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PROPERTIES OF THE REVERSIBLE, K^+-COMPETITIVE INHIBITOR OF THE GASTRIC (H^+/K^+)-ATPase, SK&F 97574. II. PHARMACOLOGICAL PROPERTIES

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Abstract—SK&F 97574 [3-Butryl-4-(2-methylamino)-8-(2-hydroxyethoxy) quinoline] is a potent, reversible inhibitor of the gastric (H^+/K^+)-ATPase. In an anaesthetised lumen-perfused rat preparation, it inhibited pentagastrin-stimulated gastric acid secretion with intravenous and intraduodenal inhibitory ED_{50} values of 2.40 μmol/kg and 4.43 μmol/kg, respectively. In the conscious fistula rat model, doses of 10 μmol/kg IV and 25 μmol/kg PO produced mean peak inhibitions of basal acid output of 91% and 97%, respectively. In these experiments, the duration of action of SK&F 97574 was much shorter than that of the covalent (H^+/K^+)-ATPase inhibitor, omeprazole. In the conscious Heidenhain pouch dog, SK&F 97574 inhibited histamine-stimulated gastric acid secretion after both intravenous and oral administration with ED_{50} values of 0.49 μmol/kg and 0.89 μmol/kg, respectively. In this model, duration of action studies showed that significant residual inhibition of acid secretion remained 8 hours after intravenous dosing with SK&F 97574 (producing peak inhibition of 92%). However, 24 hours after oral dosing of SK&F 97574 (10 μmol/kg), no significant inhibition remained. These data indicate that the duration of action of SK&F 97574 is longer than that of the histamine H_2 receptor antagonists such as cimetidine, but shorter than that of covalent (H^+/K^+)-inhibitors such as omeprazole. Overall, the pharmacological properties of SK&F 97574 suggest that it could be a potentially useful clinical treatment for acid-related diseases.

Key words: gastric (H^+/K^+)-ATPase; anti-secretory; inhibitor; mechanism; pharmacology

The development of inhibitors of the gastric (H^+/K^+)-ATPase, the ion pump responsible for acid secretion within the stomach, has led to improvements in the treatment of acid-related diseases through better control of acid secretion than can be obtained with H_2-receptor antagonists (e.g. cimetidine, ranitidine). The only class of (H^+/K^+)-ATPase inhibitor presently used clinically is substituted benzimadazoles, such as omeprazole and lanzoprazole. These compounds are acid-activated prodrugs that covalently inactivate the (H^+/K^+)-ATPase. Consequently, they are very powerful inhibitors of acid secretion that are rather slow in onset and give very long-lasting inhibition (because acid secretion only returns when new ion pumps are synthesised, [1]). Reversible inhibitors of the gastric (H^+/K^+)-ATPase may therefore have some advantages over the substituted benzimadazoles, because their duration of action should be determined solely by their pharmacokinetic properties.

A preceding paper [2] describes the *in vitro* properties of SK&F 97574,‡ which is a potent, reversible inhibitor of the gastric (H^+/K^+)-ATPase. Moreover, the physicochemical properties of SK&F 97574 (it is a lipophillic weak base) suggest that it may be targeted to its site of action *in vivo*, the outside face of the acid-secreting parietal cell. In this paper, we describe the activity of SK&F 97574 in a number of pharmacological models of both basal and scretagogue-stimulated acid secretion. Where appropriate, a comparison of the pharmacological profile of SK&F 97574 has been made with that of the substituted benzimadazole (H^+/K^+)-ATPase inhibitor, omeprazole, and a previously described reversible inhibitor of the gastric proton pump, SK&F 96067 [3, 4]. The results show that SK&F 97574 is a potent inhibitor of acid secretion *in vivo*, with a duration of action significantly longer than H_2-receptor and antagonists and SK&F 96067, but shorter than omeprazole.

