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Local effect of transdermal isosorbide dinitrate ointment on hand vein diameter

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Abstract Objective: To assess the effect of topically applied isosorbide dinitrate (ISDN) ointment on superficial hand veins precontracted with phenylephrine. **Methods:** Using the hand vein compliance technique, venous diameter changes were measured in a double-blind, randomised, placebo-controlled cross-over trial in 12 healthy volunteers. During precontraction with phenylephrine, placebo or ISDN ointment was administered to assess the dilator effect of transdermal ISDN. Finally a single i.v. dose of nitroglycerine was administered into the hand vein to assess the maximal venous response to organic nitrovasodilators.

Results: ISDN ointment (equivalent to 13.4 ± 3.61 mg ISDN) caused a significant dilator effect of $39.1 \pm 21.7\%$ (mean \pm SEM, $P = 0.02$) which reached its maximum after 42.5 ± 16.6 min. Maximum ISDN effects were inversely correlated with venous baseline diameter ($r^2 = 0.38$, $P = 0.03$) and independent of the amount of ointment applied or the extent of precontraction ($P > 0.3$).

Conclusion: Similar to nitroglycerine, topical ISDN may relax superficial hand veins within 60 min after application, suggesting that it might ease venepuncture particularly of small vessels. The large variability of the effect and the time to reach the effect, however, restrict its practical usefulness.

Keywords Venodilation · Isosorbide dinitrate · Venous administration

Introduction

Venepuncture is still the most frequently used invasive procedure in hospitalised patients. While invariably associated with emotional distress for the patient, this procedure may also challenge physicians and nursing staff – particularly when the target veins are small and venous access is difficult. Because of the rich α -adrenergic innervation of superficial veins, activation of the sympathetic nervous system may profoundly reduce venous diameter [1] and thus modulate the ease of i.v. insertion of needles. Several previous studies have suggested that nitroglycerine may facilitate venepuncture when applied topically. Nitroglycerine efficiently reverses α -adrenergic venoconstriction [2, 3] by activation of the nitric oxide–cyclic guanosine monophosphate (NO-cGMP) cascade, a pathway which opposes α -adrenergic effects under physiological conditions. However, non-responders were frequent [4], the optimum timing with respect to nitrate application has not been established [4, 5, 6, 7, 8, 9, 10] and the extent of venodilation has not been thoroughly investigated. The aim of this study was therefore to quantify venous relaxation over time using a double-blind, placebo-controlled design. Because no studies with organic nitrates other than nitroglycerine have been published, we chose to study the effect of topical isosorbide dinitrate (ISDN) which may also penetrate intact skin after transdermal application [11, 12, 13].

Materials and methods

Individuals

Twelve healthy male non-smokers with a mean age of 25 years (22–32 years) and a mean body mass index of 23.3 kg/m^2 (21.8 – 25.8 kg/m^2) not taking any drugs were enrolled after full explanation of all study procedures and after they had given their written consent. The study was approved by the ethics committee of the University Hospital in Basel.

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Study protocol

This was a single-dose, double-blind, two-arm, placebo-controlled, randomised cross-over study. The two study parts were separated by a wash-out phase of at least 1 week. Drug effects were assessed using the dorsal hand vein compliance technique [14] with slight modifications as described recently [15]. First normal saline solution at a constant rate of 0.25 ml/min was infused and the vein's baseline diameter was determined (defined as 100%). Then increasing dose rates of the full selective α_1 -agonist phenylephrine were administered (250–8000 ng/min) to constrict the vessel to approximately 30% of its initial diameter. Once a stable response was reached (defined as 0% relaxation), the ointment (ISDN; Isoket, Schwarz Pharma, Switzerland) or matching placebo was applied using a flat-pointed spatula onto a skin area of approximately 1×1.5 cm. Diameter changes were then measured after 5, 10, 15, 20, 30, 40, 50 and 60 min. Finally, nitroglycerine (Perlinganit, Schwarz Pharma) was administered directly into the studied hand vein at a dose rate exerting maximum relaxation (1500 ng/min; [3]) to assess the maximum local venous response to organic nitrates (measurements after 5 min and 8 min). The ISDN dose was determined by measuring the weight of the ointment applied.

To rule out systemic cardiovascular effects, blood pressure and heart rate were measured repeatedly throughout the study and 3 h after application of ointment, and the volunteers were asked to report any adverse event until study termination.

