically-active transmitters as a result of a counter-irritant response. Indeed, stimulation of mucosal prostaglandin production has been claimed for all of the agents in this category but whether this is anything more than an epiphenomenon has not been established.

**Carbenoxolone**

This compound is a synthetic derivative of glycyrrhizic acid, a constituent of liquorice, sold in the U.K. as Biogastrone\(^\text{R}\) and Duogastrone\(^\text{R}\) (Winthrop). Carbenoxolone was the first antiulcer drug to be actively promoted on the basis of absent antisecretory activity and demonstrated that peptic ulcers could be healed by mechanisms other than reducing luminal acidity. Actions of