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Anti-ulcer Activity of Cromakalim (BRL 34915), a Potassium-channel Opener, Against Experimentally Induced Gastric and Duodenal Ulcers in Rats and Guinea-pigs

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Abstract

The effect of cromakalim, a potassium-channel opener, was studied on pylorus ligation-induced, aspirin-induced and water-immersion plus restraint stress-induced gastric ulcers in rats and on histamine-induced duodenal ulcer in guinea-pigs.

Pretreatment with cromakalim (50–500 $\mu g\,kg^{-1}$, p.o.) resulted in a significant reduction in the incidence of gastric and duodenal ulceration in each model. The anti-ulcer activity of cromakalim was comparable with that of cimetidine. Cromakalim at 100, 250 and 500 $\mu g\,kg^{-1}$ caused a reduction in the volume of the gastric content in pylorus-ligated rats, and a dose of 250 $\mu g\,kg^{-1}$ resulted in a significant reduction in total acidity ($28{\cdot}81 \pm 11{\cdot}73$ mEq L^{-1}, $P < 0{\cdot}02$) in the pylorus ligation model. A significant reduction in total acid output was observed at doses of 250 $\mu g\,kg^{-1}$ ($84{\cdot}27 \pm 22{\cdot}33$ mEq H^+, $P < 0{\cdot}02$) and 500 $\mu g\,kg^{-1}$ ($120{\cdot}17 \pm 24{\cdot}49$ mEq H^+, $P < 0{\cdot}01$) in pylorus-ligated rats. A significant reduction in the ulcer index in pylorus-ligated rats was observed at all cromakalim doses: 50 $\mu g\,kg^{-1}$ ($0{\cdot}23 \pm 0{\cdot}09$, $P < 0{\cdot}05$), 100 $\mu g\,kg^{-1}$ ($0{\cdot}15 \pm 0{\cdot}09$, $P < 0{\cdot}02$), 250 $\mu g\,kg^{-1}$ ($0{\cdot}12 \pm 0{\cdot}05$, $P < 0{\cdot}01$) and 500 $\mu g\,kg^{-1}$ ($0{\cdot}14 \pm 0{\cdot}03$, $P < 0{\cdot}02$). A significant reduction in the ulcer index of aspirin-treated rats was also observed at all cromakalim dose levels: 50 $\mu g\,kg^{-1}$ ($0{\cdot}39 \pm 0{\cdot}03$, $P < 0{\cdot}01$), 100 $\mu g\,kg^{-1}$ ($0{\cdot}28 \pm 0{\cdot}06$, $P < 0{\cdot}01$), 250 $\mu g\,kg^{-1}$ ($0{\cdot}22 \pm 0{\cdot}04$, $P < 0{\cdot}001$) and 500 $\mu g\,kg^{-1}$ ($0{\cdot}28 \pm 0{\cdot}03$, $P < 0{\cdot}01$). In the water-immersion plus restraint stress-induced gastric ulcer model, cromakalim significantly reduced gastric ulceration at all the dose levels: 50 $\mu g\,kg^{-1}$ ($28{\cdot}2 \pm 2{\cdot}12$, $P < 0{\cdot}001$), 100 $\mu g\,kg^{-1}$ ($20{\cdot}24 \pm 1{\cdot}71$, $P < 0{\cdot}01$), 250 $\mu g\,kg^{-1}$ ($19{\cdot}95 \pm 1{\cdot}46$, $P < 0{\cdot}001$) and 500 $\mu g\,kg^{-1}$ ($21{\cdot}61 \pm 3{\cdot}00$, $P < 0{\cdot}001$) but there was no consistent reduction of gastric bleeding. In addition to gastric ulcers, duodenal lesions were also reduced by pretreatment with cromakalim at all dose levels: 50 $\mu g\,kg^{-1}$ ($97{\cdot}87 \pm 20{\cdot}03$ mm^2, $P < 0{\cdot}02$), 100 $\mu g\,kg^{-1}$ ($70{\cdot}72 \pm 12{\cdot}82$ mm^2, $P < 0{\cdot}02$), 250 $\mu g\,kg^{-1}$ ($48{\cdot}32 \pm 8{\cdot}42$ mm^2, $P < 0{\cdot}01$) and 500 $\mu g\,kg^{-1}$ ($55{\cdot}50 \pm 12{\cdot}50$ mm^2, $P < 0{\cdot}01$). Cromakalim at a dose of 100 $\mu g\,kg^{-1}$ also reduced total acidity ($99{\cdot}36 \pm 9{\cdot}12$ mEq L^{-1}, $P < 0{\cdot}02$) and total acid output ($172{\cdot}22 \pm 45{\cdot}33$ mEq of H^+, $P < 0{\cdot}05$) in this model.