MATERIALS AND METHODS

Anaesthetised rat IV studies

A modification of the perfused rat stomach method of Ghosh and Schild [5] was used to study the effect of intravenously administered SK&F 97574. Fasted female Wistar rats (ca 200 g) were anaesthetised with urethane (1 g/kg i.p.) and treated with atropine sulphate (1 mg/kg i.m.). The vagus nerves were sectioned and the stomach perfused via cannulae placed in the oesophagus and pyloric antrum. The perfusate was collected by a funnel placed in the non-secretory rumen. The pyloric cannula had a solid piece of acrylic (perspex) at one end designed to fill dead space in the stomach cavity. Perfusion was carried out with 5.4% w/v glucose, preheated to 37°C, at a rate of 3 mL/min driven by a roller pump. The body temperature of the rat was also maintained at 37°C by a rectal thermistor controlling an overhead heating lamp.

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‡ Abbreviations: DMSO, dimethyl sulfoxide; SK&F 97574, 3-Butryl-4-(2-methylamino)-8-(2-hydroxyethoxy) quinoline; SK&F 96067, 3-Butryl-4-(2-methylamino)-8-methoxyquinoline; and SEM, standard error of the mean.

The perfusate was passed through a microflow pH glass electrode system and the pH of the perfusate converted to a function of hydrogen ion activity by an antilog function generator and recorded continuously on a potentiometric chart recorder. Both jugular veins were cannulated for drug administration. Pentagastrin (2 μg/kg/min) was infused throughout the experiment and produced, in most preparations, a stable plateau of near maximal (ca 70%) gastric acid secretion for 1–2 hours. When the response had reached the plateau, SK&F 97574 was administered by rapid intravenous injection. Percentage inhibition was obtained by comparing the secretory response immediately prior to the injection of SK&F 97574 with the secretory response at maximal inhibition. Basal secretion, which had been reduced to a minimum by the atropine and vagotomy, was subtracted in both cases.

Anaesthetised rat ID studies

For the studies using intraduodenal administration of SK&F 97574, the original Ghosh and Schild [6] method was employed. Some additional IV studies were also performed using this preparation. Fasted female Sprague-Dawley rats (ca 200 g) were anaesthetised with urethane (1.5 g/kg i.m.). The left femoral vein was cannulated for pentagastrin infusion and the duodenum for drug administration. An oesophageal cannula was inserted transorally and a pyloric cannula inserted through the duodenum. The stomach was continuously perfused with warm (37°C) 0.9% saline at a rate of 0.5 mL/min. The effluent perfusate was collected at 15 minute intervals, the pH value determined, and acid output was determined by titration with 0.01 M NaOH to pH 7.0. Body temperature was maintained at 37°C by a rectal temperature probe connected to an overhead heating lamp and an electric cushion.

Gastric acid secretion was stimulated by an intravenous infusion of pentagastrin (1 μg/kg/min) after two basal values had been determined. SK&F 97574 was administered intraduodenally 60 minutes after the commencement of the pentagastrin infusion. Percent inhibition was calculated from a comparison of acid output at peak inhibition with the pre-treatment acid output.

Chronic fistula rat studies

Female Wistar rats (180–250 g) were implanted with titanium gastric cannulae. Surgery was carried out under halothane anaesthesia, in which one end of the cannula was inserted and tied into the lumenal part of the stomach, the other being exteriorised through a stab wound in the abdominal wall. The lumen of the cannula was plugged to permit normal feeding. Animals were allowed a two-week recovery period post operatively, and were then checked for the stability of their basal acid secretion.

Secretory studies were carried out after fasting for 22–24 hours. At the start of the study the cannula plug was removed and any residual stomach contents flushed out with warm saline. A collecting tube was then inserted into the lumen of the cannula and basal acid secretion collected in small vials for between six to eight 45-minute collection periods. The pH of juice was noted. Then the volume of gastric juice was measured and a 0.2 mL (or 0.1 mL if the volume was small) sample was titrated to pH 7.4 to calculate the acid concentration. Rats showing low or very erratic control of basal gastric acid secretion were rejected from this study.

On drug study days, two 45-minute control basal samples were taken. For the intravenous studies, the compound was administered via a fine polythene cannula inserted into the tail vein. For oral administration, the lumen of the gastric cannula was plugged and the drug administered via an oral dosing needle. One hour was allowed for drug absorption, and the 45-minute sample collection recommenced for a further 4 hours. Data were expressed as either pH or mean acid output per 45 minutes in μEq HCl. Peak percentage inhibition was calculated relative to the acid output in the period immediately prior to drug administration.

