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Heating and cooling of the nitroglycerin patch application area modify the plasma level of nitroglycerin

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Summary. 19 healthy volunteers wore a nitroglycerin patch releasing 10 mg per 24 h for 2 h. Subsequently, the skin area surrounding the patch was exposed to 15 min of local heating with an infrared bulb (Group A, n = 10), or local cooling with an ice-pack (Group B, n = 9). The patch was protected by an insulating shield (Styrofoam).

After 10 min of heating, the median (Walsh) plasma nitroglycerin level increased from 3.1 to 7.6 nmol·l^{-1}. Body temperature remained constant. After 15 min of cooling the median plasma level had dropped from 2.1 to 1.4 nmol·l^{-1}.

The results demonstrate that changes in skin temperature may cause extensive short-term changes in the bioavailability of nitroglycerin. Presumably, a subcutaneous or cutaneous reservoir builds up during transdermal treatment, and changes in regional cutaneous blood flow affect the rate of drainage from the reservoir into the systemic circulation.

Key words: Glyceryl trinitrate; transdermal patch, pharmacokinetics, cutaneous circulation, skin temperature

Transdermal administration of drugs through patch systems has been available for more than 10 years; this method of drug delivery is particularly widely used for nitroglycerin (glyceryltrinitrate, GTN). The patch treatment approaches zero order kinetics and usually provides a stable plasma nitrate level for a period up to 24 h. Drug delivery from the patch is limited to a rate lower than the maximal skin permeation rate, and therefore nitrate uptake depends almost solely on the surface area [1, 2]. The drug is further metabolized rapidly and at an almost constant rate after it enters the systemic circulation.

Since 1986, however, several authors have reported that the plasma concentration of GTN may increase considerably if a patch carrier exercises [3–6], or stays in a sauna [3]. Several mechanisms could contribute to the increase during exercise; reduced nitrate metabolism, changes in the nitrate distribution volume and changes in cutaneous blood flow [6]. The rise in plasma GTN occurs rapidly and has been observed even after 5 min of exercise [6].

To examine the influence of cutaneous blood flow on transdermal nitrate kinetics, plasma GTN concentrations were measured in healthy patch carriers prior to and after the skin area surrounding the GTN patch had been heated or cooled.

Subjects and Methods

The protocol was approved by the regional Ethics Committee. Twenty healthy hospital employees volunteered for the study, 12 F and 8 M. Their mean age was 28.9 y, and none was taking any medication. They were examined clinically and an electrocardiogram was recorded before inclusion. During the experiment no drugs were allowed, except acetaminophen, which was given (if needed) as standard therapy against headache. The study was open, and the volunteers were recruited into two groups (A and B), each of 10 persons.

A GTN patch releasing 10 mg/24 h (Transiderm-Nitro®, CIBA-GEIGY) was placed on the lateral side of the right upper arm at 09.00 h, and was carried for 2 h so the plasma level would reach a steady state [2, 7, 8]. During those 2 h the probands continued their daily activities, except for avoiding physical exercise. The upper arm was selected as the application site to limit the effect of the heating and cooling solely to the patch application area, and thereby minimize any systemic influence of these interventions.

At 11.00 h the probands in Group A had the right upper arm exposed to 15 min of local infrared heating from a 250 Watt heating bulb placed 50 cm from the arm. The patch was covered by an 10 mm thick insulating shield (Styrofoam) of the same size that was kept in place with adhesive strips. The cover was applied to avoid physical or chemical change in the patch itself. The temperature in the opposite axilla was measured before and after the heating period.

For probands in Group B, a 15 × 15 cm package of icecubes wrapped in two layers of plastic and cotton cloth was placed on the right upper arm. Again, the patch was covered by an insulating shield.

Blood for plasma GTN assay was collected 5 min before and immediately before the intervention (baseline), and after 10 and 15 min of local heating or cooling.

