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Effect of Calcium Channel Blockers on Postprandial Gastrointestinal Motility in the Dog

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Abstract—We have compared the ability of nifedipine and lacidipine, a new 1,4-dihydropyridine, to interfere with postprandial gastrointestinal motility. Five conscious dogs, fitted with 8 bipolar electrodes along the gastrointestinal tract, were studied. Gastrointestinal spike activity was evaluated by means of a computer system. Lacidipine (8 $\mu g\ kg^{-1}$) was administered as an i.v. bolus immediately followed by a 10 $\mu g\ kg^{-1}\ h^{-1}$ i.v. infusion for 3 h, starting 30 min before a standard meal. This dose of lacidipine decreased systolic blood pressure by approximately 20%. Nifedipine was used at equihypotensive doses (30 $\mu g\ kg^{-1}$ i.v. bolus followed by 300 $\mu g\ kg^{-1}\ h^{-1}$ i.v. infusion). Lacidipine had no effect on either gastric or intestinal postprandial spike activity. Nifedipine significantly delayed the appearance of the fed pattern and reduced the number of spikes in the small bowel, while it had no effect on gastric spike activity. We conclude that equihypotensive doses of lacidipine and nifedipine differ in their effects on the gastrointestinal tract, lacidipine having a better cardiovascular selectivity profile than nifedipine, and that the sensitivity to nifedipine varies in different parts of the gut.

Fasting gastrointestinal motor activity is characterized by a cyclical pattern, the so-called migrating motor complex (MMC (Szurszewski 1969)). This cyclical pattern in some species, including man and dog, is interrupted by feeding, which initiates a period of irregular spike activity (fed pattern) within a few minutes (Weisbrodt 1987).

Currently available calcium channel blockers, besides their well-known effects on vascular smooth muscle, also have a marked effect on intestinal smooth muscle (Narducci et al 1985; Godfraind et al 1986; Prior et al 1987). Previous studies performed in our laboratory have shown that equihypotensive doses of three prototype calcium channel blockers (nifedipine, verapamil and diltiazem) inhibit fasting intestinal spike activity to a different extent (De Ponti et al 1989). Thus, it can be hypothesized that these agents may, in part, differ in their pharmacological profile. Indeed, lacidipine, a new 1,4-dihydropyridine calcium entry blocker with potent and long lasting antihypertensive activity (Micheli et al 1990), had no effect on fasting intestinal spike activity at doses endowed with a significant hypotensive effect (Toson et al 1990). These findings prompted us to investigate further the gastrointestinal action of nifedipine and lacidipine and to extend our studies to the postprandial state, which is prevalent during daytime. To this end, we compared the effects of equihypotensive doses of the two agents on postprandial gastric and intestinal motility in the dog.

Materials and Methods

Experimental model

Experiments were carried out on five female mongrel dogs, 13–16 kg, purchased from Allevamento Alserio (Castelgabbiano, Italy). The animals were operated on with aseptic techniques and assisted respiration under general thiopentone anaesthesia (25 mg kg^{-1}, i.v.). Through a midline laparotomy, 8 bipolar electrodes (nichrome wire, 0·12 mm diam., Driver Harris, Rho, Italy) were implanted along the stomach and the small bowel. The position of the electrodes was as follows: (i) gastric electrodes—E_1: distal corpus, 7 cm proximal to the pylorus; E_2: proximal antrum, 4 cm proximal to the pylorus; E_3: distal antrum, 1 cm proximal to the pylorus. (ii) Duodenal electrodes (E_4 and E_5)—10 and 20 cm from the pylorus, respectively. (iii) Jejunal electrodes (E_6, E_7 and E_8)—15, 30 and 45 cm from the ligament of Treitz, respectively.

Connecting wires were then exteriorized through a subcutaneous tunnel in the midscapular region.

Experimental procedure

Experiments were performed on conscious animals, allowing at least 15 days for recovery after surgery. Before each experimental session, the dogs were fasted for at least 18 h.

Myoelectrical activity was recorded by means of a multichannel recorder (R711, Sensormedics, Anaheim, CA, USA) with a time constant of 0·03 s and simultaneously digitized by a computerized system (De Ponti et al 1988a, b).

At the beginning of each study, fasting myoelectrical activity was monitored until the appearance of an activity front (phase III of the MMC). An intravenous line was then established for drug administration. Infusions of pharmacological agents or vehicle (6 mL h^{-1}, Perfusor Secura, Braun, Milan, Italy) were started after the end of phase III at the most distal electrode and were maintained for 3 h. A standard meal (one can of Ciappi Partners, Unisabi, St Denis de l'Hôtel, France) was given 30 min after the start of the intravenous infusion. This meal was invariably consumed within 2 min.