Conscious Heidenhain pouch dog studies

The intravenous and oral studies were carried out on male Beagle dogs weighing between 12 and 20 kg. The dogs had been prepared with Heidenhain pouches 1–6 years beforehand. The dogs, who had been trained to stand in Pavlov slings, were investigated in groups of three, and at least one week elapsed between tests on one dog. Before each experiment, the dogs were given no food, but allowed water ad libitum, for 18–24 hours. The dogs were put into slings and allowed to settle for one hour. During this time a cannula was inserted into a leg vein, saline infused at a rate of 30 mL/hr, and a basal pouch secretion collected. The inter-digestive secretion in Heidenhain pouch dogs is either absent or present in very small amounts. After the control period, a continuous intravenous infusion of histamine was started at a rate of 150 μg/kg/hr. This dose caused a sub-maximal secretion of gastric acid, the response reaching a plateau after about 1.5 to 2 hours, and was maintained for up to 5 hours. The saline infusion was continued at 30 mL/hr to compensate for loss of fluid in the gastric juice. The gastric juice was collected at 15-minute intervals and titrated with 0.1 M NaOH solution to both pH 3.5 and 7.4. The rate of secretion (total acid output) was expressed as the product of the volume and total acid concentration. After infusion of histamine for 1.5–2 hours, when acid secretion had reached a plateau, SK&F 97574 was administered.

In the intravenous studies, SK&F 97574 was given via a three-way tap into the histamine infusion in a volume of 3.0 mL/18 kg body weight and a rate of 1.0 mL/minute. For the oral dosing studies, the compound was loose-filled into hard gelatin capsules and given by mouth. Acid secretion was measured for up to 5 hours after drug administration, and the percentage inhibition was calculated with reference to the secretory response immediately before dosing.

In studies addressing the question of duration of action, two different experimental designs were used. In an eight-hour study, a plateau secretion to histamine was established and then SK&F 97574 was infused for one hour and secretory inhibition monitored. The dogs were then returned to their home pens, but not fed. Eight hours later, the histamine infusion was repeated and the secretory plateau compared with that obtained in control studies (repeated infusions of histamine in the absence of compound).

In a 24-hour study, on day 1 a plateau secretion to histamine was established, the compound given orally, and the inhibitory effect followed for three hours. The dogs were then returned to the animal unit, food was

given and then removed. On day 2 of the experiment, gastric acid secretion was again stimulated with histamine and a plateau secretion established. This plateau rate of secretion was compared to that obtained on day 1 to estimate the degree of any residual inhibition remaining.

Chemicals

SK&F 97574, SK&F 96067, and omeprazole were synthesised in-house. For oral administration, the compounds were loose filled into hard gelatin capsules. SK&F 97574 was dissolved in 1 M HCl and made up to volume with saline for intravenous administration. Pentagastrin was given as Peptavlon® (ICI Pharmaceuticals) or Gastrodiagnost® (Merck, FRG). Histamine acid phosphate (BDH Chemicals, Poole, Dorset, U.K.) was dissolved in saline. Omeprazole was dissolved in a mixture of polyethlene glycol and $NaHCO_3$. All other chemicals were obtained from Sigma or Aldrich, and were of the highest grade available.

RESULTS

Effects in the anaesthetised stomach lumen perfused rat

SK&F 97574 given by rapid intravenous injection in the dose range 0.5 to 30.0 μmol/kg produced a dose-related inhibition of pentagastrin-stimulated gastric acid secretion. The mean peak level of inhibition at each dose was 0.5 μmol/kg = 28%, 1.0 μmol/kg = 48%, 3.0 μmol/kg = 52%, 10.0 μmol/kg = 68%, 30 μmol/kg = 75%. From these data, an ED_{50} (the dose to produce 50% inhibition of near-maximal acid secretion) was calculated to be 2.4 μmol/kg with 95% confidence limits of 1.3–4.3 μmol/kg ($n = 20$). Using the original Ghosh and Schild technique [6], an intravenous inhibitor ED_{50} of 2.1 μmol/kg was obtained (95% confidence limits 1.7–2.7 μmol/kg IV ($n = 28$) against pentagastrin-stimulated acid secretion.

