

LIVER, BILIARY, AND PANCREAS

Controlled study of the effect of nifedipine and ceruletide on the sphincter of Oddi

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Abstract

Although sphincter of Oddi dysfunction is a recognised cause of post cholecystectomy pain, the control mechanisms involved in sphincter of Oddi function are poorly understood. Pharmacological relaxation of the sphincter of Oddi may have a beneficial effect particularly in sphincter of Oddi dysfunction where basal sphincter pressure is high. The aim of this study was to investigate the effects of calcium channel blockade (nifedipine) and synthetic cholecystokinin (ceruletide) on sphincter of Oddi pressures. Nineteen patients (median age 49 years; range 21-75) attending for routine endoscopic retrograde cholangio-pancreatographic (ERCP) examination were studied. No patients with evidence of sphincter of Oddi dysfunction were included in the study. Each patient was randomly allocated to receive a three minute intravenous infusion of nifedipine 3 mg (six) ceruletide 5 ng/kg (seven) or placebo (six). Endoscopic biliary manometry was done with recording of basal sphincter of Oddi pressures, sphincter of Oddi phasic wave amplitude and frequency before and after intravenous infusions. In the nifedipine group patients showed a decrease in both basal and phasic amplitude sphincter of Oddi pressure (mm Hg) from the preinfusion values (mean (SEM)) of 24.7 (3.6) and 112.3 (13.4) to 12.9 (2.9) ($p < 0.01$) and 89.9 (12.4) ($p < 0.03$) after infusion respectively. Ceruletide produced a decrease in sphincter of Oddi phasic wave frequency (c/min) from 3.4 (0.3) before infusion to 2.6 (0.5) after infusion ($p < 0.05$). We conclude that nifedipine effectively decreases sphincter of Oddi pressure. This drug may therefore be of value in the treatment of sphincter of Oddi dysfunction where raised sphincter pressures are thought to be the primary pathogenic feature.

pharmacological relaxation of the sphincter of Oddi may be of value. Cholecystokinin and its synthetic analogue ceruletide (CCK-10) are known to have a relaxant effect on the sphincter of Oddi.¹³⁻¹⁵ Calcium channel blockade relaxes smooth muscle and may also have a relaxant effect on the sphincter of Oddi.¹⁶ This effect, however, has had only limited study in man.¹⁷

The aim of this study was therefore to investigate the effect of nifedipine, a calcium channel blocker on sphincter of Oddi function and to compare this with ceruletide acting as standard and saline acting as placebo.

Methods

STUDY DESIGN

This was a randomised three group parallel study carried out single blind but using a double observer technique. There was both a placebo control, saline and a standard control, ceruletide (CCK-10). For each patient the study was performed before ERCP. The patients were randomly allocated to receive intravenously either nifedipine 3 mg (group 1), ceruletide 5 ng/kg (group 2) or saline (group 3). All the infusions were made up to 20 ml and administered over a three minute period by an independent observer. The effect of each infusion on sphincter of Oddi pressures was monitored by endoscopic biliary manometry. In addition patients had blood pressure and heart rate measured throughout the study. Neither the endoscopist nor the manometry physician was aware of the patient's grouping before analysis.

Biliary manometric readings were taken for two minutes before and two minutes after the infusion of the study drug.

MANOMETRIC TECHNIQUE

Endoscopic biliary manometry was undertaken with an Arndorfer based capillary perfusion system with a reservoir pressure of 400 mm Hg and flow rate of 0.25 ml/minute of distilled water.⁷ Standard polyethylene triple lumen

Sphincter of Oddi dysfunction has been implicated in patients with postcholecystectomy pain,¹⁻³ and recurrent idiopathic pancreatitis.⁴ Despite recent advances in diagnostic techniques⁵⁻⁷ its true prevalence in these conditions remains undetermined. Although the pathogenesis of this condition is unclear manometric studies have suggested that it may represent a smooth muscle disorder.^{6,9} Despite this current treatment of the condition relies on sphincter pressure ablation by either surgical¹⁰ or endoscopic means.^{11,12} It is possible, however, that

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TABLE I Study exclusion criteria

Ischaemic heart disease
Left ventricular impairment
Hepatic disease
Diabetes
Suspected sphincter of Oddi dysfunction
Previous gastric surgery

TABLE II Demographic details of study groups

	Nicardipine (Group 1) (n=6)	Ceruletide (Group 2) (n=7)	Placebo (Group 3) (n=6)
Age median (range)	45 (38-56)	56 (33-75)	59 (21-72)
Sex (female)	4	5	4
Weight (kg) median (range)	72 (55-90)	62 (49-75)	67 (50-89)
Previous cholecystectomy	1	3	3
Final clinical diagnosis	Choledocholithiasis (2) IBS* (3) Oesophagitis (1)	Choledocholithiasis (1) Cholelithiasis (1) Cholangitis (1) IBS (4)	Choledocholithiasis (2) IBS (3) Oesophagitis (1)