The cardiovascular effects of the pharmacological agents were also assessed. Heart rate and systolic blood pressure were taken with the tail-cuff method (Blood Pressure

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Recorder, model 8005, Basile, Comerio, Italy) at the following times: 0 (control, immediately before drug administration), 15, 30, 60, 120 and 180 min.

Pharmacological agents

Lacidipine (Glaxo, Verona, Italy) and nifedipine (Sigma, St Louis, Missouri, USA) were dissolved in ethanol (5 mg mL^{-1}) and diluted to the final concentration in a vehicle containing 30% polyethylene glycol and 70% 0·9% NaCl (v/v) (saline). It had previously been verified that this vehicle had no effect on the parameters to be studied. Since lacidipine and nifedipine are photosensitive, all solutions were prepared under sodium light and then administered by means of syringes protected by aluminium foil (bolus injections) or using opaque infusion sets (Perfusor syringe and tubing, Braun, Milan, Italy).

The doses were: lacidipine 8 $\mu g\ kg^{-1}$ i.v. bolus immediately followed by 10 $\mu g\ kg^{-1}\ h^{-1}$ i.v. infusion for 3 h; nifedipine 30 $\mu g\ kg^{-1}$ i.v. bolus immediately followed by 300 $\mu g\ kg^{-1}\ h^{-1}$ for 3 h. These doses were chosen on the basis of previous dose-response studies in renal hypertensive dogs, where it was found that they lowered systolic blood pressure by approximately 30% (Micheli et al 1990 and unpublished data). Administration by i.v. bolus followed by continuous infusion was preferred in order to minimize the possible interference of pharmacokinetic differences between the two drugs.

Experimental design

Each dog acted as its own control, i.e. spike activity parameters obtained during treatments were compared with those calculated during vehicle administration. An interval of at least three days was allowed between two experimental sessions with the same dog.

Data analysis

Myoelectrical signals were analysed by means of an upgrade of a software detailed elsewhere (De Ponti et al 1988a, b), which automatically calculated the number of spikes for a given unit of time (30 s or 30 min in the present experiments, see Results section). The beginning of the fed pattern was identified by the occurrence of a period of at least 4 min when spike activity had the features of the fed pattern (i.e. the percentage of slow waves with superimposed spikes exceeded 20% on at least three channels).

For each experimental condition, means ($\pm$s.e.m.) were calculated and compared with one-way analysis of variance applying the Bonferroni's correction for multiple comparisons. $P<0·05$ was considered significant.

Results

Gastrointestinal effects

In all dogs, feeding disrupted MMC cycling and induced the fed pattern (Fig. 1) with a latency of 4·9 $\pm$ 0·8 min.

Lacidipine had no effect on either latency for induction of the fed pattern (4·8 $\pm$ 0·8 min) or spike activity (Fig. 2). The total number of spikes in the postprandial period did not significantly differ from control in the stomach (Fig. 3) or in the small bowel (Fig. 4).

Nifedipine significantly delayed the appearance of the fed pattern after the standard meal (latency 12·1 $\pm$ 1·7 min, $P<0·01$ vs control) and significantly ($P<0·01$) reduced postprandial spike activity in the small bowel (Figs 4, 5), while it had no effect on gastric spike activity (Fig. 3).

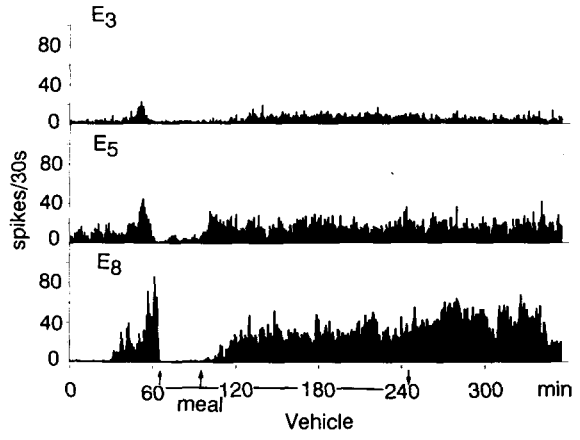

FIG. 1. Effect of vehicle on gastrointestinal spike activity in one representative animal. Note the occurrence of an activity front (phase III) before the start of the infusion and induction of the fed pattern by the standard meal.

Cardiovascular effects

The cardiovascular effects of lacidipine and nifedipine are reported in Table 1. Blood pressure was reduced to the same extent by lacidipine and nifedipine and remained fairly constant throughout the infusion period. Both drugs significantly increased heart rate.