The effect of intra-duodenal dosing of SK&F 97574 was investigated using the original Ghosh and Schild technique [6]. In the dose range 1.0 to 30.0 μmol/kg, SK&F 97574 produced a dose-related inhibition of pentagastrin-stimulated gastric acid secretion (Fig. 1). The mean peak level of inhibition at each dose was 1.0 μmol/kg = 27%, 3.0 μmol/kg = 39%, 10.0 μmol/kg = 63%, 30.0 μmol/kg = 87%. From these data, an inhibitory ED_{50} of 4.4 μmol/kg was calculated with 95% confidence limits of 3.2–6.2 μmol/kg ($n = 28$). The onset of the inhibitory effect of SK&F 97574 was rapid after intraduodenal administration, with significant inhibition observed within the first 15 minutes after dosing. Peak inhibition was obtained after 30–45 minutes. At doses of 10–30 μmol/kg, there was little recovery from peak inhibition in the three and a half hours after administration of the dose (Fig. 1).

Effects in the chronic fistula rat

In this model, SK&F 97574 inhibited basal acid secretion after administration by both intravenous and oral routes. A dose of 10 μmol/kg IV reduced acid output at peak by an average of 91 ± 8. % (mean ± SEM; $n = 12$) and elevated the mean pH of the gastric juice from 2.3 ± 0.3 to 4.3 ± 0.5 (means ± SEM; $n = 12$). Marked inhibition of acid secretion was obtained in the first 45-minute sample. Acid concentration was reduced to a greater extent than the volume of juice secreted (Table 1). Gastric secretion returned to control levels around 4 hours after administration of SK&F 97574. In a parallel study, omeprazole at the same dose (10 μmol/kg IV) caused a similar peak inhibition of mean acid output (97 ± 3%; $n = 12$), but had a longer duration of action, still exerting its maximum antisecretory effect after four hours (Fig. 2).

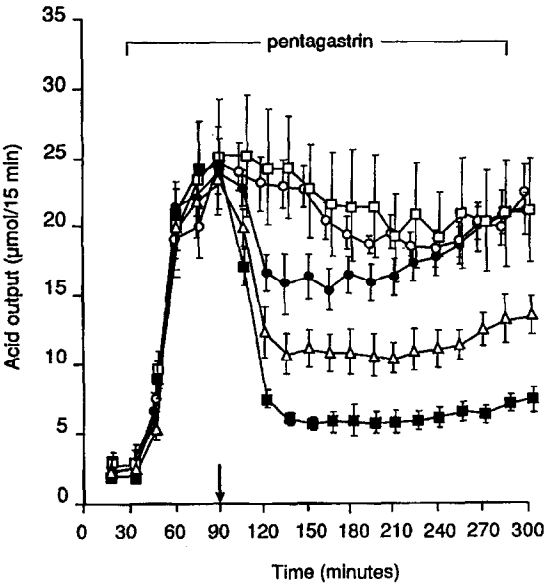

Fig. 1. Influence of SK&F 97574 on acid output in the lumen-perfused rat stomach under continuous pentagastrin stimulation (1 mg/kg min^{-1} i.v.) after intraduodenal administration of SK&F 97574 at doses of 0, (□), 1 (○), 3 (●), 10 (△), and 30 (■) mmol/kg. Other experimental details were as described in Materials and Methods.

When dosed orally, SK&F 97574 (25 μmol/kg) reduced mean peak acid output by 97 ± 3%, and elevated the pH of the gastric juice from 1.9 ± 0.3 to 5.1 ± 0.4 (mean ± SEM; $n = 12$). However, in this experiment the volume of gastric juice secreted was only reduced by 55% (Table 1). In contrast, omeprazole at the same oral dose level totally inhibited acid output. This was a consequence of complete abolition of acid in the secreted juice, although the inhibition of secretion volume was the same as that observed with SK&F 97574 (58%; Table 1). In the study with ompeprazole (and in a previous study with the SK&F 96067, an analogue of SK&F 97574; Parsons, unpublished data, cited with permission) the Na^+ concentration of the gastric juice sampled after inhibition of acid secretion doubled (e.g. from 37 ± 6 μEq/L to 75 ± 10 μEq/L in the case of omeprazole).