These findings demonstrate the anti-ulcer activity of cromakalim in different experimental models and suggest its potential use in ulcer therapy.

Peptic ulcers are a major health problem. Research advances during recent years have offered new insight into therapy and the prevention of gastroduodenal ulcers. The potassium-channel openers cromakalim, nicorandil and pinacidil have been found to cause hyperpolarization in various tissues at different concentrations (Weir & Weston 1986). Calcium influx also plays an important role in stimulation secretion coupling and smooth muscle contraction (Kasbekar & Chugani 1976). Besides contractions, calcium flux also plays an important role in gastric secretion (Kirkegaard et al 1982). Potassium-channel openers have been reported to prevent depolarization-induced calcium influx in a variety of smooth muscle cells, including those of blood vessels, by causing an increase in potassium conductance. The increased potassium conductance fixes the equilibrium potential of the smooth muscle cell membrane at sufficiently negative values to prevent calcium entry (Hamilton et al 1986). Because the vasodilation thus produced might indicate involvement of potassium-channel openers in gastric mucosal protective mechanisms, the effects of cromakalim have been evaluated against experimentally induced ulcers such as pylorus ligation-induced, aspirin-induced and water-immersion plus restraint stress-induced gastric ulcers, and histamine-induced duodenal lesions.

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Materials and Methods

Wistar albino rats of both sexes, 180–220 g, and guinea-pigs of both sexes, 400–500 g, were selected for the gastric and duodenal ulcer studies, respectively. Rats were fed standard chow diet; guinea-pigs were fed standard chow diet and vegetables.

The animals were divided into groups of eight. The distribution of animals in the groups, the sequence of trials and the treatment allotted to each group were randomized. The solutions or suspensions of the ulcerogenic drugs and cromakalim were freshly prepared before administration. The animals were killed by ether anaesthesia after the completion of the experiments. The stomachs were removed, opened along the greater curvature, washed with saline and examined with a 6·4 binocular magnifier. Lesions were assessed by two observers unaware of the experimental protocols. Cromakalim (BRL 34915; SmithKline Beecham Pharmaceuticals) at doses of 50, 100, 250 or 500 $\mu g\,kg^{-1}$ was administered orally as aqueous suspensions in 1% carmellose. Single oral doses were given 30 min before the ulcerogenic procedure. Each set of experi-

ments included one group of animals receiving cimetidine 50 mg kg^{-1} as standard drug for the purpose of comparison.

Experimental gastric ulcers

The animals were fasted for 36 h with free access to water before subjecting them to one of the following procedures.

Pylorus-ligated rats (Shay et al 1945). The pylorus was ligated under light ether anaesthesia, care being taken not to cause bleeding or to occlude blood vessels. Nineteen hours after ligation the animals were killed and the stomachs removed. The contents were collected, measured, centrifuged and subjected to analysis for total acidity by titration against 0·01 M NaOH to pH 8·0 using phenolphthalein as indicator. Each stomach was examined for lesions; these were expressed in terms of the ulcer index which was calculated as:

$$\text{Ulcer index} = 10/X$$

where X = (total mucosal area)/(total ulcerated area)

ED50 was calculated on the basis of the reduction in the ulcer index.

Aspirin-induced gastric lesions (Hemmati et al 1973). Aspirin was suspended in 1% carmellose in water and administered orally at a dose of 500 mg kg^{-1} to 36-h-fasted rats. The animals were killed 6 h after aspirin administration and the ulcer index of glandular mucosa was determined. ED50 was calculated on the basis of the reduction in this index.

Water-immersion plus restraint stress-induced gastric ulcer. The method described by Hayase & Takeuchi (1986) was followed. Each rat was immobilized in a restrainer and then immersed to the level of the xiphoid process in a water bath maintained at room temperature. After 16 h, they were taken out and killed by ether overdose. The stomachs were removed and examined for the severity of intraluminal bleeding according to the scale: 0, no blood detectable; 1, thin blood follows the rugae; 2, thick blood follows the rugae; 3, thick blood follows the rugae with blood clots in certain areas; and 4, extensive covering of the whole of the mucosal surface with thick blood. The blood was wiped off and the total area of lesions in each stomach was scored as described above. ED50 was calculated on the basis of the reduction in the ulcerated area.

