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SECRETORY AND MOTOR ACTIVITIES AT THE GASTRODUODENAL JUNCTION IN DOGS

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ABSTRACT

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Motor patterns of the canine gastroduodenal junction were investigated by electromyography under different secretory conditions: enhancement by pentagastrin and reduction by proglumide, cimetidine or CMN 131. The intravenous administration of these antisecretory agents did not affect the spiking activity or the slow-wave frequency of the antrum and duodenum, with the exception of CMN 131 which induced duodenal hyperactivity.

Pentagastrin slowly infused intravenously increased the frequency of antral slow waves and spiking activity by 25 and 30% respectively. The simultaneous infusion of proglumide or CMN 131 significantly reduced this antral hypermotility.

It was concluded that gastroduodenal motility was not affected by a reduction in acid secretion and it is suggested that the hypermotility observed during pentagastrin infusion may be a specific effect unrelated to increased acid secretion.

INTRODUCTION

Many experiments have been performed to analyse the effects of antisecretory drugs on gastric acid secretion but not on the motility of the gastroduodenal area. Information on the changes in the pattern of gastrointestinal motility resulting from both basal and postprandial gastric acid release is still lacking in respect of its cyclical organization in migrating myoelectric complexes (Szurszewski, 1969; Grivel and Ruckebusch, 1972).

This work was undertaken to evaluate the effects on gastrointestinal electrical activity of three antisecretory substances selected for their different modes of action and to test their effect on gastrin-induced changes in motility.

MATERIALS AND METHODS

Animals and procedures

Four adult mongrel dogs weighing 14 to 22 kg, housed in individual cages allowing them free movement and receiving 600 g of canned food once each day were used.

Under general anaesthesia, pairs of insulated nichrome wire electrodes were placed 2 mm apart on the antrum at 5 and 10 cm before the pylorus and at 20 and 50 cm beyond it on the duodenum. The free ends of electrodes were brought subcutaneously to the back of the neck. An indwelling polyethylene catheter was inserted in the jugular vein.

Recordings were started 5-10 days after operation. The electrical activity was amplified through an EEC machine (Reega VIII, Alvar) at a time constant of 0.3 sec without filters.

Intestinal slow waves were eliminated using a high pass filter and the spike bursts continuously plotted at 20-sec intervals for uninterrupted periods of 6-8 weeks for the 4 groups of electrodes using a multichannel integrator circuit (Latour, 1973) connected to a potentiometric recorder. Both the slow-wave frequency and the level of spiking activity of the antrum were determined. An electronic device in which the slow waves were detected with a trigger and the output signal containing spike bursts obtained from a window circuit having a delay equivalent to the duration of slow wave and a gate function of maximal spike burst duration was used (Latour, 1978).

Drugs

Each dog received an antisecretory substance, either proglumide¹, cimetidine² or CMN 131³, intravenously at a dose of 10 mg.kg^{-1} , twice with a 4-day interval. On other occasions, pentagastrin (Peptaylon^R) was administered either as a single intravenous injection ($3 \text{ } \mu\text{g.kg}^{-1}$) or as a slow infusion ($3 \text{ } \mu\text{g.kg}^{-1}.\text{h}^{-1}$) for 2 hours. One hour after starting the pentagastrin infusion, one of the 3 antisecretory substances was infused for one hour at a dose of 10 mg.kg^{-1} .

RESULTS

Influence of antisecretory drug administration on the basic gastroduodenal motility

The slow-wave frequency of the antrum was about 4.6/min in a 12-h fasted dog and arrhythmias occurred when bursts of spikes were irregularly superimposed on the duodenal slow waves (Fig. 1 - RSA). The selective record of antral spiking activity showed a cyclic occurrence of periods of spiking activity lasting from 25 to 42 min at intervals of 87 ± 13 min during which spiking bursts were irregularly superimposed on slow waves in the ratio of 4.2/10 (Fig. 1 - ISA). The electrical spiking activity of the small intestine was characterized by the cyclic recurrence of a phase of irregular spiking activity (ISA) followed by a phase of regular

1 Milide, Lab. Fournier, Paris

2 Tagamet, Smith Kline & French

3 Lab. Servier, Suresnes

spiking activity (RSA) lasting 6 to 8 min.