Data analysis

Data are expressed as mean \pm SEM. Effects were compared using the paired student's *t*-test. Effects over time were compared using analysis of variance (ANOVA) for repeated measures. The relationship between hand vein diameter and ISDN effect was evaluated with linear regression analysis. A two-tailed *P* value of ≤ 0.05 was considered significant. The data were performed using Statview for Macintosh (Version 4.5, Abacus Concept Inc.).

Results

The study drugs were well tolerated; mild headaches occurred in two volunteers approximately 30 min after application of ISDN ointment. Before and after administration of placebo heart rate was 53.4 ± 2.0 and 55.6 ± 2.1 beats/min ($P=0.35$) and mean blood pressure was 86.8 ± 2.3 and 89.6 ± 2.5 mmHg ($P=0.06$), respectively. The respective values before and immediately after ISDN administration were 59.5 ± 2.4 and 57.0 ± 1.9 beats/min ($P=0.36$) and mean blood pressure was 87.6 ± 2.0 and 89.3 ± 2.4 mmHg ($P=0.22$). The diameter of the superficial hand vein under investigation before administration of any drug was similar in both treatment groups (placebo 1.25 ± 0.13 mm; ISDN 1.1 ± 0.16 mm; $P=0.31$). Also, precontraction of the veins with phenylephrine was similar in the two treatment groups (placebo $35.3 \pm 11.3\%$; ISDN $38.3 \pm 13.4\%$; $P=0.47$) as was the amount of ointment applied [placebo 159 ± 66.8 mg; ISDN 134.1 ± 36.1 mg (ointment containing 13.4 ± 3.6 mg ISDN); $P=0.08$]. Sixty minutes after the local application of ISDN, the vein was relaxed by $28.7 \pm 25.8\%$ (placebo $2.2 \pm 12.8\%$; $P<0.005$; Fig. 1) with a maximum of $39.1 \pm 21.7\%$ (range 13–72%). Expressed in absolute diameter changes, maximum ISDN-induced venodilation was 0.23 ± 0.12 mm and occurred after a lag time of

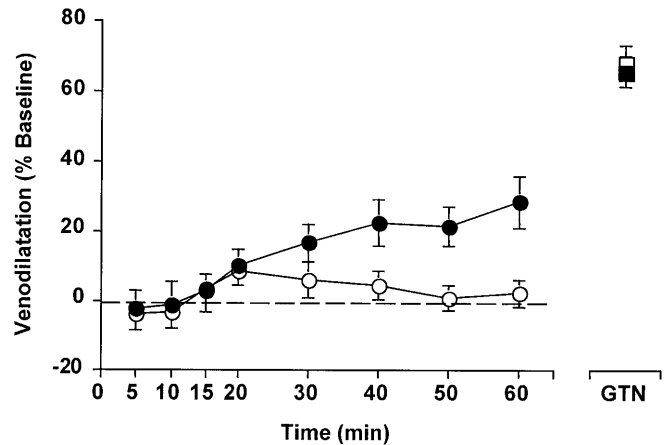


Fig. 1 Effect of topical isosorbide dinitrate (ISDN) or placebo on hand veins precontracted with phenylephrine in 12 healthy non-smokers. The vasodilator effect is expressed as percentage of the difference of vein diameter before drug administration (set as 100% relaxation) minus diameter during precontraction with phenylephrine (set as 0%). The dilator effect of ISDN was significantly different from the effect of placebo ointment (analysis of variance, $P=0.05$). As a control, infusion of nitroglycerine (GTN) into the precontracted hand vein markedly relaxed the veins in both groups

42.5 ± 16.6 min (range 10–60 min). In 4 of the 12 individuals, ISDN relaxed the vein under investigation by at least 50%; in an additional 6 volunteers, at least 25% venodilation was reached (Fig. 2). Maximum ISDN effects (expressed as percentage dilation) were inversely correlated with venous baseline diameter ($r^2=0.38$, $P=0.03$; Fig. 2) and independent of the amount of ointment applied or the extent of precontraction ($P>0.3$).

Nitroglycerine administered locally into the studied hand vein 60 min after ISDN or placebo application markedly relaxed the veins (placebo $68.3 \pm 5.3\%$; ISDN $66.0 \pm 4.4\%$; $P=0.76$).

Discussion

Access to the venous bed is a key requirement for both the diagnostic sampling of blood and the parenteral administration of drugs and fluids. Venepuncture may be difficult because of vasospastic states that are common in patients with activation of the sympathetic nervous system such as those with volume losses, pain or emotional distress. Organic nitrates have been shown to reverse the effect of the two main sympathetic mediators of vasoconstriction, norepinephrine [2] and neuropeptide Y [16], making them suitable candidates for venous relaxation under these conditions.