Effects in the conscious Heidenhain pouch dog

SK&F 97574 is given by rapid intravenous injection in the dose range 0.5 to 2.0 μmol/kg produced a dose-related inhibition of histamine-stimulated gastric acid secretion in the Heidenhain pouch dog model. The mean peak level of inhibition at each dose was 50.6 ± 2.7% at 0.5 μmol/kg, 64.2 ± 5.2% at 1.0 μmol/kg, and 89.1 ± 4.0% at 2.0 μmol/kg (mean ± SEM, $n = 8$). From these data an IV inhibitory ED_{50} of 0.49 μmol/kg was calcu-

Table 1. The effect of (H^+/K^+)-ATPase inhibitors on basal acid secretion in the conscious fistula rat. Results are the mean ± SEM from 12 animals in all cases. For other experimental details, see Materials and Methods

Treatment	Juice volume (mL)	$[H^+]$ (μEq/L)	Acid output (μEq/15 min)
Control	1.27 ± 0.21	48.0 ± 6.7	61.0 ± 13.2
SK&F 97574 (10 μmol/Kg IV)	0.55 ± 0.12	10.1 ± 2.2	5.5 ± 1.1
% inhibition	57	79	91
Control	1.14 ± 0.18	56.2 ± 7.1	64.1 ± 12.1
SK&F 97574 (25 μmol/Kg P.O.)	0.51 ± 0.11	3.8 ± 0.9	1.9 ± 0.21
% inhibition	55	93	97
Control	1.20 ± 0.30	52.4 ± 8.6	55.2 ± 9.3
omeprazole (25 μmol/Kg P.O.)	0.50 ± 0.09	N.D.	0.0
% inhibition	58	100	100

N.D. = Not detectable.

lated with 95% confidence limits of 0.38–0.65 μmol/kg (n = 24). Significant inhibition remained two to three hours after drug administration at all dose levels.

Oral administration of SK&F 97574 also produced a dose-related inhibition of histamine-stimulated gastric acid secretion in the Heidenhain pouch dog. Doses of 1.0, 2.0, and 4.0 μmol/kg p.o. produced mean peak inhibitions of acid output of 54.0 ± 1.0%, 75.3 ± 3.8%, and 96.0 ± 2.4% (mean ± SEM, n = 5), respectively. From these data an oral inhibitory ED_{50} of 0.89 μmol/kg was calculated with 95% confidence limits of 0.68–1.21 μmol/kg (n = 15). In a separate study SK&F 97574 was given to a larger group of dogs at a dose of 8 μmol/kg, and produced a mean peak inhibition of acid output of 95.0 ± 0.8% (mean ± SEM, n = 22). After oral dosing, there was little recovery from peak inhibition up to three hours after administration at all dose levels. Interestingly, even when nearly 100% inhibition of acid output was obtained the gastric juice was still highly acidic (Table 2).

The duration of action of SK&F 97574 was investigated by monitoring acid output in the conscious Heidenhain dog up to 8 hours after dosing. In the first part of the study, acid secretion was first stimulated using an infusion of histamine. After acid secretion had reached a plateau, SK&F 97574 was infused for one hour at a dose of 50 μmol/hr and produced a mean peak level of inhibition of 92 ± 4% (mean ± SEM; n = 3) of histamine-stimulated gastric acid secretion (Fig. 3). In the second part of the experiment, the histamine infusion was repeated eight hours after the initial dosing of SK&F 97574. At this time, 67% inhibition still remained relative to the plateau secretion established in a control study (Fig. 3). In contrast, the previously described reversible (H^+/K^+)-ATPase inhibitor SK&F 96067 [3, 4], when infused to produce a peak inhibition similar to that obtained with SK&F 97574 in the first period, produced no significant inhibition when acid secretion was re-stimulated after 8 hours (Fig. 3, n = 3).

To investigate, whether residual inhibition of acid secretion could be detected in a longer study, SK&F 97574 was dosed orally at 10 μmol/kg, which totally abolished histamine-stimulated gastric acid secretion. Acid secretion was then re-stimulated 24 hours later. The second stimulation of acid secretion produced a level of acid output not significantly different from that observed before SK&F 97574 was dosed (85 ± 16%, n = 3). These data indicate that the duration of action of SK&F 97574 is clearly shorter than that of the irreversible inhibitor, omeprazole, which at a dose level producing abolition of secretion has been shown to exert a significant inhibitory effect two to three days later [7].

