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Local effect of transdermal isosorbide dinitrate ointment on hand vein diameter

Abstract Objective: To assess the effect of topically applied isosorbide dinitrate (ISDN) ointment on superficial hand veins preconstricted 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 preconstriction 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 ± 21.7% (mean ± SEM, P = 0.02) which reached its maximum after 42.5 ± 16.6 min. Maximum ISDN effects were inversely correlated with venous baseline diameter (r² = 0.38, P = 0.03) and independent of the amount of ointment applied or the extent of preconstriction (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

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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 venuconstriction [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/m² (21.8–25.8 kg/m²) 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.
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 "alpha"-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; Isolet, Schwarz Pharma, Switzerland) or matching placebo was applied using a flat-pointed spatula onto a skin area of approximately 1x1.5 cm. Diameter changes were then measured after 5, 10, 15, 20, 30, 40, 50 and 60 min. Finally, nitroglycerine (Perlinonat, 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 ± 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, preconstriction of the veins with phenylephrine was similar in the two treatment groups (placebo 35.3 ± 11.3%; ISDN 38.3 ± 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 ± 25.8% (placebo 2.2 ± 12.8%; P < 0.005; Fig. 1) with a maximum of 39.1 ± 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 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 (r² = 0.38, P = 0.03; Fig. 2) and independent of the amount of ointment applied or the extent of preconstriction (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 ± 5.3%; ISDN 66.0 ± 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].