Experimental duodenal ulcers

Histamine-induced duodenal ulcer (Eagleton & Watt 1967). Guinea-pigs were fasted for 12–16 h but allowed free access to drinking water. Eight histamine injections (0·25 mg kg^{-1}, i.m.) were given at 30-min intervals. Cromakalim was administered 30 min before the first injection of histamine and animals were killed 30 min after the last histamine injection. The stomach and duodenum were opened along the greater curvature and the total lesion area was measured. Lesions were scored from 0–3 on the scale: 0, no ulcer; 1, superficial mucosal lesion; 2, deep ulcer or transmucosal necrosis; and 3, perforated or penetrating ulcer (into the pancreas or liver). Gastric contents were collected and subjected to analysis. The ulcer index is the sum of the arithmetic mean of the intensity in a group and the ratio of positive/total multiplied by 2. ED50 was calculated on the basis of the reduction in the total lesion area.

Statistical analysis

Statistical analysis of the severity of gastric and duodenal lesions, total acidity and total acid output was performed using the unpaired Student's *t*-test.

Results

Pylorus-ligated rats

Pylorus ligation for 19 h resulted in the accumulation of gastric secretory volume and an increase in the total acid output of the gastric juice. Circular and linear lesions and petechiae were frequently seen in the rumenal and glandular mucosa of the stomachs of all the control animals. Administration of cromakalim at all doses resulted in a significant reduction in ulcer index. Total acid output was also found to be reduced significantly at higher doses (250 and 500 μg kg^{-1}; Table 1). The ED50 of cromakalim, on the basis of the reduction in ulcer index, was found to be 143·7 μg kg^{-1}. Cimetidine at 50 mg kg^{-1} had a significant protective effect against acid secretory parameters and gastric ulceration (Table 1).

Aspirin-induced gastric lesions

Aspirin treatment resulted in the production of gastric lesions mainly in the glandular segments of stomach, and the stomach wall was frequently fragile and thin. It is apparent from the significant ($P < 0·01$) reduction in the ulcer index (Table 2) that pretreatment with cimetidine and cromakalim at all the doses studied resulted in a significant reduction in the intensity of aspirin-induced gastric mucosal damage. When stomach wall thickness was viewed by back-lighting it was apparent that administration of cromakalim resulted in a marked increase in thickness compared with the control group (ED50 = 199·3 μg kg^{-1}).

Table 1. Effect of cromakalim (p.o.) on pylorus-ligated rats.

Treatment	n	Dose (μg kg^{-1})	Volume of gut content (mL kg^{-1})	Total acidity (mEq L^{-1})	Total acid output (μEq of H^+)	Ulcer index
Control	8	–	39·7 ± 15·4	67·44 ± 07·22	311·43 ± 39·63	0·57 ± 0·12
Cromakalim	8	50	76·7 ± 36·8	113·98 ± 25·97	555·98 ± 59·47	0·23 ± 0·09*
Cromakalim	8	100	36·8 ± 16·7	62·38 ± 26·07	322·00 ± 40·08	0·15 ± 0·09**
Cromakalim	8	250	11·1 ± 05·8	28·81 ± 11·73**	84·27 ± 22·33**	0·12 ± 0·05***
Cromakalim	8	500	14·3 ± 09·3	43·98 ± 12·73	120·17 ± 24·49***	0·14 ± 0·03**
Cimetidine	8	5×10^4	20·7 ± 07·3	39·55 ± 10·09*	127·00 ± 20·95***	0·11 ± 0·04***

*$P < 0·05$; **$P < 0·02$; ***$P < 0·01$; compared with control group.

Table 2. Effect of cromakalim (p.o.) on aspirin-induced gastric ulcers in rats.

Treatment	n	Dose ($\mu g\,kg^{-1}$)	Ulcer index (mean ± s.e.m.)
Control (aspirin, p.o.)	8	5×10^5	1·08 ± 0·19
Cromakalim	8	50	0·39 ± 0·03*
Cromakalim	8	100	0·28 ± 0·06*
Cromakalim	8	250	0·22 ± 0·04**
Cromakalim	8	500	0·28 ± 0·03*
Cimetidine	8	5×10^4	0·24 ± 0·03**

*$P < 0.01$; **$P < 0.001$ compared with control group.

