Topical diltiazem and bethanechol decrease anal sphincter pressure without side effects

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Abstract

Background—Topical nitrates lower anal sphincter pressure and heal anal fissures, but a majority of patients experience headache. The internal anal sphincter has a calcium dependent mechanism to maintain tone, and also receives an inhibitory extrinsic cholinergic innervation. It may therefore be possible to lower anal sphincter pressure using calcium channel blockers and cholinergic agonists without side effects.

Aims—To investigate the effect of oral and topical calcium channel blockade and a topical cholinomimetic on anal sphincter pressure.

Methods—Three studies were conducted, each involving 10 healthy volunteers. In the first study subjects were given oral 60 mg diltiazem or placebo on separate occasions. They were then given diltiazem once or twice daily for four days. In the second and third studies diltiazem and bethanechol gels of increasing concentration were applied topically to lower anal pressure.

Results—A single dose of 60 mg diltiazem lowered the maximum resting anal sphincter pressure (MRP) by a mean of 21%. Once daily diltiazem produced a clinically insignificant effect but a twice daily regimen reduced anal pressure by a mean of 17%. Diltiazem and bethanechol gel produced a dose dependent reduction of the anal pressure; 2% diltiazem produced a maximal 28% reduction, and 0.1% bethanechol a maximal 24% reduction, the effect lasting three to five hours.

Conclusions—Topical diltiazem and bethanechol substantially reduce anal sphincter pressure for a prolonged period, and represent potential low side effect alternatives to topical nitrates for the treatment of anal fissures.

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Keywords: diltiazem; bethanechol; anal sphincter pressure; anal fissures

Chronic anal fissures have traditionally been treated by surgical division of the internal anal sphincter, causing a fall in anal canal pressure and allowing fissure healing. However, faecal incontinence can follow the procedure. Because of the possibility of permanent soiling or occasional major incontinence after surgical treatment,^{1,2} alternative treatments for this painful condition were sought. The discovery of nitric oxide as a major inhibitory neurotransmitter, involved in internal anal sphincter

relaxation, presented such an opportunity. Topical glyceryl trinitrate (GTN), a nitric oxide donor, has been shown to reduce anal pressure³ and heal chronic anal fissures in a majority of patients,^{4,5} thus becoming a first line treatment. Although effective, treatment with topical GTN is accompanied by the side effect of headache in a large number of patients. It would therefore be advantageous if an alternative therapy for lowering anal pressure could be devised which is equally effective as GTN, but without the side effects.

There are at least two important mechanisms by which this might be achieved. A calcium dependent mechanism is required to maintain internal sphincter smooth muscle tone, and calcium channel blockers cause relaxation of gastrointestinal smooth muscle.^{6,7} Sublingual nifedipine has been shown to lower the resting anal sphincter pressure in both controls and patients with anal disease,⁸ although the therapeutic effect on these anal conditions was not studied. Oral diltiazem has also been shown to reduce the resting anal pressure.⁹

A second important mechanism involves the sacral parasympathetic cholinergic innervation which is inhibitory to the internal anal sphincter.¹⁰ Cholinomimetics such as carbachol and bethanechol relax internal anal sphincter smooth muscle in vitro¹¹ via muscarinic receptors.¹²

We have explored the possible use of a calcium antagonist and cholinomimetic to lower anal sphincter pressure. We investigated the effect of oral diltiazem against placebo, as well as topical gels containing varying concentrations of diltiazem and bethanechol, on the resting anal sphincter pressure of healthy adult volunteers, with a view to determining the dose-response characteristics of these agents.