Discussion

Studying the actions of calcium channel blockers in non-vascular areas can give useful information on possible side effects as well as on new therapeutic applications. Indeed, gastrointestinal motor disturbances are frequently reported side effects of calcium channel blockers (Krebs 1983) when they are used to treat cardiovascular disorders. On the other hand, nifedipine and nicardipine reduce the colonic motor

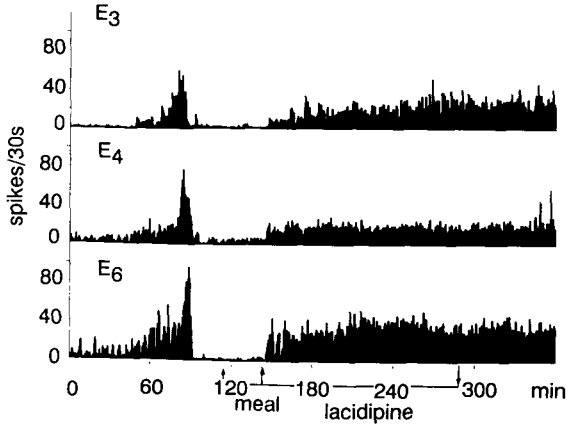

FIG. 2. Effect of lacidipine (8 $\mu g\ kg^{-1}$ i.v. bolus followed by 10 $\mu g\ kg^{-1}\ h^{-1}$ for 3 h) on gastrointestinal spike activity in one representative animal. Note lack of effect of lacidipine on the fed pattern.

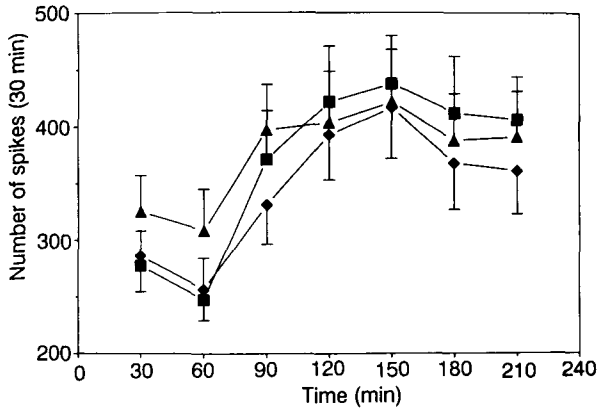

FIG. 3. Effect of lacidipine (◆) and nifedipine (▲) on canine postprandial gastric spike activity. Note lack of effect of lacidipine and nifedipine. ■ = vehicle control. Time 0 corresponds to feeding; drug infusion was started at −30 min and stopped at 150 min (see experimental procedure). Each point represents the grand mean (±s.e.m., n = 5) of the mean number of spikes calculated, in each dog, for the 3 gastric electrodes in the corresponding 30 min interval.

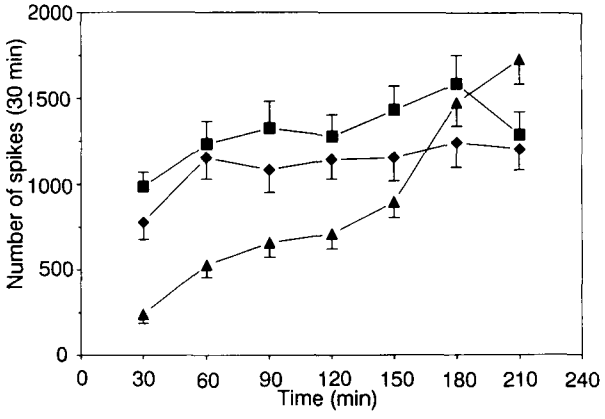

FIG. 4. Effect of lacidipine (◆) and nifedipine (▲) on canine postprandial intestinal spike activity. Note lack of effect of lacidipine while nifedipine significantly ($P < 0.01$) reduced the spike activity. ■ = vehicle control. Time 0 corresponds to feeding; drug infusion was started at −30 min and stopped at 150 min (see experimental procedure). Each point represents the grand mean (±s.e.m., n = 5) of the mean number of spikes calculated, in each dog, for the 5 intestinal electrodes in the corresponding 30 min interval.

response to feeding (Narducci et al 1985; Prior et al 1987), but their use in the treatment of bowel motility disorders would be hampered by their hypotensive effects.