Water-immersion plus restraint stress-induced gastric lesions
The animals subjected to the restraint procedure showed considerable ulcerogenicity in the form of haemorrhagic mucosal lesions in the stomach. The area of involvement in all the animals was confined to the glandular segment only. There was evidence of intraluminal bleeding in these animals. Pretreatment with cromakalim at all the dose levels studied resulted in a significant reduction in the ulcerated area (ED50 = 143·7 $\mu g\,kg^{-1}$). Cimetidine also significantly reduced the area of stress ulcers (Table 3).

Histamine-induced duodenal ulcer
Administration of histamine to guinea-pigs caused the formation of lesions in the duodenum and the area surrounding the pyloric sphincter of the stomach. Pretreatment with cromakalim resulted in a significant reduction in the score for intensity and total lesion area at all dose levels (Table 4). Cromakalim treatment also resulted in a significant reduction in acid secretory parameters such as volume of gastric content, total acidity and total acid output when compared with the control group (Table 5). On the basis of the reduction in total lesion area the ED50 of cromakalim was found to be 166·5 $\mu g\,kg^{-1}$. Cimetidine also had a protective effect against duodenal lesions.

Discussion

In this study, cromakalim has been found to inhibit the development of gastric and duodenal lesions induced by various ulcerogenic procedures. As the mechanisms involved in

Table 3. Effect of cromakalim (p.o.) on water-immersion plus restraint stress-induced gastric ulcers in rats.

Treatment	n	Dose ($\mu g\,kg^{-1}$)	Score for intensity	% of control	Ulcerated area (cm^2)	% of control
Control	8	–	1·30 ± 0·33	100	52·21 ± 3·49	100
Cromakalim	8	50	1·50 ± 0·62	115	28·20 ± 2·12**	35
Cromakalim	8	100	1·67 ± 0·42	128	20·24 ± 1·71*	36
Cromakalim	8	250	1·30 ± 0·61	100	19·95 ± 1·46**	33
Cromakalim	8	500	1·67 ± 0·33	128	21·61 ± 3·00**	37
Cimetidine	8	5×10^4	1·09 ± 0·10	92	13·20 ± 2·01**	29

*$P < 0.01$; **$P < 0.001$ compared with control group.

Table 4. Effect of cromakalim (p.o.) on histamine-induced duodenal ulcer model in guinea-pigs.

Treatment	n	Dose ($\mu g\,kg^{-1}$)	Score for intensity	Total lesion area (mm^2)
Control (histamine acid phosphate, i.m.)	8	250	2·33 ± 0·17	226·83 ± 52·09
Cromakalim	8	50	1·50 ± 0·30*	97·87 ± 20·03**
Cromakalim	8	100	1·33 ± 0·21***	70·72 ± 12·82**
Cromakalim	8	250	1·29 ± 0·20***	48·32 ± 08·42***
Cromakalim	8	500	1·37 ± 0·31**	55·50 ± 12·50***
Cimetidine	8	5×10^4	1·15 ± 0·19***	50·52 ± 09·39***

*$P < 0.05$; **$P < 0.02$; ***$P < 0.01$; compared with control group.

Table 5. Effect of cromakalim (p.o.) on secretory parameters of duodenal ulcer in guinea-pigs.

Treatment	n	Dose ($\mu g\,kg^{-1}$)	Vol. gastric content ($mL\,kg^{-1}$)	Total acidity ($mEq\,L^{-1}$)	Total acid output
Control (histamine acid phosphate, i.m.)	8	250	21·1 ± 1·70	150·73 ± 13·50	300·80 ± 38·40
Cromakalim	8	50	23·2 ± 4·40	88·73 ± 25·97	204·50 ± 48·43
Cromakalim	8	100	17·4 ± 0·50	99·36 ± 9·12**	172·22 ± 45·33*
Cromakalim	8	250	13·2 ± 1·60	45·12 ± 7·67	65·32 ± 12·91
Cromakalim	8	500	15·8 ± 1·70	101·37 ± 10·12	154·05 ± 12·66
Cimetidine	8	5×10^4	15·5 ± 1·90*	43·55 ± 5·49***	109·00 ± 8·89***

*$P < 0.05$; **$P < 0.02$; ***$P < 0.001$ compared with control group.