Materials and methods

Three studies were conducted. Ten healthy volunteers with no anorectal disease were recruited for each of the oral and topical diltiazem studies and 10 further volunteers for the bethanechol study. Each subject underwent anal manometry using an eight channel water perfused catheter. A station pull through technique was used to determine the maximum resting anal pressure (MRP); recordings were taken over five minutes until a steady reading was obtained. Anodermal blood flow was measured using a DRT4 laser Doppler flowmeter (Moor Instruments, Devon, UK), and expressed as flux (ml/min/mm Hg/100 ml

Abbreviations used in this paper: GTN, glyceryl trinitrate; LAS, lateral internal sphincterotomy; MRP, maximum resting anal sphincter pressure.

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Figure 1 Resting anal sphincter pressure in response to oral placebo* and 60 mg diltiazem†. * $p=0.4$, 97 (17) v 94 (16) cm H₂O, pre- versus post-treatment mean (SD) maximal resting pressure (MRP) (ANOVA); † $p<0.0001$, 97 (17) v 77 (11) cm H₂O.

tissue). Ethical approval was obtained from the regional ethical committee.

ORAL DILTIAZEM

Ten subjects (seven men) aged 24–53 years (median 44) were studied. All subjects were given a placebo tablet or 60 mg diltiazem on two separate occasions. Measurements of MRP and anodermal blood flow as well as pulse rate and blood pressure were taken before and one hour after ingestion of each tablet. On a separate occasion, each subject was given 60 mg diltiazem once daily for four days and measurements taken at the end of this period. Recordings were taken one hour after the morning dose on the fourth day. Further readings were taken before and after a further four days during which the subjects were given 60 mg diltiazem twice daily. Dose and period of administration of diltiazem were based on the known effect in cardiovascular disease and known drug half life (4–6 hours).¹³

TOPICAL DILTIAZEM GEL

Five men and five women aged 20–49 years (median 30) were studied. Concentrations of 0.1%, 0.5%, 1%, 2%, 5%, and 10% wt/vol diltiazem gel and placebo gel were made up. All gels looked identical, and were supplied in identical tubes. A 2.5 cm (0.5 ml) application of gel provided a measured dose of diltiazem. The gels were formulated to enhance skin permeability. They were applied in a double blind manner; the investigator was given a gel at random by the research assistant who kept the identity of the gel concealed until the end of the study. Gel was applied to the anal margin, not into the anal canal. As with oral dosing, readings of resting anal sphincter pressure and anodermal blood flow were taken before and one hour after each application of gel. If a particular gel produced an effect after one hour, subsequent recordings were made at two hourly intervals thereafter until the readings returned to the baseline pressure recorded prior to the application of the gel.

TOPICAL BETHANECHOL GEL

The 10 subjects (six women) were aged 21–49 years (median 36). Concentrations of 0.05%, 0.1%, 0.5%, and 1% bethanechol gel, equivalent to doses of 0.2 mg, 0.4 mg, 2 mg, and 4 mg

bethanechol, respectively, were tested. The study was otherwise identical in methodology to the diltiazem gel study described above.

STATISTICAL ANALYSIS

Statistical analysis was undertaken using analysis of variance (ANOVA) to determine whether there was a significant effect of the dose of diltiazem or bethanechol on sphincter pressure and anodermal blood flow, or whether the variation in measurements observed was due to variation between individuals. Two analyses were performed, looking at blood flow and sphincter pressure separately. A value of $p<0.05$ was considered significant.

Results

ORAL DILTIAZEM

There was negligible (3%) reduction in the mean MRP one hour after placebo ($p=0.4$). Diltiazem produced a 21% reduction ($p<0.0001$) in the mean MRP (fig 1). Once daily diltiazem did not produce a sustained effect, lowering the MRP by 5% only ($p=0.2$). There was no reduction in arterial blood pressure with this regimen. The twice daily regimen of diltiazem produced a 17% reduction in the MRP ($p=0.0003$), although in two subjects there was no effect. In addition, although there was only minimal reduction of the mean arterial blood pressure (from 148/88 to 143/92, mean of 10 subjects) with twice daily diltiazem, two subjects did complain of troublesome postural dizziness. These were the only side effects reported. There was no significant difference between the mean anodermal blood flow before and after either dose of diltiazem or placebo.

