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Effect of intra-colonic nicardipine on colonic motility in irritable bowel syndrome

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SUMMARY

Intravenous nicardipine has previously been shown to abolish the effect of a 1000-calorie meal on colonic motility. The purpose of this study was to use the same experimental design to assess the effect of nicardipine instilled directly into the colon. Each patient was studied three times when receiving either placebo, 15 mg or 30 mg nicardipine infused over 2 h. Blood concentrations of nicardipine remained very low, but neither dose of the drug affected either basal or post-prandial colonic motility. Topical nicardipine does not appear to have therapeutic potential and its activity is probably dependent on systemic absorption.

INTRODUCTION

Nicardipine, a new dihydropyridine calcium channel-blocker, is a potent hypotensive agent via its effect on relaxation of vascular smooth muscle. Gastrointestinal smooth muscle contraction is also dependent upon calcium ion influx across the cell membrane[1] and, therefore, this group of drugs may also influence gut motility. Intravenous nicardipine has been previously shown to abolish the colonic motor response to food in patients with irritable bowel syndrome[2] and may therefore have therapeutic potential in this condition. However, oral administration of this and other calcium antagonists for therapy of irritable bowel syndrome may be severely limited by vascular side-effects. If these drugs could be shown to be

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surface-acting with respect to the colon, without systemic absorption, a delivery system could be devised to avoid these adverse effects. The purposes of this study were to establish whether nicardipine is active when applied to the surface of the colon and to ascertain the degree of drug absorption from this route of administration.

MATERIALS AND METHODS

Six patients with the irritable bowel syndrome (five women, one man: age range 24–64 years) were studied. The irritable bowel syndrome was diagnosed on clinical history and normal investigations including contrast radiology or colonoscopy. Symptoms had been present for 3–10 years.

Each subject was studied on three occasions separated by at least 7 days. Before the study days all medication was discontinued for 48 h and subjects fasted overnight. Without bowel preparation, a triple lumen polyethylene catheter was inserted using a colonoscope and the openings position 30, 25 and 20 cm above the anal verge. Ten minutes after insertion, the catheter was perfused in random order with either placebo, 15 mg nicardipine (low dose) or 30 mg nicardipine (high dose) in 300 ml of buffer solution. This resulted in calculated intracolonic concentrations of 50 mg/L (0.05 mg/ml, low dose) and 100 mg/L (0.1 mg/ml, high dose) delivered to the colon at a total of 2.5 ml/min. Perfusion was maintained using an Arndorfer capillary infusion system.

Twenty minutes after catheter insertion (10 min after the start of drug perfusion) motility recording was commenced. A 30 min baseline fasting period was documented then patients were given a standard 1000-calorie liquid meal consisting of 200 g double cream flavoured with one sachet of Build Up (Carnation Ltd, Croydon, UK). Colonic motor activity was recorded for a further 60 min.

Venous blood samples for serum nicardipine levels were obtained at catheter insertion and 30, 60, 90 and 120 min later. Pulse and blood pressure were also measured at these times.

Changes in colonic intraluminal pressure were recorded on a Lectromed multichannel pen recorder (Ormed Ltd, Welwyn Garden City, UK). For each of the three recording levels, the number of contractions and motility index (the sum of amplitude/2 × length of contraction) were calculated over a 10 min interval. The results at each level were then summated to obtain an overall value. Baseline motility values were summated over the whole 30-min period then divided by 3 to produce activity indices over 10 min. As the numbers of contractions, motility indices and serum nicardipine concentrations were all found to have positively skewed distributions, they were converted to natural logarithms for statistical evaluation. The two motility variables were analysed individually using a two-factor repeated measures analysis of variance and the Tukey multiple comparison test. The two factors evaluated were nicardipine dose (0, 15 or 30 mg) and assessment time (10-min intervals). The results of the statistical analyses have been detransformed into the original units for presentation; mean values are reported along with their 95% confidence limits. Statistical significance was set at the conventional 5% level throughout.