the causation of ulcers depend upon the experimental model selected for the study (Parmar and Desai 1993), it is not possible to propose a single mechanism for the anti-ulcer effect of a particular drug. A dose-dependent reduction in gastric acid output and of the intensity of gastric ulceration in pylorus-ligated rats by cromakalim might account for its anti-ulcer activity in those models where increased gastric acidity is responsible for the pathogenesis of gastric and duodenal lesions. The stomach digestive effect of accumulated gastric juice in the induction of gastric ulcers is well documented in the pylorus ligation model (Brodie 1966) and increased gastric secretion is also implicated in the causation of gastric ulcers by anti-inflammatory agents (Rainsford 1984). The significant reduction in the intensity of gastric mucosal damage induced by aspirin further confirms the potential anti-ulcer activity of cromakalim. Aspirin is a well known gastric mucosal barrier breaker (Davenport 1967). It is, therefore, possible that cromakalim acts by a mechanism leading to increased gastric mucosal resistance against ulcerogenic drugs in rats. In addition to gastric acid secretion, reflex or neurogenic effects have also been suggested as playing an important role in the formation of gastric ulcers in the pylorus ligation model (Anichkov et al 1971). Experimental stress-induced ulcers have been suggested as resulting from disturbance of gastric mucosal microcirculation (Guth 1972), alteration of gastric secretion (Kitagawa et al 1979) and abnormal gastric motility (Watanabe 1966). Apart from peripheral events, central mechanisms including vagal over-activity have also been considered for the pathogenesis of stress ulcer (Henke 1982; Ogle et al 1985). In this study administration of cromakalim resulted in a significant decrease in the area of gastric ulceration in a stress ulcer model. It has been reported that cromakalim dilates gastric blood vessels and increases blood flow to the heart and small intestine in anaesthetized rabbits (Cook & Hof 1988). It is also well established that cromakalim reduces the contractility of smooth muscles because of its vasodilator or hyperpolarization properties, or both (Hamilton et al 1986). The anti-ulcer activity of cromakalim observed in this work might, therefore, be partly a result of its inhibitory action on gastric motility.

The exact mechanism of pathogenesis in the histamine-induced duodenal ulcer model is not known. A significant reduction in the incidence and severity of such ulcers was, however, observed by Anderson & Watt (1959) when guinea-pigs were pretreated with acid-inhibitory substances such as antacids and carageenin. Cromakalim has also been reported as inhibiting the guinea-pig intestinal contraction induced by histamine and other agonists (Allen et al 1986; Arch et al 1988a, b; Taylor et al 1988a, b). Histamine is considered to be of major importance in the pathogenesis of gastroduodenal ulcers (Szabo et al 1982). The reduction in the acid secretory parameters, and the scores for intensity and total lesion area observed by us in this model reflect the protective activity of cromakalim against duodenal ulcers. It can, therefore, be speculated that the inhibitory effect on gastric acid secretion and intestinal motility could be one of the mechanisms of the anti-ulcer effect of cromakalim against histamine-induced duodenal ulcers.

Cromakalim has an activating effect on the sodium-potassium pump in muscle strips from rat fundus (Hoda et al 1989). It also blocks Ca^{2+} currents and reduces K^+ currents in canine colonic smooth muscle cells. These findings suggest that cromakalim, in addition to acting as a potassium-channel agonist, possesses significant calcium-channel antagonist properties (Post et al 1990), and calcium flux plays an important role in gastric secretion (Kirkegaard et al 1982). It is also well established that potassium-channel openers interfere with calcium influx (Hamilton et al 1986), which can be taken as one of the mechanisms of the anti-ulcer activity of cromakalim.

It can be concluded from this study that cromakalim shows anti-ulcer activity in pylorus ligation and aspirin-induced gastric ulcers in rats as a result of its inhibitory action on gastric acid secretion. Increase in gastric mucosal resistance might also be a contributory factor in inhibiting aspirin-induced ulcers. Improvement in gastric blood flow and reduction in gastric motility appear to be the main mechanisms of the protective effect shown by cromakalim in the water-immersion plus restraint stress-induced gastric ulcer model. Reduced gastric acid secretion and reduced gastric motility as a result of cromakalim treatment seem to be responsible for its anti-ulcer effect in the histamine-induced guinea-pig duodenal ulcer model.

Our study demonstrates the protective effect of cromakalim on various experimentally induced ulcers in different animal models. This study offers evidence that potassium-channel openers might play an important role in protection against chemically induced gastric lesions and thereby offers insight into the mechanism of gastric ulcer formation. This knowledge might prove important in the development of new and improved therapies for the treatment and prevention of gastric and duodenal ulcers in man.

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