In 5 subjects the effect of the intervention on the cutaneous circulation was explored by photoplethysmography. Recordings were made prior to and after local heating or cooling, using a Vasculab®, Model PPG 113, with a PH77A PhotoPulse sensor (Medasonics®,

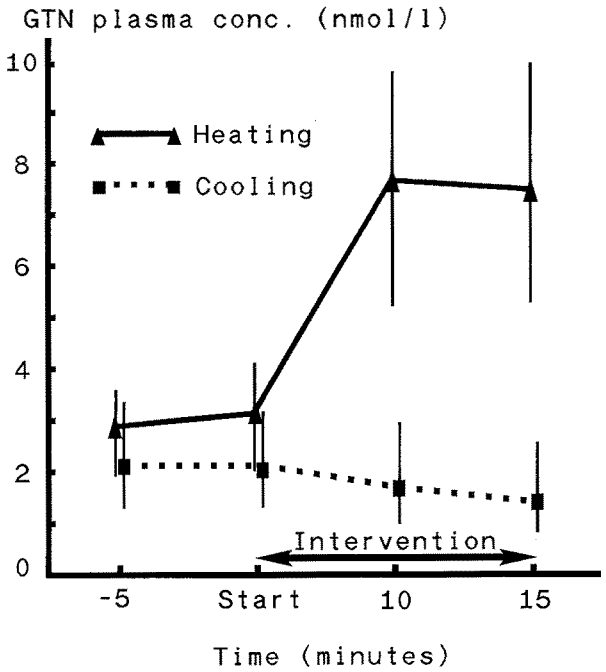

Fig. 1. The influence of local heating and local cooling on transdermal nitrate kinetics in healthy volunteers after 2 h of treatment with a GTN patch releasing 10 mg/24 h. The triangles and squares denote the median (Walsh) glyceryl trinitrate (GTN) plasma concentrations with 95 % confidence intervals (thin vertical lines), measured 5 min and immediately before and 10 and 15 min after local heating ($n = 10$; continuous line), and local cooling ($n = 9$; dotted line)

Mountain View, California). The total power (peak to peak amplitude) of the AC signal reflects the microvascular perfusion [9].

Blood sampling

Blood specimens were collected with the subject sitting, to avoid any influence of variation in posture. Blood was obtained from a cubital vein in the left arm through a 19 gauge teflon cannula (Venflon®, Viggo Products, Sweden), and was placed in pre-cooled glass tubes containing sodium heparin (Vacutainer®, Becton Dickinson, France). The samples were kept on ice for 10 to 30 min until centrifugation, and the plasma was then transferred by glass pipettes to similar glass tubes that were stored at − 70 °C until analysis. The analyses were performed on coded samples.

GTN analysis

GTN concentrations were measured by gas-liquid chromatography with an electron capture detector [10]. The coefficient of variation (within-day variation) in the concentration range (0.5–10 nmol/l) was 5 %. The four different samples from each subject were always analysed in the same series.

Statistical analysis

The median plasma GTN levels with 95 % confidence intervals were calculated by the Walsh method for each sampling time. The null hypotheses were that the median plasma GTN concentration would not be altered by the interventions, and Friedman's variance test was applied to the data. Testing was two-sided.

Results

Tolerability/side effects

The majority of the subjects experienced a pounding headache, which was light in most cases. However, three subjects had a more pronounced headache, and one (who was excluded before the temperature intervention) had a migraine attack that lasted for 1 day. One subject experienced temporary dizziness and nausea after the insertion of the cubital cannula. There was no sustained or serious adverse experience.

In Group B, adequate analysis of plasma GTN was impossible for technical reasons in 2 volunteers, and two additional subjects were therefore included. The mean age and sex ratio were similar in the two groups.

Plasma GTN concentrations

The median plasma GTN levels with 95 % confidence intervals (Walsh) in Groups A and B are shown in Fig. 1. In one subject in Group B it was noted that the ice-package had been displaced, and as the cooling of the patch area had been inadequate, the results from this subject were excluded.