Several controlled and uncontrolled trials with different formulations of nitroglycerine have consistently shown that topical nitroglycerine may relax superficial veins when measured with subjective scores [5, 6, 7, 8] or when ease [5, 6, 8, 9, 10] or success of venepuncture were assessed [6].

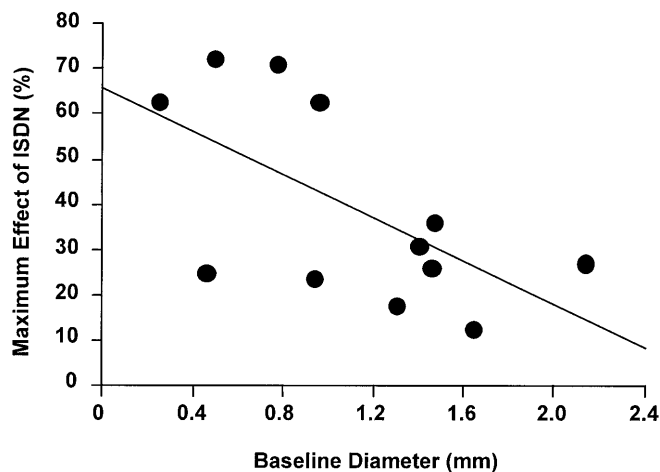


Fig. 2 Relationship between venous diameter at baseline, i.e. before drug administration, and maximum isosorbide dinitrate (ISDN)-induced relaxation of superficial hand veins precontracted with phenylephrine ($n = 12$; $r^2 = 0.38$, $P = 0.03$)

Thus far, nitroglycerine is the only organic nitrate studied in this regard and its effects have been evaluated 15 [4], 20 [6, 10], 60 [7, 8, 9] and 120 min [5] after local application of ointments or tape. Whenever and however measured, the effects were highly variable and the optimum time for nitroglycerine application before venepuncture has not been established. Moreover, only one study attempted to assess venous diameter changes objectively using a slide gauge 15 min after application of ointment. In this trial, vasodilator responses were found in only 34% of the patients [4] suggesting that either non-responders were frequent, the dose was too small or that the duration of treatment and/or effect was too short. Since nitroglycerine is a rather efficient vasodilator, it is also conceivable that some patients were relaxed, venous tone therefore minimal and its pharmacological reversal thus not evident.

In this study we therefore attempted to define the extent and time course of venous relaxation induced by topical nitrate application in superficial veins that were all precontracted with the α 1-selective adrenoceptor agonist phenylephrine. Because tissue metabolism of organic nitrates is excessive, it appeared possible that the local metabolism of organic nitrates might modulate local effects. We thus chose not to study nitroglycerine because its rather short half-life relative to other organic nitrates was suspected to be one of the reasons for the substantial variability of effects reported in previous studies. At the same time, we attempted to evaluate whether topical ISDN, which was known to penetrate the skin as well, would be a useful alternative to relax superficial veins.

This study revealed a significant vasodilator effect of ISDN ointment confirming the effectiveness of organic nitrates other than nitroglycerine. Indeed, administered at well below the therapeutic dose (<2% of regular dose), ISDN relaxed the vein on average by $39.1 \pm 21.7\%$. In the small vessels studied in this study, this resulted in an average absolute diameter change of

0.23 mm which almost equals the diameter difference between a 19-G and a 21-G needle. The fact that in one-third of the individuals the vein was almost completely relaxed (Fig. 2) indicates that important prerequisites for successful punctures are indeed met in a sizeable proportion of applications. Whether this translates into more successful venepunctures remains to be studied.

The primary endpoint of our study was ISDN-induced reversal of α -adrenergic precontraction which was inversely correlated with the size of the exposed vein. Our study design was not suitable to elucidate the mechanism of this correlation. However, because all volunteers were exposed to almost identical ISDN doses irrespective of the vessel size, we believe that a likely explanation is that smaller veins were exposed to relatively higher amounts of drug.

While it may not be excluded that in some volunteers vasodilation will further increase beyond the observation period, effects occurring later than 1 h after administration were considered impractical in a clinical setting. The time course of ISDN-induced relaxation with rather late occurrence of the maximum effect renders this procedure not suitable for those states that require immediate intervention. Topical application of ISDN ointment may, however, be helpful in the many instances in which venepuncture can be planned (e.g. before regular surgery or in hospitalised patients) because the extent of effect observed in this study suggests that ISDN may indeed facilitate venepuncture particularly in smaller vessels which are more difficult to access.

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