*Irritable bowel syndrome

catheters were used (Arndorfer Medical Specialities Inc, Greendale, Wisconsin, USA) with an outer diameter of 1.7 mm and an inner luminal diameter of 0.5 mm. Performance of the recording system was tested by measuring the post occlusion pressure rise rate of the perfused catheter system.¹⁸ Under study conditions this gave a satisfactory post occlusion pressure rise rate of 450 mm Hg/s. Biliary manometry was done after an overnight fast just before ERCP under light diazepam sedation only (5-10 mg iv). No analgesia or smooth muscle relaxants were used. Active sphincter segment pressure recordings were taken for eight to nine minutes before confirmation of the catheters position by contrast injection.

PATIENTS

All patients aged between 16 and 80 years attending for routine ERCP were considered for study entry although predetermined exclusion criteria were applied (Table I).

Nineteen patients, 13 women, six men with a median age of 49 years (range 21-75) were entered into the study. All patients had been referred for routine ERCP and agreed to participate in the study before this examination. The demographic details of these 19 patients randomly allocated to receive nicardipine (group 1) (six), ceruletide (group 2) (seven) and saline (group 3) (six) are shown in Table II. Twelve patients had a normal subsequent ERCP, five had common bile duct stones, one had intrahepatic sclerosing cholangitis and one patient had gall bladder stones. Previous studies have shown similar sphincter of Oddi pressure profiles in patients with and without common bile duct stones.^{19,20} All patients gave their written informed consent before study entry which was approved by the local hospital Ethical Committee.

ANALYSIS

Endoscopic biliary manometry

Sphincter of Oddi pressures were analysed for the pre and post infusion periods with duodenal pressure referenced as 0. Basal pressure was defined as the mean pressure at the base of phasic amplitude contractions over the two minute recording period. Phasic amplitude pressure was defined as the mean amplitude pressure wave rise above basal over the two minute recording period. The frequency of phasic contractions

was defined as the mean cycles per minute over the two minute recording period. Each of these parameters was calculated and compared for the pre and post infusion period.

Manometric analysis was performed without knowledge of the patients drug grouping.

STATISTICAL ANALYSIS

For each measurement, differences between the preinfusion and post infusion values were calculated and the three treatment groups were compared with respect to these changes using a one-way analysis of variance model. The statistical significance of each of the three paired comparisons was assessed along with an estimate of the mean treatment difference and its 95% confidence interval.

For each of the three treatment groups, the within group changes between preinfusion and post infusion were analysed, for each of the 0 pressure measurements, using the paired *t* test. All statistical tests were two tailed with significance taken at the 5% level ($p < 0.05$).

Results

BASAL SPHINCTER OF ODDI PRESSURE

Intergroup comparison of the difference between preinfusion and post infusion measurements showed no difference between nicardipine and ceruletide, while both active treatment were significantly different from placebo (nicardipine $p = 0.01$, ceruletide $p = 0.02$). The mean treatment difference between nicardipine and placebo was 16.3 mm Hg, with a 95% confidence interval of 4.4 to 29.1 mm Hg. The mean treatment difference between ceruletide and placebo was 14.4 mm Hg, with a 95% confidence interval of 2.5 to 26.3 mm Hg.

In the nicardipine group, all patients showed a decrease in basal sphincter pressure (mm Hg) from the preinfusion values of 24.7 (3.6) (mean (SEM)) to 12.9 (2.9) after infusion. The decrease of 11.8 mm Hg was significant ($p < 0.01$) (Fig 1). Similarly, in the ceruletide group, all patients except one showed a decrease in basal sphincter pressure from the preinfusion values of 21.9 (4.1) to 12.5 (3.2) after infusion (Fig 1). The mean decrease of 9.5 mm Hg was not significant. One patient had a paradoxical increase in basal sphincter pressure from 15.5 before to 30.8 after ceruletide infusion. This patient was included in the analysis and may be the reason for the lack of a significant result. In the placebo group compared with the preinfusion values of 15.8 (1.3) patients showed a small increase in basal sphincter pressure after infusion to 20.7 (1.3) (Fig 1). The mean increase of 4.9 mm Hg was significant ($p < 0.05$).