In Group A the median plasma GTN concentration was 2.8 (95 % confidence intervals; 1.9–3.6) and 3.1 (2.0–4.1) $nmol \cdot l^{-1}$ at baseline, which had increased to 7.6 (5.2–9.8) after 10 min and was 7.4 (5.3–10.0) $nmol \cdot l^{-1}$ after 15 min of local heating. The increase was highly significant, $p < 0.0001$ (Friedman). The mean temperature in the left axilla was 36.3 °C (SE 0.12) prior to heating, and 36.3 °C (0.13) after the heating period.

In Group B, the median plasma GTN level was 2.1 (1.3–3.4) and 2.1 (1.3–3.2) nmol/l at baseline, and it fell to 1.6 (0.9–3.0) after 10 min and 1.4 (0.8–2.6) $nmol \cdot l^{-1}$ after 15 min of local cooling. The reduction was significant at $P = 0.02$ (Friedman).

Photoplethysmography

An example of a photoplethysmographic recording from the right upper arm in one volunteer is shown in Fig. 2. A marked change in the peak to peak amplitude can be seen after local heating and cooling, indicating a considerable alteration in perfusion.

Discussion

The study has revealed that the short-term pharmacokinetics of transdermal nitroglycerin are considerably affected by local heating and cooling of the skin surrounding the patch. The plasma GTN level increased considerably and became more than twice as high after local heating. The drop in plasma GTN after local cooling was moderate and was more variable. It should be interpreted with caution considering the lack of a control group.

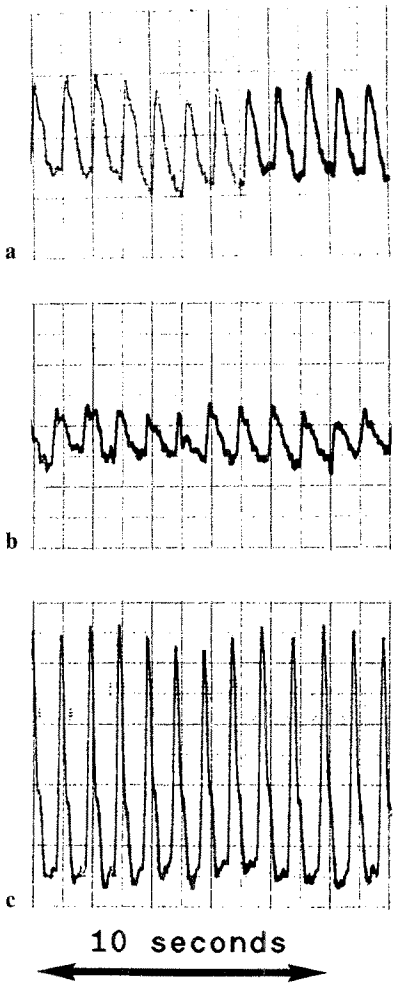

Fig. 2. Photoplethysmographic recordings from the same area on the right upper arm in one volunteer under a) control conditions; room temperature 25 °C, b) after 10 min of local cooling, and c) after 10 min of local heating. The peak to peak pulse amplitude reflects the microvascular perfusion, which is reduced after cooling and increased after heating

During the patch treatment the plasma GTN level reached steady state within 2 h [2, 7, 8], as reflected in the baseline values. Thus, the large increase observed after local heating cannot be explained by spontaneous fluctuation.

The insulating cover was applied to prevent the interventions from altering the temperature in the patch or in the underlying stratum corneum, which might change skin permeability. Even if minor temperature changes might have occurred despite this precaution, they are probably unimportant, since plasma GTN levels may increase during exercise, even after the patch has been removed [6].

The changes in plasma GTN can best be ascribed to the observed alterations in cutaneous blood flow (Fig. 2). The body temperature was not influenced by the heating, and although the interventions may have caused minor systemic effects (for example upon sympathetic tone), the latter could hardly have resulted in important changes in hepatic blood flow, cardiac output or fluid distribution.

