Topical 0.2 Percent Glyceryl Trinitrate Ointment Has a Short-Lived Effect on Resting Anal Pressure


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PURPOSE: Glyceryl trinitrate ointment applied to the anal verge lowers anal resting pressure, but its duration of action is uncertain. This study investigated the effect and duration of action of 0.2 percent glyceryl trinitrate on anal resting pressure and hemodynamic parameters. METHODS: A total of 15 volunteers, 9 male, with a median age of 30 (range, 20–71) years, underwent continuous static anal manometry using a solid state catheter for ten minutes before and two hours after applying 0.2 percent glyceryl trinitrate ointment to the anoderm with a gloved finger. Pulse and blood pressure were recorded every 15 minutes. RESULTS: A significant reduction in maximal anal resting pressure compared with preglyceryl trinitrate values was observed at 15, 30, 45, 60, and 90 minutes after application, but no significant difference thereafter. There was no significant change in pulse during the study. Systolic and diastolic blood pressures dropped significantly after application of glyceryl trinitrate, but had recovered and were not significantly different from original values after 90 minutes. A significant fall in blood pressure did not correlate with the onset or duration of side effects. CONCLUSIONS: Continuous static manometry (as opposed to interval measurements reported in previous studies) demonstrates that 0.2 percent glyceryl trinitrate ointment significantly lowers anal resting pressure, but only for 90 minutes. Twice daily application of topical 0.2 percent glyceryl trinitrate ointment heals two-thirds of fissures after eight weeks, but the apparently short duration of action may indicate that more frequent application might heal more fissures, more rapidly. [Key words: Glyceryl trinitrate; Internal anal sphincter; Anal resting pressure; Anal fissure; Duration of action]

Topical glyceryl trinitrate (GTN) ointment is widely used as the first line treatment for chronic anal fissure; twice daily application of 0.5 g of GTN is reported to heal up to two-thirds of fissures.1–3 GTN is metabolized at a cellular level to release nitric oxide, the nonadrenergic noncholinergic neurotransmitter identified as mediating relaxation of the internal anal sphincter.4, 5 The resultant reduction in anal resting pressure (RAP) is associated with an increase in local blood flow,6, 7 and this is likely to be important in promoting fissure healing.

Sublingual GTN in treatment of angina pectoris provides rapid symptomatic relief during an acute attack, but is known to have a short duration of action on vascular smooth muscle.8, 9 Topical GTN ointment has been shown to have a more prolonged effect, reducing blood pressure for up to seven hours,10 but the duration of action of topical GTN ointment on the internal anal sphincter is uncertain. Two studies, using different concentrations and doses of GTN applied to different sites (intra-anally and externally), have reported greatly different durations of action of GTN of 48 minutes and 9 hours.

There are no reports of attempts to determine whether the onset or duration of side effects after topical application of GTN to the anoderm correlates with significant changes in hemodynamic parameters or side effects. This study aimed to determine the duration of the effect of GTN on the RAP in healthy volunteers monitored continuously using static anal manometry for two hours and to identify any corresponding changes in hemodynamic parameters and any correlation with the onset and duration of side effects.

PATIENTS AND METHODS

Nottingham Medical School Ethics Committee approval was obtained, and 15 healthy volunteers were recruited to the study having given informed written consent. Persons with a known allergy or sensitivity to GTN or on any medication were excluded, as were pregnant or breast-feeding women.

Subjects had a solid state anal manometry catheter with four anal pressure sensors arranged radially...
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(Gaeltec, Isle of Skye, UK) positioned to record maximal RAP and secured in place by taping to the skin. After 10 minutes, having obtained steady state readings of anal canal pressure, subjects applied 1 cm (approximately 0.5 g) of 0.2 percent GTN ointment (2 percent Percutol®, Cusi, Hazelmere, Surrey, UK, diluted to 0.2 percent in soft white paraffin in the Pharmacy Department, University Hospital, Nottingham, UK) to the distal anal canal and anal margin using a gloved finger. Continuous static anal manometry was performed for two hours after application of GTN with patients lying on one side. Anal pressures for each of the four radial pressure sensors on the anal manometry catheter were determined from the pressure trace at 15-minute time intervals: the mean anal pressure over a 10-minute period centered on times t = 0, 15, 30, 45, 60, 75, and 90 minutes was calculated using Flexisoft III software (Oakfield Instruments, Whitney, Oxfordshire, UK). A mean of these four values was then calculated to give a single value for anal resting pressure at each time interval.

Measurements of pulse and blood pressure were recorded, with subjects lying on their sides, before the application of GTN and then at 15-minute intervals during the study. The onset and duration of side effects were recorded.

Statistical Analysis

Statistical analysis was with the Wilcoxon’s signed-rank test to compare pre and post-GTN RAP, pulse, and blood pressure. Pearson’s correlation test was used to identify any correlation between the onset and duration of headaches and changes in blood pressure.

RESULTS

Fifteen volunteers, 9 male, with a median age of 30 (range, 20-71) years participated in the study. A significant reduction in maximal RAP compared with pre-GTN values was observed at 15, 30, 45, 60, 75, and 90 minutes after application of GTN ointment, but no significant difference thereafter (Fig. 1 and Table 1). Systolic blood pressure was significantly reduced after 30 minutes and diastolic pressure after 15 minutes; both were no longer significantly lower than pre-GTN values by 90 minutes (Fig. 2 and Table 1). Six volunteers developed light-headedness or headaches after administration of GTN, but a significant fall in blood pressure did not correlate with either the onset or duration of side effects.

DISCUSSION

In this study topical application of 0.5 g of 0.2 percent GTN ointment to the distal anal canal and anal margin caused a significant reduction in RAP within 15 minutes of administration, but this effect was not sustained beyond 90 minutes. These findings contradict previous reports of a greatly longer duration of action of topical 0.2 percent GTN in which a significant reduction in RAP was observed as long as nine hours after application of GTN. In that study, measurements were made in only two patients after an

<table>
<thead>
<tr>
<th>Time post-GTN (min)</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>75</th>
<th>90</th>
<th>105</th>
<th>120</th>
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<tbody>
<tr>
<td>RAP</td>
<td>0.002</td>
<td>0.005</td>
<td>0.026</td>
<td>0.029</td>
<td>0.011</td>
<td>0.014</td>
<td>0.112</td>
<td>0.306</td>
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<tr>
<td>Pulse</td>
<td>0.777</td>
<td>0.074</td>
<td>0.783</td>
<td>0.629</td>
<td>—</td>
<td>0.211</td>
<td>—</td>
<td>0.055</td>
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<tr>
<td>Systolic blood pressure</td>
<td>0.191</td>
<td>0.033</td>
<td>0.019</td>
<td>0.025</td>
<td>—</td>
<td>0.125</td>
<td>—</td>
<td>0.820</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.010</td>
<td>0.057</td>
<td>0.018</td>
<td>0.027</td>
<td>—</td>
<td>0.094</td>
<td>—</td>
<td>0.044</td>
</tr>
</tbody>
</table>

GTN = glyceryl trinitrate; RAP = resting anal pressure.