PHASIC AMPLITUDE PRESSURE (mm HG)

Intergroup comparison of the differences between preinfusion and post infusion measurements showed no difference between nicardipine and ceruletide. The mean difference of 35.5 mm Hg (95% confidence interval of -3.8 to 74.8 mm Hg) between nicardipine and placebo was not

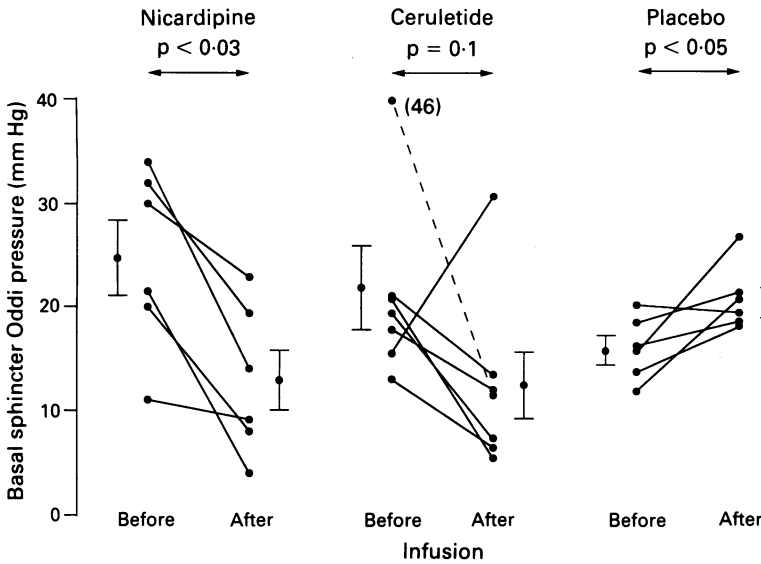


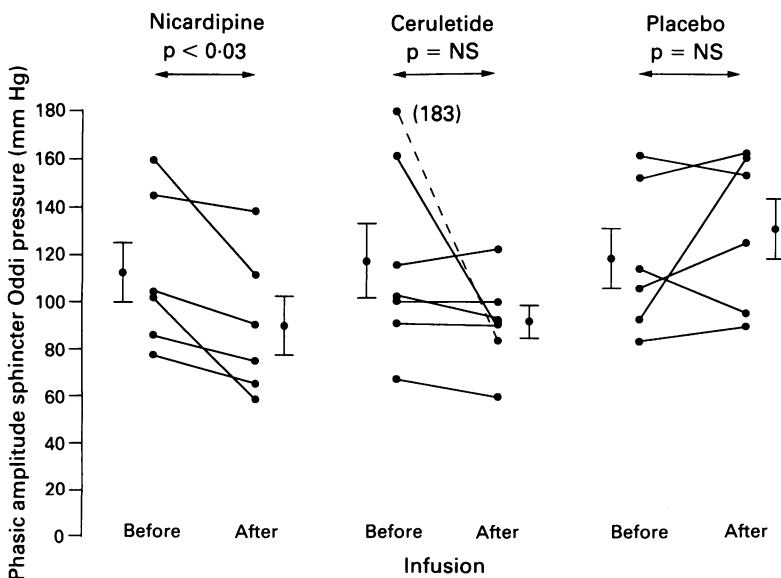
Figure 1: Basal sphincter of Oddi pressures (mm Hg) before and after intravenous infusions of nicardipine 3 mg (group 1), ceruletide 5 ng/kg (group 2) or saline (group 3) Bar=mean (SEM).

significant. The mean difference of 38.6 mm Hg (95% confidence interval of 0.6 to 76.5 mm Hg) between ceruletide and placebo was significant ($p < 0.05$).

In the nicardipine group, all patients showed a decrease in phasic pressure (mm Hg) from the preinfusion values of 112.3 (13.4) to 89.9 (12.4) after infusion (Fig 2). The mean decrease of 22.4 mm Hg was significant ($p < 0.03$). Similarly, in the ceruletide group, five of the seven patients showed a decrease in phasic pressure after infusion (Fig 2). The mean decrease of 25.5 mm Hg in phasic pressure in the ceruletide group was not significant. In the placebo group, four of the six patients showed an increase in phasic pressure post infusion compared with preinfusion (Fig 2). The mean increase of 13.0 mm Hg was not significant.

FREQUENCY OF PHASIC SPHINCTER OF ODDI WAVES
Comparison between treatment groups of the differences between preinfusion and post infusion measurements showed no significant differences between nicardipine and ceruletide, nicardipine and placebo or between ceruletide and placebo. There was no difference in phasic

Figure 2: Phasic amplitude sphincter of Oddi pressures (mm Hg) before and after intravenous infusions of nicardipine 3 mg (group 1), ceruletide 5 ng/kg (group 2) or saline (group 3)



wave frequency (c/min) after nicardipine (4.2 (0.5)) or saline (4.2 (0.8)) compared with the respective preinfusion values (4.0 (0.6) and 4.8 (0.5)). In the ceruletide group phasic frequency decreased from 3.4 (0.3) before to 2.6 (0.5) after infusion ($p < 0.05$).

