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A STUDY OF THE INHIBITORY EFFECTS OF SCH 28080 ON GASTRIC SECRETION IN MAN

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1 SCH 28080 (2-methyl-8-(phenyl methoxy) imidazo-(1-2-a) pyrine-3-acetonitrile) is a novel drug unrelated to existing anti-ulcer agents.

2 The effect of placebo and increasing doses of the drug on gastric acid output and peptic activity was examined in four healthy men, in the resting state and following pentagastrin stimulation.

3 Significant inhibition of gastric acid secretion and peptic activity occurred with the 50 mg dose in both the stimulated and unstimulated states. Approximately 90% inhibition of acid output was achieved with the 200 mg dose.

4 Antisecretory activity of SCH 28080 is confirmed in man. This drug or an analogue may have potential in anti-ulcer therapy.

Introduction

Ulcer healing drugs may either inhibit gastric acid output or may protect the gastric mucosa against noxious agents (cytoprotection). Cimetidine is predominantly an inhibitor of gastric secretion (Bodemar & Walan, 1977), whereas carbenoxolone improves the gastric mucosal barrier by stimulating mucus production (Johnston, Lindup, Shillingford, Smith & Parke, 1974). Prostaglandin analogues have both cytoprotective and anti-secretory actions but toxic effects have so far limited their development for use in man (Robert, 1976). SCH 28080 (2-methyl-8-(phenyl methoxy) imidazo-(1-2-a) pyrine-3-acetonitrile; see Figure 1) is a novel chemical compound which has been shown in dogs to be effective in inhibiting histamine-stimulated gastric secretion, and in rats to be four to ten times more potent than cimetidine in this respect. Gastric lesions induced in rats by aspirin, indomethacin and ethanol were prevented by pretreatment with SCH 28080. It has no histamine H_2-receptor blocking activity or anticholinergic properties and is chemically unrelated to prostaglandins (Long, Steinberg & Derelanko, 1981). The antisecretory and cytoprotective effects of SCH 28080 make it a drug of interest for study in man with a view to development as an anti-ulcer agent.

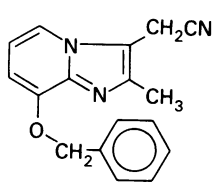

Figure 1 Structural formula of SCH 28080 (2-methyl-8-(phenyl methoxy) imidazo-(1-2-a) pyrine-3-acetonitrile).

Methods

Four healthy male volunteers aged 19 to 27 years participated in a two stage open, non-randomized study which was approved by the Ethics Committee of the Bristol Royal Infirmary. In each stage of the study there were four study days separated by at least one week. Stage 1 of the study examined the effects of placebo and 50 mg, 100 and 200 mg doses of SCH 28080 on unstimulated gastric secretion. Stage 2 examined the effects of placebo and the same doses of SCH 28080 on pentagastrin-stimulated gastric secretion.

Each study day in Stage 1 was preceded by a 12 h overnight fast. An orogastric tube and continuous suction by a low pressure pump were used to collect gastric secretions, and 15 min samples of basal secretions were collected for 1 h. The treatment appropriate for the study day was then given via the tube as a 50 ml suspension. Aspiration of gastric secretions was resumed 55 min after dosing. The first sample of gastric aspirate after dosing was collected over 5 min. A further eight consecutive 15 min samples were collected during the second and third hours after dosing.

The study days in stage 2 were similar except for a subcutaneous injection of pentagastrin (6μg/kg body

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wt.) given 1 h after dosing with placebo or SCH 28080.

The volume, pH, titratable acidity and peptic activity of each sample of gastric aspirate were measured. Titratable acidity was measured by titration to pH 7.0 with NaOH using an automatic titrator. Pepsin was assayed by use of a modified haemoglobin substrate (Berstad, 1970).

Heart rate and blood pressure were monitored at half-hourly intervals up to 3 h post-dose, when the orogastric tube was removed. Haemoglobin, white cell and platelet counts and determinations of plasma viscosity, urea, sodium, potassium and bicarbonate, serum alkaline phosphatase, creatinine, transaminases, total protein and albumin, and urine microscopy were performed on each subject before the study, and 5 days after each study day.

Dose-response relationships were constructed for volume, acid output and peptic activity by summating the values for the 15 min samples in the second and third hours after dosing.

Differences between doses were examined by a two-way analysis of variance. Statistical significance was taken at $P < 0.05$.

Results

All three doses of SCH 28080 caused significant reductions in the volume, acid output and peptic activity of gastric secretions in the unstimulated state (stage 1) (Figure 2). Gastric acid concentration was markedly reduced and pH increased by the drug (see Table 1). The maximum effect dose appeared to be between 50 and 100 mg in all four parameters.

