The anti-inflammatory and analgesic action of transdermal glyceryltrinitrate in the treatment of infusion-related thrombophlebitis

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Summary: We have carried out a prospective double-blind randomized study in 40 patients with infusion-related thrombophlebitis. Twenty-two patients were included in the glyceryltrinitrate (GTN) ointment group and 18 patients in the control heparinoid group. Pain was assessed by an analogue scale. At 48 hours the analgesic index was 84.6 ± 18 units with GTN and 49 ± 45 units with heparinoid ointment ($P < 0.01$). Faster relief of oedema was also observed in the GTN-treated group. All signs of thrombophlebitis were relieved in less than 4 days in the GTN group compared with 9 days in the controls ($P < 0.005$). We conclude that transdermal GTN is useful therapy for infusion-related thrombophlebitis showing evidence of anti-inflammatory and analgesic effect.

Introduction

Infusion-related thrombophlebitis ('thrombophlebitis') occurs in between 30 and 70% of intravenous infusions in hospital.^{1–3} The origin could be injury of the endothelium produced by the catheter, chemical damage induced by pharmacological substances or infection through the catheter.⁴ Treatment has included local heat, elevation of the extremity, anti-inflammatory non-steroidal drugs and sometimes transdermal heparinoid substances, although these measures have only doubtful beneficial effects.^{5–8}

Recently good results have been obtained in preventing thrombophlebitis using transdermal glyceryltrinitrate (GTN)^{9,10} but until now its effects as a treatment of thrombophlebitis were unknown.

The vascular endothelium produces nitric oxide, a vasodilator substance,¹¹ which also regulates the interaction of platelets with each other and with the vascular endothelium.^{12,13} Nitric oxide (NO) also has other actions not related to the cardiovascular system.¹⁴ Many vasodilator substances act by inducing the liberation of this potent mediator by the vascular endothelium. Nitrovasodilators, including GTN, act independently of the endothelium, by

releasing NO.¹⁵ Both endothelium-derived and GTN-derived NO act via a second messenger, guanosine-3', 5'-cyclic monophosphate (cGMP).¹⁵

To test whether GTN has anti-inflammatory and analgesic effects, we conducted a prospective double-blind randomized and controlled clinical study in patients with infusion-related thrombophlebitis, comparing transdermal GTN treatment against a control group that was treated with an ointment of heparinoid substance (sulphuric polyholoside ester sodium salt, SPE). We also measured changes in the urinary levels of cGMP induced by the treatment.

Patients and methods

The study was carried out using patients from different units of the hospital, all of whom had developed a thrombophlebitis of a superficial forearm vein during a therapeutic venous infusion. Thrombophlebitis was defined as the presence of two or more of the following signs: pain, local warmth, erythema, local oedema and/or palpable venous cord. The patients had not received any previous treatment for thrombophlebitis. After patient acceptance they were included in the previously randomized group. It was accepted by the ethical committee and we obtained an informed consent of all patients.

The exclusion criteria applied were: local infection, hypovolaemia and arterial hypotension,

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severe renal failure, glaucoma, hypersensitivity to nitrates or anti-inflammatory drugs, and cases treated previously for thrombophlebitis with another drug.

Patients were evaluated before treatment was initiated and every 24 hours until complete healing of thrombophlebitis, recording every sign as present or not. Pain was assessed in an analogue scale.¹⁶ An analgesic index was calculated using the formula: $100 - ((\text{post-treatment pain intensity/pre-treatment pain intensity}) \times 100)$. The results were considered excellent when the values were over 75%, good if they were between 75 and 50%, reasonable when they were between 49 and 25%, and bad when lower than 25%.

The severity of signs allowed thrombophlebitis to be graded into five stages as follows: Grade I, pain, without other inflammatory signs; Grade II, pain with erythema or swelling; Grade III, pain, erythema, oedema and a palpable venous cord extending less than 5 cm; Grade IV, all signs of Grade III in a extension of more than 5 cm with perivein induration; and Grade V adds frank vein thrombosis with or without suppuration. Grade I thrombophlebitis was rejected for study.