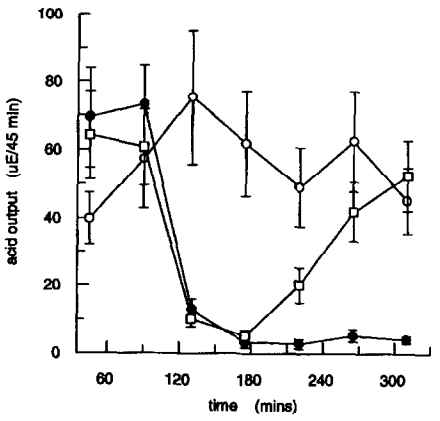

Fig. 2. Effects of SK&F 97574 (□), omeprazole (●), or vehicle control (○) on basal gastric acid secretion in the conscious fistula rat. Drug (10 μmol/kg for both compounds) was administered at 90 min via the tail vain. Other conditions were as described in Materials and Methods.

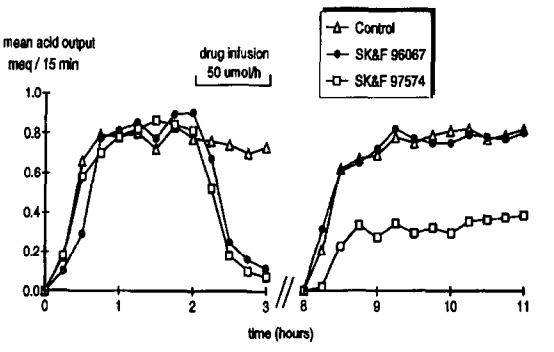

Fig. 3. Comparison of the duration of action of SK&F 96067 (●), SK&F 97574 (□), or vehicle control (△) against histamine-stimulated gastric acid secretion in the Heidenhain pouch dog. After infusion of histamine to achieve steady-state acid secretion, drug was infused at 50 μmol/h for one hour. Acid secretion was re-stimulated at 8 hours to test the residual level of inhibition. Other experimental conditions were as described in Materials and Methods.

Table 2. The effect of SK&F 97574 (8 μmol/Kg, PO) on histamine-stimulated gastric acid secretion in the conscious Heidenhain pouch dog. Data shown are the mean ± SEM from 7 animals. For other experimental details, see Materials and Methods

Treatment	Juice volume (mL)	$[H^+]$ (μEq/L)	Acid output (μEq/15 min)
Control	4.4 ± 0.73	145.8 ± 2.6	0.64 ± 0.11
SK&F 97574 (8 μmol/Kg PO)	0.09 ± 0.06	106.3 ± 3.4	0.01 ± 0.007
Peak inhibition (%)	98.0	27	99.8

DISCUSSION

As predicted from the biochemical characteristics described in the accompanying paper [2], SK&F 97574 is a potent and effective inhibitor of basal and secretagogue-evoked gastric acid secretion in the rat and dog by both the parenteral and oral routes of administration. In all cases, the inhibitory responses were dose-related and reproducible.

In the anaesthetised rat, the potency of SK&F 97574 against pentagastrin-stimulated secretion (after intravenous administration) was similar to that of cimetidine (ED_{50} = 1.4 μmol/kg; [8]). A comparison of the inhibitory ED_{50} values for the intravenous and intraduodenal routes in the rat using the original Gosh and Schild technique (2.1 and 4.7 μmol/kg, respectively) suggest that the compound is well absorbed in this species after intraduodenal administration. The onset of inhibition of acid secretion was rapid, with peak inhibition obtained after 30–45 min. Although the studies in the rat were not designed to examine the duration of the inhibitory activity of SK&F 97574, examination of the inhibitory patterns at single doses suggested that the compound had a longer duration of action than either cimetidine or ranitidine [8].

The results in the conscious fistula rat indicated that SK&F 97574 is an effective inhibitor of basal secretion which, in this preparation, is primarily driven by the parasympathetic vagus nerve [9]. In the rat, SK&F 97574 is clearly somewhat less potent than omeprazole and has a much shorter duration of action, as would be predicted for a freely reversible inhibitor of the (H^+/K^+)-ATPase [10]. However, in this model both types of proton pump inhibitor had a more marked effect on the acid concentration than on the volume of secretion. This probably reflects the fact that a significant proportion of the fluid content of the gastric juice is nonparietal in origin. This is supported by the fact that the juice contains a relatively high proportion of Na^+, which may be associated with bicarbonate secretion [11].