In stage 2, pentagastrin-stimulated acid output and volume of gastric secretion were suppressed in a dose-related manner by SCH 28080 (Figure 2). The plateau of the dose-response curve was not reached within the dose-range studied. However, an 86% inhibition in mean acid output occurred after the 200 mg dose. At this dosage, pH of gastric secretions was nearly neutral (pH 6.07). The pentagastrin-stimulated rise in pepsin output was suppressed only by the 200 mg dose.

None of the subjects experienced side effects. No haematological or biochemical abnormalities occurred and there were no significant changes in heart rate and blood pressure.

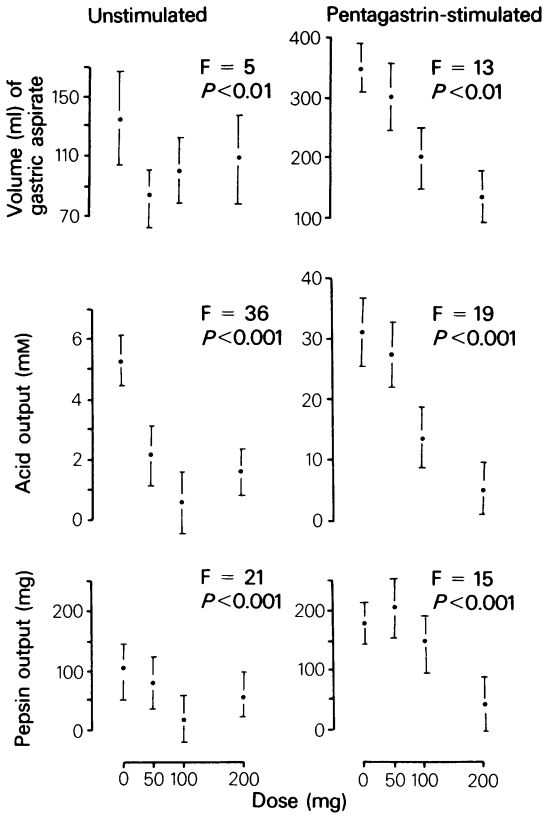

Figure 2 Volume of gastric secretion, acid output and peptic activity during the 2nd and 3rd hours following intragastric administration of SCH 28080 to four normal individuals Mean values are shown; vertical lines indicate s.e.mean.

Discussion

We have shown that SCH 28080 is a potent inhibitor of unstimulated and pentagastrin-stimulated gastric secretion in man. The dose-response relationships in both stages of the study were similar for volume of gastric secretion, acid output, peptic activity and pH. However, the maximally-effective dose appeared to be different in the two stages of the study. In the unstimulated state, 100 mg produced a maximal response of about 90% inhibition of acid output,

Table 1 Mean pH (± s.e.mean) of gastric aspirate in four healthy male subjects following intragastric administration of SCH 28080 unstimulated and following subcutaneous pentagastrin

Dose of SCH 28080	*0 mg*	*50 mg*	*100 mg*	*200 mg*	P *value*
Unstimulated	1.75 ± 0.12	2.97 ± 0.96	6.18 ± 1.05	4.77 ± 1.48	< 0.05
Pentagastrin stimulated	1.43 ± 0.22	1.21 ± 0.06	3.07 ± 1.29	6.07 ± 1.47	< 0.05

whereas in the stimulated state maximal suppression of pentagastrin effect was not achieved. However, after the 200 mg dose 86% inhibition of pentagastrin effect was seen; thus, increasing the dose above 200 mg would be unlikely to achieve a further clinically significant effect. We, therefore, concluded that 200 mg was a suitable dose for future clinical studies.

Currently there are two lines of drug therapy for peptic ulcer disease; drugs that protect the mucosa (e.g. carbenoxolone and bismuth chelate) and those that prevent the secretion of acid and pepsinogen. In the latter category are the anticholinoceptor drugs and the H_2-receptor antagonists. The antisecretory activity of SCH 28080 shown in this study differs from that of the anticholinoceptors in that SCH 28080 supresses acid and pepsin output and increases the pH, while the anticholinoceptor drugs reduce volume of secretion only, with the acid concentration remaining unchanged, or even rising (Weiner, 1980). Furthermore, there is no evidence of an anticholinoceptor effect of SCH 28080 either in animal or man outside the gastrointestinal tract. The degree of suppression of acid and pepsin obtained with SCH 28080 in both resting and stimulated phases was comparable to that produced by cimetidine and ranitidine in other published studies (Halparin & Ruedy, 1980; Sheer & Roberts, 1981). In addition to this potent antisecretory activity, work in animals suggests that SCH 28080 also has mucosal protective activity. If cytoprotection is eventually confirmed in man for this drug or an analogue, a unique pharmacological agent for potential use in peptic ulcer disease would have been developed.

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