The present study has shown that equihypotensive doses

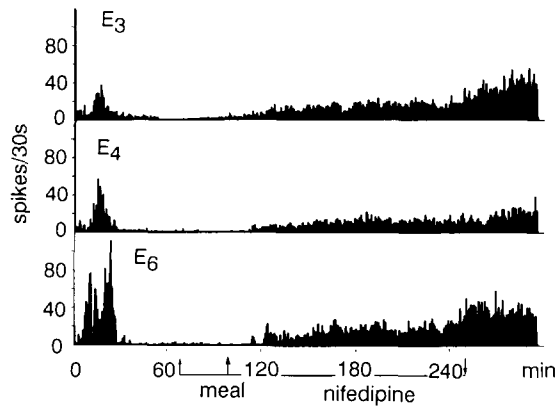

FIG. 5. Effect of nifedipine (30 μg kg^{-1} i.v. bolus followed by 300 μg kg^{-1} h^{-1} for 3 h) on gastrointestinal spike activity in one representative animal. Note delayed appearance of the fed pattern after the standard meal and reduced spike activity during nifedipine infusion.

of lacidipine and nifedipine differ in their effects on the gastrointestinal tract. While nifedipine significantly reduced postprandial intestinal motility, lacidipine had no effect. These results are in good agreement with those obtained in the rat where lacidipine exhibited gastrointestinal effects, but at doses 5–50 times higher than those having antihypertensive activity (Toson et al 1990). In conscious, normotensive dogs, other calcium channel blockers (nifedipine, verapamil and diltiazem) significantly decreased fasting intestinal spike activity at doses lowering systemic blood pressure by 10–20% (De Ponti et al 1989). The fact that lacidipine, in the same in-vivo model (i.e. fasting conscious dog (Toson et al 1990)), had no effect, taken together with the data presented in this paper, suggests a more favourable cardiovascular selectivity profile for lacidipine.

Two mechanisms may be postulated for the inhibition by nifedipine of the postprandial intestinal spike activity: (1) direct action on smooth muscle cells via inhibition of calcium influx through voltage-sensitive calcium channels, which is probably the major mechanism, since nifedipine is one of the most effective agents in inhibiting calcium currents in smooth muscle cells (Mitra & Morad 1985); (2) modulation of transmitter release. The latter, however, seems unlikely since type N calcium channels, which are known to play an important role in transmitter release from nerve terminals (Hirning et al 1988), are almost insensitive to dihydropyridines.

Table 1. Effect of calcium channel blockers on systolic blood pressure and heart rate.

	Time (min)					
	0	15	30	60	120	180
Nifedipine (30 μg kg^{-1} + 300 μg kg^{-1} h^{-1})						
Systolic blood pressure (mm Hg)	137 ± 3	108 ± 3*	109 ± 2*	106 ± 2*	106 ± 2*	107 ± 3*
Heart rate (beats min^{-1})	84 ± 5	168 ± 6*	170 ± 5*	165 ± 4*	163 ± 7*	166 ± 4*
Lacidipine (8 μg kg^{-1} + 10 μg kg^{-1} h^{-1})						
Systolic blood pressure (mm Hg)	136 ± 4	107 ± 3*	103 ± 2*	106 ± 2*	103 ± 2*	105 ± 2*
Heart rate (beats min^{-1})	82 ± 4	174 ± 8*	173 ± 6*	171 ± 4*	168 ± 6*	171 ± 6*

Values are means (±s.e.m., n = 5); *$P < 0.01$ vs time 0.

It remains to be determined why nifedipine significantly reduced intestinal spike activity without affecting gastric spike activity. Both in-vitro (Coruzzi & Poli 1987; Lecchini et al 1991) and in-vivo (De Ponti et al 1989) data indicate that nifedipine is one of the most potent calcium channel blockers in inhibiting intestinal motility. On the other hand, nifedipine does not affect gastric emptying of liquids or solids (Traube et al 1985), an observation consistent with the present data, which suggest that type L calcium channels have only a minor, if any, relevance in generating postprandial gastric spike activity. Both influx of extracellular calcium and calcium release from intracellular stores seem to contribute to initiate contraction in corporal and antral smooth muscle (Bitar et al 1986; Collins 1986; Szurszewski 1987). A different contribution of different mechanisms in generating the postprandial spike activity in the stomach with respect to the small bowel might explain the lack of effect of nifedipine on gastric spike activity. Indeed, the change in pattern induced by feeding is brought about by several interacting factors, both locally (because of the presence of intraluminal contents) and at distant sites via neural pathways or hormones (Wingate et al 1978; Weisbrodt 1987).

In conclusion, the present study has shown that calcium channel blockers may differ in their pharmacological profile in different systems in-vivo: while nifedipine had both cardiovascular and intestinal effects, lacidipine exhibited a higher degree of selectivity for the cardiovascular system. Furthermore, the sensitivity to dihydropyridines may vary in different parts of the gut.

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