In the conscious Heidenhain pouch dog, SK&F 97574 was around twice as potent an inhibitor of gastric acid secretion than cimetidine (ED_{50} = 0.5 μmol/kg c.f. 1.7 μmol/kg for cimetidine against histamine-stimulated acid secretion; [8]). This difference was even more marked after oral dosing; SK&F 97574 was around five times more potent than cimetidine and slightly more potent than the previously described reversible (H^+/K^+)-ATPase inhibitor, SK&F 96067 (ED_{50} = 0.9 μmol/kg c.f 1.6 μmol/kg for SK&F 96067; [4]). Similarly to the rat, the oral/IV ED_{50} ratio of 2.3 for SK&F 97574 suggests that the compound is well absorbed in the dog. In the Heidenhain pouch dog, the ability of SK&F 97574 to produce nearly 100% inhibition of acid output whilst the remaining juice was highly acidic probably reflects the almost pure parietal cell secretion following histamine stimulation in this preparation (Parsons, unpublished observation; cited with permission).

The lower potency of SK&F 97574 in the rat compared to the dog probably reflects the more rapid and extensive metabolism of the compound in the former species (Griffiths, unpublished observation; cited with permission). As in the rat, however, the rate of onset of inhibition with SK&F 97574 on the dog was rapid after both oral and intravenous administration. The duration of action of SK&F 97574 is longer than that of the H_2 antagonists cimetidine and ranitidine. For example, a study in the Heidenhain pouch dog previously showed that, at a cimetidine dose of 2 μmoles/kg (i.v.), acid secretion returned to control levels within 2.5 hours of dosing [8]; yet under similar conditions, considerable residual inhibition was observed with SK&F 97574 eight hours after dosing (Fig. 3). However, the duration of action of SK&F 97574 is much shorter than that of omeprazole, which still exerts a significant inhibitory effect up to three days after the administration of a single dose in both experimental animal models [7] and humans [12]. The difference in duration of action of the two (H^+/K^+)-ATPase inhibitors, SK&F 97574 and SK&F 96067, identified in the eight-hour Heidenhain pouch dog study (Fig. 3), reflects the fact that the duration of action of these compounds is determined by their blood kinetic behaviour, which is different for SK&F 97574 and SK&F 96967 (Griffiths, unpublished observation; cited with permission). This is in contrast to the behaviour of covalent (H^+/K^+)-ATPase inhibitors, such as omeprazole, whose duration of action is basically determined by the rate of turnover of the (H^+/K^+)-ATPase, which has a half-life of 30–48 hours in humans [13]. Freely reversible inhibitors therefore provide a potential dosing flexibility, and hence, the potential for more optimal control of acid-secretion than can be obtained with covalent (H^+/K^+)-ATPase inhibitors. In addition, the lack of significant accumulation on repeated dosing differentiates SK&F 97574 from omeprazole, which does not exert its maximum secretory effect until three to four days after the commencement of dosing [12]. This is because the effectiveness of the first dose of omeprazole is determined by the secretory status at the time of dosing, since the compound must be acid activated to inhibit the (H^+/K^+)-ATPase [14], and the acid-activated sulfenamide form of the drug is relatively unstable. A logical consequence of these properties is that they may lead to variable responsiveness in the early days of dosing, a problem that should not occur with the reversible inhibitors.

The fact that a single administration of SK&F 97574 in the dog can produce a marked inhibition of acid se-

cretion for at least 8 hours, whilst secretion had returned to normal after 24 hours, suggests that, upon repeat dosing, the compound would be effective against a range of acid-related diseases, including gastro-eosophageal reflux disease, but avoiding the possibility of microbial overgrowth associated with the profound anacidity caused by covalent ATPase inhibitors [15]. In conclusion, the pharmacological properties of SK&F 97574 reflect its biochemical characteristics as a reversible inhibitor of the gastric (H^+/K^+)-ATPase, and its potency and duration of action suggest that it could represent a useful addition to the armamentarium of drugs for the treatment of acid-related diseases.

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