Table 1. Mean motility indices and numbers of contractions over time (with 95% confidence limits)

Time periods post-meal (min)	No. contractions			Motility index		
	Placebo	Low-dose nicardipine	High-dose nicardipine	Placebo	Low-dose nicardipine	High-dose nicardipine
Baseline	5.5 (1.7–14.7)	10.2 (3.6–26.3)	6.6 (2.1–17.4)	443 (98–1997)	361 (81–630)	443 (98–1997)
0–10	15.6 (5.8–39.2)	7.6 (2.6–19.9)	12.2 (4.4–31.1)	1078 (239–4855)	736 (163–3313)	924 (205–4162)
10–20	10.5 (3.7–26.9)	5.0 (1.5–13.6)	13.9 (5.2–35.2)	955 (213–4302)	191 (42–865)	1174 (260–5286)
20–30	13.9 (5.2–35.2)	4.1 (1.1–11.3)	15.4 (5.8–38.9)	1443 (320–6495)	461 (88–2398)	1456 (323–6554)
30–40	8.1 (2.8–21.1)	3.3 (0.8–9.7)	16.3 (6.1–40.9)	376 (83–1696)	85 (18–387)	1403 (311–6316)
40–50	7.8 (2.6–20.4)	12.1 (4.4–30.9)	22.7 (8.0–61.6)	434 (96–1958)	800 (177–4324)	2170 (417–11277)
50–60	11.9 (4.3–30.3)	4.5 (1.3–12.4)	8.4 (2.2–26.8)	837 (160–4352)	106 (20–554)	1729 (205-14500)

Table 2. Plasma nicardipine concentrations after intra-colonic infusion (ng/ml)

Time (min)	Low dose	High dose
0	< 1	< 1
30	0.68 (0–2.94)	0.56 (0–2.28)
60	1.76 (0.06–6.20)	3.98 (0.94–11.80)
90	2.41 (0.16–8.97)	5.31 (1.19–17.21)
120	2.39 (0.09–9.56)	10.47 (4.22–24.17)

Mean (95% confidence limits). $n = 6$.

RESULTS

Motility index and number of contractions per 10-min period are shown in Table 1. Both the baseline and post-prandial parameters of motility were not significantly different during colonic infusion of either placebo or nicardipine. The post-prandial rise in motility after low-dose nicardipine appeared to be slightly blunted, but this was well within the variability of the method and thus not significant. No significant difference in pulse or blood pressure was observed during any treatment phase and no side-effects recorded.

Mean serum nicardipine concentrations are given in Table 2. Peak blood levels occurred 2 h after infusion but absorption was both low and variable. Thus with

15 mg nicardipine (low dose) infusion blood concentrations were less than 3 ng/ml during most of the study. Nicardipine (30 mg) (high dose) instilled directly into the colon also resulted in low serum concentration, less than 10 ng/ml during the peak of post-prandial motility.

DISCUSSION

Nicardipine, a potent calcium antagonist, when delivered directly into the distal colonic lumen, does not influence fasting colonic motility nor prevent the post-prandial rise in motility. Intravenous nicardipine[2] and both oral nifedipine and nicardipine[3,4] preparations, however, do reduce colonic and anorectal motility after a meal. Thus the failure in this study to observe a similar effect on motility with colonic infusion, without significant absorption, suggests systemic absorption is necessary for activity. Serum concentrations achieved after oral or intravenous dosing are substantially higher than those observed after direct colonic instillation in this study. Thus a single oral dose of 30 mg nicardipine resulted in peak serum concentration approaching 100 ng/ml, over seven times the peak concentration from the same intracolonic dose.[5] Further, an intravenous nicardipine infusion of 5 mg/h resulted in 2-h peak concentrations of over 100 ng/ml[5]. This compares with peak concentrations of 4 ng/ml with 7.5 mg/h perfused directly into the distal colon. The absence of detectable cardiovascular changes during colonic infusion of nicardipine also suggests that little is absorbed.

If calcium antagonists were found to be effective in irritable bowel syndrome, their topical application, either by suppository or delayed-release capsule, is a possible way of avoiding systemic side-effects. The results of this study suggest that this route of administration is not promising for nicardipine.

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REFERENCES

1 Karaki H, Weis G B. Calcium channels in smooth muscle. Gastroenterology 1984; 87: 960–70.
2 Prior A, Harris S R, Whorwell P J. Reduction of colonic motility by intravenous nicardipine in irritable bowel syndrome. Gut 1987; 28: 1609–12.
3 Sun W M, Edwards C A, Read N W. Effects of nicardipine on anorectal function in normal controls and IBS patients. Gut 1987; 28: 1364. (Abstract.)
4 Narducci F, Bassotti G, Garburri M, Faroni F, Morelli A. Nifedipine reduces the colonic motor response to eating in patients with irritable colon syndrome. Am J Gastroenterol 1985; 80: 317–9.
5 Graham D, Dow R, Freedman D, Mroszczak E, Ling T. Pharmacokinetics of nicardipine following oral and intravenous administration in man. Postgrad Med J 1984; 60 (Suppl. 4), 7–10.