Intravenous injection of cimetidine (10 mg.kg^{-1}) did not affect the antral and duodenum slow-wave frequencies (Table I), nor the antro-duodenal cyclic spiking activity, except transiently for the antrum (Fig. 2). This short-term antral inhibition varied from dog to dog and from day to day. Proglumide (10 mg.kg^{-1}) did not affect the fasted pattern of antro-duodenal spiking activity (Fig. 2) but slightly reduced the slow-wave frequency of the antrum (Table I). A 60-min inhibition of antral motility associated with an increase in duodenal spiking activity followed the CMN 131 injection (10 mg.kg^{-1}) (Fig. 2). An arrhythmia of antral slow waves was also observed, slow-wave frequency varying from 4.9 to 5.4 c/min.

Fig. 1. Slow-wave frequency and patterns of spiking activity of the gastroduodenal junction of dog. Three different stages : quiescence, irregular spiking activity (ISA) and regular spiking activity (RSA) are shown on the direct records. At bottom, slow-wave frequency of the antrum and integrated records of the spiking activity of the antrum and the duodenum.

TABLE I

Effects of cimetidine, proglumide and CMN 131 on antral and duodenal slow-wave frequencies. Values (mean $\pm$ SD) per min measured during 10 min before and following intravenous injection of the antisecretory substance (10 mg.kg^{-1})

	Control	Cimetidine	Proglumide	CMN 131
Antrum	4.6 ± 0.3	4.5 ± 0.1	$4.1 \pm 0.2^*$	$3.6 \pm 0.4^{**}$
Duodenum	17.6 ± 0.5	17.9 ± 0.4	18.2 ± 0.6	17.7 ± 0.4

Difference from control values: * $P \leq 0.05$, ** $P \leq 0.01$

TABLE II

Effects of antisecretory substances on antral slow-wave frequency during pentagastrin infusion. Values (mean $\pm$ SD) per min before and during pentagastrin infusion and after infusion of the antisecretory substance ($10 \text{ mg.kg}^{-1} \cdot \text{h}^{-1}$)

	n	Control	Pentagastrin infusion	Antisecretory substance under pentagastrin
Cimetidine	4	4.21 ± 0.17	$5.32 \pm 0.10^{(a)}$	5.22 ± 0.22
Proglumide	6	4.13 ± 0.15	$5.25 \pm 0.19^{(a)}$	$4.84 \pm 0.33^{(b)}$
CMN 131	4	4.43 ± 0.07	$4.82 \pm 0.11^{(a)}$	$4.57 \pm 0.21^{(b)}$

(a) Different at $P \leq 0.05$ from control values

(b) Different at $P \leq 0.05$ from values obtained under pentagastrin alone

Effects of the antisecretory substances on the gastrin-induced hypermotility

When pentagastrin ($3 \mu\text{g.kg}^{-1}$) was injected intravenously, the slow-wave frequency increased from 4.61 ± 0.05 to $6.18 \pm 0.14/\text{min}$ during about 10 min. This injection was followed by a period of continuous spiking activity on both antrum and small intestine, resembling the postprandial pattern but lasting 20 to 40 min.

During the infusion of pentagastrin ($3 \mu\text{g.kg}^{-1} \cdot \text{h}^{-1}$), the antral slow-wave frequency was increased by 35% at the beginning of the infusion. Spiking activity was also increased during the infusion by 12 to 20%, an effect prolonged in 4 of the 6 trials for more than 2 hours.

The infusion of cimetidine ($10 \text{ mg.kg}^{-1} \cdot \text{h}^{-1}$) did not alter the effects of pentagastrin on slow-wave frequency (Table II). Pentagastrin-induced spiking activity was transiently reduced for 10–15 min at the beginning of cimetidine infusion. The recovery of a normal cyclic activity with typical phases of RSA was obtained earlier than with pentagastrin alone (Fig. 3). A transient increase in the slow-wave frequency always occurred just after the end of the cimetidine infusion.

Proglumide ($10 \text{ mg.kg}^{-1} \cdot \text{h}^{-1}$) decreased by 36% for 10–15 min the slow-wave

frequency induced by pentagastrin infusion. In addition, cyclic arrhythmias of the antral slow waves which were reduced by pentagastrin increased in frequency after proglumide administration. Both antral and duodenal total spiking activity were reduced and a more rapid recovery of the cyclic activity was recorded.