TOPICAL DILTIAZEM GEL

Placebo produced a 5% reduction in the MRP (105 (12) versus 100 (12) cm H₂O, pre- versus post-treatment, mean MRP (SD), $p=0.19$). Diltiazem gel produced a dose dependent reduction of the MRP with concentrations of 1% and above up to a maximum effect. Two per cent diltiazem gel produced a maximal effect of 28% reduction in the MRP (105 (12) versus 76 (11), $p<0.0001$). Higher concentrations produced no additional effect (fig 2). Repeat measurements showed a sustained inhibition of the resting anal sphincter tone for a period of three to five hours after a single

Figure 2 Diltiazem gel dose-response curve in 10 healthy volunteers. * $p<0.0001$, maximal resting pressure (MRP) compared with pretreatment MRP (ANOVA).

Figure 3 Duration of action of 2% diltiazem gel following a single application in 10 healthy volunteers. MRP, maximal resting pressure.

Figure 4 Bethanechol gel dose-response curve in 10 healthy volunteers. * $p < 0.0001$, maximal resting pressure (MRP) compared with pretreatment MRP (ANOVA).

Figure 5 Duration of action of 0.1% bethanechol gel following single application in 10 healthy volunteers. MRP, maximal resting pressure.

application of 2% diltiazem gel (fig 3). There was no change in the anodermal blood flow with either placebo or diltiazem, and no local or systemic side effects were reported.

TOPICAL BETHANECHOL GEL

As with diltiazem there was a dose dependent reduction of the MRP with bethanechol gel. Maximal effect was produced by the 0.1% gel which lowered MRP by 24% (108 (12) versus 82 (11) cm H₂O, pre- versus post-treatment, mean MRP (SD), $p < 0.0001$). Higher doses did not produce a greater effect (fig 4). A single application of bethanechol resulted in a decrease in MRP sustained for four (range 3–5) hours (fig 5). No side effects were reported.

Discussion

Patients with anal fissure have an abnormally high resting anal sphincter pressure.¹⁴ Healing and relief of symptoms is usually associated with reduction of the maximum resting anal sphincter pressure,¹⁵ and lateral internal sphincterotomy (LAS) and manual anal dilatation have been used to achieve this.^{16,17} However, it is increasingly recognised that there is an appreciable morbidity following these procedures.¹

In this study we have shown that oral diltiazem, and both topical diltiazem and bethanechol, can lower the resting anal sphincter pressure. Oral diltiazem produced a decrease in the resting anal tone which was not sustained with a once daily dose; the twice daily regimen produced a moderate anal sphincter relaxation but caused side effects in two subjects. The topical preparations were more effective in lowering anal pressure, and were not associated with side effects, these two features suggesting that they are the preferred mode of administration. We have also determined the optimal doses of these agents (2% diltiazem gel and 0.1% bethanechol gel) to achieve sphincter relaxation, and showed a duration of action of several hours. The absence of side effects is presumably due to low systemic absorption of the small doses applied locally.

Topical nitric oxide donors have been used to heal successfully up to two thirds of chronic anal fissures.⁵ However, side effects such as headaches and dizziness are common with nitrates, which may limit their application and reduce patient compliance. In addition, tolerance to nitrates is well recognised¹⁸ and this may be a problem with their use for treatment of fissures.⁴ Injectable botulinum toxin can also lower resting anal pressure and allow fissure healing¹⁹ but it is expensive and care needs to be taken with this potentially toxic therapy. This study has shown that topical diltiazem and bethanechol can substantially lower the resting anal pressure for several hours. These new agents should now be considered as low side effect alternatives to nitric oxide donors. Their further evaluation in controlled studies, either separately or in combination as a single topical agent, are now needed to substantiate their value in clinical practice for the treatment of anal fissures.

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