For analysis of the results the number of days required for complete disappearance of symptoms was assessed. The assessment was made blindly by the same clinical investigator in each case every 24 hours after ointment application.

On the basis of a previous pilot study, GTN ointment as a 2% gel solution was used at a daily dose of 12 mg (2 cm), applied gently without massage along the surface of the swelling. An occlusive bandage to prevent evaporation was not used. The control group was treated with SPE ointment of identical physical characteristics to those of the GTN ointment, using the same technique.

Urinary cGMP was measured by direct radioimmunoassay using the kit furnished by Advanced Magnetics Inc., Cambridge, USA. In all patients urine was collected during one hour before and during an hour after the first application of the ointment. Urine creatinine was determined by a Hitachi 737 autoanalyser. The results are expressed as the ratio cGMP/creatinine (Cr).

Group data are expressed as mean $\pm$ standard deviation. Differences between the groups in cGMP levels were analysed using a Student's *t*-test. Differences between treatment results in both groups of patients were tested by the non-parametric Mann-Whitney's rank-sum test. The level of significance was $P < 0.05$. The calculations were made using BMDP statistical programme 1990, for personal computers.¹⁷

Results

Forty-seven patients were admitted to this study. Of these, seven patients were excluded, three because they were discharged from the hospital before the last evaluation and four because the protocol was not completed. The study population consisted of 40 patients; 20 men and 20 women, mean age 60.5 ± 19.4 years. The group treated with transdermal GTN comprised 22 patients and 18 were treated with SPE. Table I gives the baseline characteristics including pain and severity of the thrombophlebitis, drugs used in venous infusion, days of venous infusion, previous thrombophlebitis and delay in treatment after diagnosis. There was no significant difference between the groups.

Follow-up for complete disappearance of signs of the thrombophlebitis in each group is shown in Figure 1. In the GTN group 18 patients show disappearance of all signs of thrombophlebitis in 1-2 days (82%) while only six patients (33%) ($P < 0.05$) were healed in the SPE group at the time. All patients in the GTN group were free of signs of thrombophlebitis within 4 days. In the SPE group 10 patients (56%) required between 4 and 9 days for complete disappearance of signs of thrombophlebitis ($P < 0.005$).

The reduction in pain was significantly higher in the GTN group than in the SPE group. The analgesic index was 84.6 ± 18 (excellent) at 48 hours in the GTN group, compared with $49 \pm 45\%$ (reasonable) in the SPE group ($P < 0.01$).

The basal level of urinary cGMP in the SPE group was $1,447.6 \pm 1,134.3$ pmol/mg Cr and

Table I Baseline characteristics of superficial thrombophlebitis. Data are given as mean $\pm$ standard deviation.

	Group GTN (n = 22)	Group SPE (n = 18)
Grade II	7	5
Grade III	5	5
Grade IV	7	6
Grade V	3	2
Pain (analogue scale)	71.4 ± 24.0	73.5 ± 18.6
Days of venous infusion	3.27 ± 2.1	2.55 ± 1.2
Delay in treatment (hours)	21.09 ± 9.1	22.8 ± 8.5
Type of cannula		
Abbotcat/Drum	16/6	15/3
Intravenous solution		
Dextrose	18	10
Glucosaline	3	7
Saline	1	1
Drugs		
KCl	4	6

GTN = glyceryltrinitrate; SPE = sulphuric polyholoside ester sodium salt

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Figure 1 Follow-up of patients treated with topical glyceryltrinitrate (solid columns) versus sulphuric poly-holositide ester (hatched columns). The columns represent the number of patients each day in whom there are still signs of thrombophlebitis.