CMN 131 inhibited the pentagastrin-induced increase in the antral slow-wave frequency (Table II). A decrease by 55% with presence of numerous arrhythmias occurred 10 min after the CMN 131 infusion was started. Antral spiking activity expressed as the percentage of slow waves superimposed by spike bursts was inhibited for 56 ± 13 min (Fig. 3). The duodenal spiking activity level already increased by pentagastrin was further increased by CMN 131 (Fig. 3).

Fig. 2. Effect of antisecretory substances on gastrointestinal spiking activity in a 12-h fasted dog.

Fig. 3. Antisecretory substances and gastrointestinal spiking activity under pentagastrin. The pentagastrin disrupted the cyclic activity for continuous spiking activity, while cimetidine and proglumide had little effect on spiking activity in the antrum, duodenum or jejunum. CMN 131 suppressed antral activity but reinforced duodenal and jejunal spiking.

DISCUSSION AND CONCLUSIONS

Action of antisecretory drugs may be explained by blockage of gastrin, acetylcholine and histamine receptors acting in series or in parallel (Hirschowitz, 1973; Grossman, 1975; Clayman, 1977; Simay et al., 1978).

The drugs used here were chosen for their different level of action: i) cimetidine, an H_2 -receptor blocking agent, developed a moderate antisecretory action upon pentagastrin-stimulated gastric secretion (Aadland et al., 1977); ii) proglumide inhibits pentagastrin-stimulated gastric secretion but not that induced by histamine (Rovati, 1968); iii) CMN 131 has a similar antigastrinic action but in addition it moderately inhibits carbachol and histamine-induced gastric acid secretion (Pascaud et al., 1974).

Histamine and acetylcholine are known to stimulate the gastric motility (Vizi et al., 1973) and gastrin stimulates both antral (Kelly, 1975) and intestinal spiking activity (Cooke et al., 1972). It is not clear whether gastrin acts directly on the smooth muscle or through a cholinergic mechanism although colinergic mechanisms might be involved as atropine-inhibited motility changes induced by pentagastrin (Jacoby and Marshall, 1969).

Absence of changes in motility following cimetidine and proglumide administrations suggested that inhibition of basal acid secretion did not affect the gastrointestinal motor profile regardless of their specific modes of action. Cimetidine had only slight effects on spiking activity induced by pentagastrin and no effects on changes in slow-wave frequency suggesting that histamine is not the common stimulator of motility changes induced by pentagastrin. Duodenal alkalization is unlikely to be a major cause of motility changes following antisecretory drugs. Cimetidine decreases acid-secretion yet has little effect on either slow-wave frequency or spiking activity. Possibly duodenal alkalization was involved in the more rapid return to a normal pattern of cyclic activity after pentagastrin infusion when cimetidine or proglumide has also been infused.

Both antigastrins reduced the pentagastrin-induced increase in slow-wave frequency and antral spiking activity, suggesting that antigastrins exert their effects by blocking the receptors on the smooth muscle as the cholinesterase inhibitor prostigmine did not alter responses to pentagastrin. The antigastrinic motor effect of proglumide is confirmed by the decrease of pentagastrin-stimulated duodenal and jejunal spiking activity. The direct (pharmacological) stimulatory action of CMN 131 probably masked these antigastrinic effects.

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RESUME

Bueno, L. et Garcia-Villar, R., 1979. Motricité gastro-intestinale et sécrétion acide de l'estomac chez le chien. *Vet. Sci. Commun.*, 3: 249-256, (en anglais).

L'influence de la sécrétion acide de l'estomac sur la motricité gastroduodénale a été évaluée chez le chien par électromyographie. L'administration intraveineuse (10 mg.kg^{-1}) de trois antisécrétoires possédant respectivement une action anti- H_2 (cimetidine), antigestrinique (proglumide) ou mixte (CMN 131) n'affecte pas le profil d'activité rapide (spikes) et les ondes lentes de l'antré et du duodénum à l'exception du CMN 131 qui provoque une hyperactivité duodénale.

L'infusion de pentagastrine ($3 \text{ } \mu\text{g.kg}^{-1}.\text{h}^{-1}$) augmente respectivement de 25 et 30% la fréquence des ondes lentes et celles des salves de potentiels de l'antré. L'infusion simultanée de proglumide ou de CMN 131 ($10 \text{ mg.kg}^{-1}.\text{h}^{-1}$) est capable de réduire significativement cette hypermotricité antrale.

Ces données suggèrent que les effets moteurs observés après modification des sécrétions acides de l'estomac sont liés à l'intervention de la gastrine.