SYSTEMIC BLOOD PRESSURE

In the nicardipine group, systolic blood pressure showed a mean decrease of 18.0 mm Hg between baseline and 10 minutes ($p < 0.05$). There were no changes seen after ceruletide or placebo compared with preinfusion values. No complications or significant side effects were noted in either group throughout the study.

Discussion

This study has shown that nicardipine decreases sphincter of Oddi pressure in man. This effect of nicardipine was similar to the reduction in sphincter of Oddi pressure noted with ceruletide (CCK-10) which has known direct relaxant effects on the sphincter of Oddi.

Nicardipine is a dihydropyridine class of calcium blocker which produces smooth muscle relaxation by inhibiting transmembrane Ca^{2+} influx in smooth muscle cells.²¹ Although its effect is primarily on vascular smooth muscle it has a similar gastrointestinal effect.^{22,23} Its effect on sphincter of Oddi function has not been studied before.

Ceruletide is a synthetic decapeptide first identified from extracts of the Australian hylid frog which has potent cholecystokinin effects.¹⁴

The factors involved in the control of sphincter of Oddi function in man are poorly understood although it is regulated by both neural²⁴ and hormonal²⁵ mechanisms. Cholecystokinin is the most important regulatory hormone in sphincter of Oddi relaxation.²⁵ This effect of cholecystokinin is mediated by a stimulation of inhibitory non-adrenergic, non-cholinergic interneurons which supply the sphincter of Oddi.²⁶ This enhanced inhibitory neural discharge overcomes the direct smooth muscle stimulant effect of cholecystokinin leading to sphincter relaxation. In the absence of these intramural interneurons or in conditions of enhanced cholecystokinin receptor sensitivity cholecystokinin may produce paradoxical sphincter of Oddi contraction. Whether this sequence of events occurs in biliary dyskinesia and may therefore be detected by cholecystokinin provocation¹⁵ remains unknown. It is interesting that in our study the one patient to show paradoxical cholecystokinin sphincter contraction also had the highest cholecystokinin plasma concentrations. It also appears that this single paradoxical sphincter response to cholecystokinin may have been the reason for our failure to demonstrate a significant relaxant effect in this group.

Sphincter of Oddi dysfunction is a recognised cause of post cholecystectomy pain in an estimated 10–20% of cases,³ a prevalence which may increase as diagnostic techniques improve. Although the pathophysiology of this interesting condition remains unclear, a significant proportion have reversible elevated sphincter

pressures or a paradoxical response to cholecystokinin (dyskinesia)^{6,27} suggesting smooth muscle hypertonicity may be involved in its pathogenesis. This abnormality may in fact exist before cholecystectomy although only limited evidence exists.²⁸ The treatment of sphincter of Oddi dysfunction at present relies entirely on sphincter of Oddi pressure ablation by surgical¹⁰ or endoscopic means.^{11,12} Current evidence, however, suggests that patients with the dyskinetic pattern of sphincter of Oddi dysfunction may not respond to sphincter division.⁹ As endoscopic sphincterotomy has a small but significant morbidity pharmacological intervention would be more appropriate in patients with sphincter of Oddi dyskinesia. Only one case report, however, exists on drug treatment of this condition.²⁹

We have shown in this study that pharmacological relaxation of the sphincter is possible with calcium channel blockade, an effect which may have therapeutic potential in sphincter of Oddi dysfunction. A previous manometric study has suggested that nifedipine also produces sphincter of Oddi relaxation.¹⁷ Additional similar studies have indicated that nitrates,³⁰ and anticholinergics³¹ may also relax the sphincter of Oddi. The current controlled study, however, has confirmed that calcium channel blockade with nicardipine results in as effective sphincter of Oddi relaxation as produced by cholecystokinin. Nicardipine, however, is a primary vascular smooth muscle relaxant designed for its cardiovascular effect. The introduction of new specific calcium channel antagonists designed to relax gastrointestinal smooth muscle may be more efficacious without cardiovascular side effects.

The small increase noted in basal sphincter of Oddi pressure after saline infusion is interesting and may suggest a spasmogenic effect of the distilled water used in the catheter infusion. This effect may explain the increased incidence of acute pancreatitis after endoscopic biliary manometry.³²

In conclusion this study has shown that nicardipine effectively decreases basal and phasic amplitude sphincter of Oddi pressures. This effect was similar to that shown with ceruletide. Nicardipine may therefore be of value in the treatment of sphincter of Oddi dysfunction where raised sphincter pressures are thought to be the primary pathogenic feature.

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