Previous studies have demonstrated an increase in plasma GTN after physical exercise and exposure to a sauna [3–6]. Both those conditions are associated with increased cutaneous blood flow and also with several other physiological effects. In contrast, the present study has shown that regional temperature changes alone can cause a major change in GTN bioavailability. Further, the magnitude of the increase after local heating indicates that enhancement of the cutaneous blood flow is the dominant cause of the increase in plasma GTN in all those situations.

Implications

The large influence of cutaneous blood flow on transdermal nitrate kinetics contrasts with the common theory of transdermal kinetics, in which the major factors considered are skin permeability and maximal delivery from the system [1, 11]. The "controlled rate drug delivery" per cm^2 contact area varies between different patch systems, but it is fixed at a rate lower than the maximal skin permeability. In some systems (Transiderm-TTS®, CIBA) drug delivery is limited by a socalled "rate controlling membrane", while others (Nitro-Dur®, Key Pharmaceuticals) have documented similar, constant plasma levels using a matrix system, or by a combination of these two principles (Nitrodisc®, Searle) [2, 8]. According to these principles, cutaneous blood flow should not influence drug bioavailability [1, 11–13].

The present results suggest that it is necessary not only to consider the drug passage through the skin, which may be called "Step 1", but also a "Step 2", the further diffusion from cutaneous and subcutaneous tissue under the patch into the systemic circulation (Table 1). GTN was still detectable in plasma 1 h after the removal of a nitrate patch [7], while after sublingual or intravenous administration GTN disappears much more rapidly from plasma [13, 14]. Further, during exercise plasma GTN increase for up to 20 min after the patch has been removed [6]. These observations indicate the existence of a cutaneous and/or subcutaneous nitrate reservoir, and its emptying is likely to be influenced by changes in the regional blood flow. Accordingly, cutaneous blood flow appears important in the short-term regulation of nitrate bioavailability, even if total drug delivery over 24 hours may be determined by the maximum patch delivery and skin permeability. Cutaneous blood flow may also influence the plasma levels of other transdermally delivered drugs, such as scopolamine and nicotine, but this does not appear to have been examined.

Table 1. Proposed major determinants of GTN bioavailability during transdermal nitrate treatment

Step 1	Step 2
Drug permation through skin	Further drug transportation
– Surface area – System rate control: membrane/matrix dissolution – Stratum corneum: Lipid and water content – Temperature?	– Permability of tissue between stratum corneum and skin vessels – Cutaneous blood flow – Temperature?

Limitations of the study

The present study was not randomized or double-blind, and there was no control group that was not exposed to changes in skin temperature. However, the stability of the average plasma GTN level under control conditions between 2 and 24 h after application of a patch is well documented [2, 3, 7, 8]. Blinding of the heating and cooling would have been impossible, but the bias seems minor, since plasma GTN concentrations only were measured, and those analyses were performed independently.

The subjects in the study were healthy volunteers and were younger than most angina patients. However, since variation in skin perfusion is a major mechanism in the regulation of body temperature, the findings can probably be applied as well to older subjects and subjects with coronary heart disease.

The importance of the observed variations in plasma GTN as regards clinical efficacy or side effects has not been established. Some authors have reported a firm dose-response relationship [15, 16], and in one study a high correlation was found between the plasma GTN level and the arterial vasodilating effect evaluated by digital plethysmography [17].

On the other hand, several authors have argued that the plasma level poorly reflects the relevant actions of GTN [14, 18, 19]. The observed inconsistency between pharmacokinetic and clinical data might theoretically be due to the known pharmacological actions of the metabolites of GTN [20], or to inaccuracies in the measurements of GTN [18].

In conclusion, the present study has demonstrated that during GTN patch treatment, changes in skin temperature and hence in cutaneous blood flow, have a major impact on GTN kinetics. While increased skin blood flow induced by local heating elevated plasma GTN concentrations two- to three-fold, reduced blood flow due to cooling caused a moderate reduction in plasma levels. The results suggest the need to modify current theories behind transdermal drug delivery. Further studies are needed to establish the clinical relevance of the observed phenomena.

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