1,448.2 $\pm$ 1,674 pmol/mg Cr in the GTN group. After application of ointment the levels were: 1,575.2 $\pm$ 1,146 pmol/mg Cr in the SPE group and 1,507.7 $\pm$ 1,703.1 pmol/mg Cr in the GTN group. There were no significant differences.

Two patients in the GTN group experienced headache as a side effect.

Discussion

Infusion-related thrombophlebitis is a common disturbance that exhibits different degrees of inflammatory symptoms.¹⁻⁴ Reports of the prevention of thrombophlebitis with GTN patches have been published,^{9,10} but it has not been shown until now that GTN could reverse the inflammatory signs of thrombophlebitis.

The development of infusion-related thrombophlebitis is independent of whether its cause is mechanical or chemical. Sometimes it is cured spontaneously in a few days, but generally it is treated with a number of different approaches, such as local heat, non-steroidal anti-inflammatory substances and semi-synthetic transdermal heparinoid substances.⁴⁻⁸

In this study we demonstrate that treatment of thrombophlebitis with transdermal GTN was more effective than the heparinoid SPE, which is commonly used in this condition.^{7,8} The time to resolution of phlebitis with SPE was similar to that which would be achieved without the use of pharmacologically active agents.⁸

The superficial vein when inflamed is easily reached by the transdermal action of GTN. The absorption of transdermal GTN is dependent on the areas of application, the blood flow in the skin and the degree of evaporation.¹⁸ Cardiovascular effects can be observed between 15 and 60 minutes after application of 2% gel at doses of 12.5–50 mg;

the maximum effect is obtained between 30 and 60 minutes, and blood levels of 3–9 ng/ml are reached one hour later and sustained for 3 hours. Furthermore, if the area of application is increased, a proportional increase in plasma levels of GTN is obtained.¹⁹

In 1987 Moncada *et al.*¹¹ demonstrated that nitric oxide is the endothelium-derived relaxing factor which is a potent endogenous vasodilator. Nitric oxide also affects platelet functions.^{12,13,20,21} Venous endothelium releases less NO than arterial endothelium²² and veins are more sensitive to exogenous NO.²³ These actions are mediated through the stimulation of the second messenger, the soluble guanylate cyclase system, thus elevating cGMP levels.¹⁴ In this context acetylcholine induces peripheral analgesia by increasing cGMP levels, via the generation of NO in presynaptic nerve terminals.²⁴ The L-arginine: NO pathway is also present in neutrophils and macrophages, but its biological significance remains to be elucidated.^{13,25,26}

The vasodilator action of GTN, like other nitrovasodilators, is due to its conversion to NO in a nonenzymatic reaction with cysteine.^{27,28} This generation of NO by GTN explains its endothelium-independent vasodilator action and its anti-aggregating properties on platelets.²⁹ These actions are well documented clinically, but until now anti-inflammatory and analgesic effects of GTN have not been shown.

The effectiveness of GTN could be due to different mechanisms, such as the vasodilator action on the venous system¹⁹ that produces a decrease in the vasoconstrictor tone induced by the inflammatory process, and could help to reduce the oedema. Endogenous NO modulate oedema formation^{30,31} but sodium nitroprusside (a direct exogenous NO donor) inhibits polycation-induced oedema.³¹ The effect of GTN on the thrombotic process (anti-adhesive and anti-aggregatory effects)¹⁴ could also contribute to the beneficial results obtained. Other mechanisms that may be involved include direct analgesic effect of NO in the peripheral nervous system, through the stimulation of postsynaptic fibres mimicking the actions of acetylcholine.²⁴

Our failure to find differences in urinary levels of cGMP in both treatment groups is in accordance with other studies showing that the infusion of GTN has no significant effect on plasma cGMP.³²

In conclusion we believe that the non-cardio-vascular effects, both anti-inflammatory and analgesic, that we have obtained with GTN, depend on a direct action on the vein and surrounding tissue inflammation. These data open up new therapeutic possibilities for GTN and related drugs.

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