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THE EFFECTS OF CARBENOXOLONE AND CIMETIDINE ON MUCUS OUTPUT IN THE RAT ILEUM

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Gastric mucus is secreted from both glands and goblet cells, whereas, mucus from the remainder of the gastrointestinal tract (GIT) is a product of goblet cells only. Anti-ulcer drugs such as carbenoxolone and H_2 receptor antagonists have previously been associated with the stimulation of gastric mucus production (Green et al 1981; Kakei et al 1986). It is unknown, however, whether these agents are capable of altering the secretory response elsewhere in the GIT.

Using a chronically isolated intestinal loop in the rat (Poelma & Tukker 1987), the production of mucus was investigated by perfusing ileal loops in four rats over a period of 24 hours. Perfusions were carried out using isotonic saline at a flow rate of 40 ml hr^{-1}. Furthermore, the mucus output was investigated in response to intraluminal perfusion of cimetidine (0.8 mg ml^{-1}) or carbenoxolone (0.5 mg ml^{-1}&1.0 mg ml^{-1}) in phosphate buffered saline.The loop was initially perfused for two hours with isotonic saline, to obtain a baseline, before the drug solutions were introduced and perfused at the same flow rate over a period of one hour. The loops were subsequently perfused for a further two hours with saline only. The perfusates were analysed for mucin content using a direct fluorimetric assay (Crowther and Westmore 1987). Results were tested for significance using a Mann Whitney U-test.

FIGURE 1.

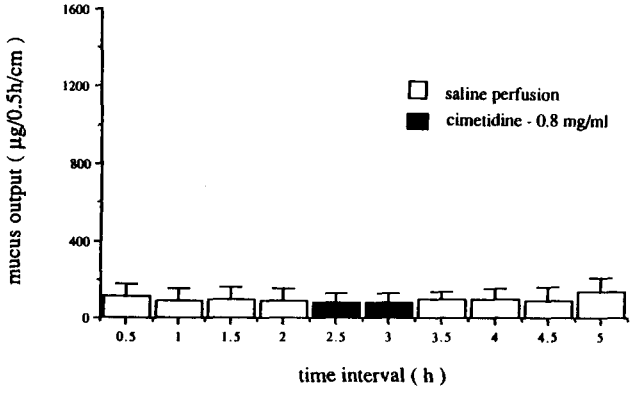

Figure 1: The effect of cimetidine on mucus output. (n=4) Mean± SD.

FIGURE 2.

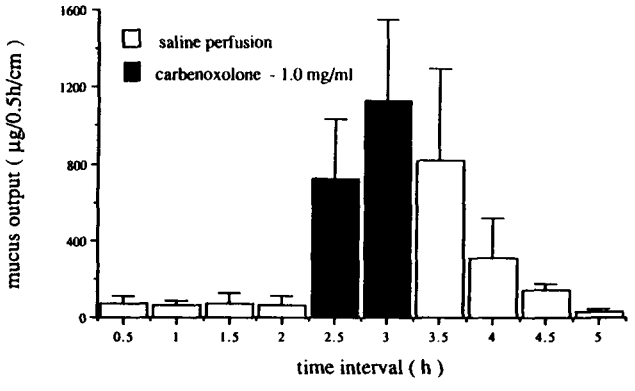

Figure 2: The effect of carbenoxolone on mucus output. (n=4) Mean± SD.

The mean 'total',ie solubilised and sloughed, mucus output during the 24 hour control period was calculated as 2.00 µg min^{-1}per cm of isolated ileum. Intraluminal perfusion of cimetidine in concentrations up to 0.8 mg ml^{-1} produced no significant change in the baseline level of mucus output. Carbenoxolone, however, elicited a dose-dependent increase in mucus output. Perfusion of 0.5 mg ml^{-1} carbenoxolone solution produced an increase in mucus output up to a maximum of 634% compared to baseline. Doubling the concentration increased mucus output to a maximum of 1531% of baseline level.

The proposed mechanism of action of carbenoxolone in the treatment of duodenal and gastric ulcer is to increase the output of protective mucus. It is apparent from these studies that this local action is also present in the ileum. Cimetidine, however, although shown to stimulate gastric mucus glycoprotein synthesis (Kakei et al 1986), appears to offer no assistance in mucosal protection by a local action in the isolated ileum. These observations illustrate the applicability of this system in elucidating the mode of action of drugs active on the gastrointestinal mucosa. Furthermore, the model may provide a useful means for predicting the fate of drugs in mucoadhesive dosage forms in the GIT.

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Kakei,M. et al (1986) Digestion 34: 122-126
Poelma,F.G.J., Tukker,J.J. (1987) J. Pharm. Sci. 76: 433-436
Crowther,R.S., Westmore,R.F. (1987) Anal. Biochem. 163: 170-174