The effects of moderate sustained exercise on the pharmacokinetics of nitroglycerine

Nitroglycerine (NTG) transdermal patches are widely used in the prevention of exertional angina pectoris. Although, the therapeutic effect of NTG patches is expected to occur during exercise, the only available pharmacokinetics data were collected at rest. Furthermore, exercise-induced variations of several major physiological parameters such as cardiac output, hepatic blood flow and cutaneous blood flow, may profoundly influence transdermal NTG pharmacokinetics, and conceivably therefore increase NTG plasma levels.

Efficacy of NTG patches is usually assessed by symptom-limited treadmill exercise tests. These tests of brief duration and rapidly increasing workload do not simulate the real life situation of progressive, moderately strenuous sustained exercise for which the protective effect of long-acting nitrates is desired. Furthermore, the brief duration of exercise (3 to 8 min) in these symptom-limited tests does not adequately evaluate the potential effects of exercise on NTG kinetics. The purpose of the present study was to evaluate the influence of moderate sustained exercise on transdermal NTG pharmacokinetics in volunteers. The pharmacokinetics of both transdermal and intravenous NTG were assessed in each subject in an attempt to differentiate the effects of exercise on presystemic and systemic clearance.

Six healthy male volunteers (mean age: 23 years) received, in a random order, on two different days with a 1 week interval, a 10 mg NTG patch (Nitriderm TTS; Ciba Geigy) on the chest wall or a 7 $\mu g\ min^{-1}$ intravenous NTG infusion via a polyethylene catheter in a cubital vein. To approximate a steady state plasma NTG level, the patch was applied to the chest wall 3 h before (Imhof *et al.*, 1984) and the infusion 30 min before the study began (Amstrong *et al.*, 1983). The study protocol consisted of three consecutive 1 h periods: rest, exercise and recovery. During rest and recovery the subjects remained supine; exercise was performed for 1 h on a bicycle ergometer, the workload being adjusted to maintain a heart rate of 110 beats min^{-1}. Every 10 min the workload was increased for a 1 min period to raise the heart rate to 150 beats min^{-1}. This exercise pattern was chosen in an attempt to mimic usual daily life exercises.

NTG plasma levels were determined from blood samples collected every 5 min during the last 20 min of each of the three periods of rest, exercise and recovery. To allow for the reported variations in NTG plasma levels even when 'steady state' is reached, the NTG plasma level for each period was expressed as the mean of the four consecutive determinations. Plasma samples were assayed by a modification of a previously reported gas chromatography technique (Rey *et al.*, 1983) in which quantitation was accomplished by mass spectrometry using electron impact ionization. The coefficient of variation of this technique was 5% at the concentration level of 1 ng ml^{-1}. Statistical analysis was performed by a two ways analysis of variance.

Differences were considered significant at $P < 0.05$. Results (mean ± s.d.) are summarized in Figure 1.

Plasma NTG levels increased significantly during exercise with both routes of administration from 0.15 ± 0.12 to 0.29 ± 0.19 ng ml^{-1} with the patch, and from 0.31 ± 0.22 to 0.50 ± 0.27 ng ml^{-1} with the infusion. In both cases NTG levels at recovery did not differ significantly from the original baseline levels. Exercise induced a more pronounced increase in plasma NTG levels with the transdermal (93% increase) than with the intravenous administration (61% increase); however this difference was not statistically significant.

Despite the finding of a wide range of inter-subject variability in plasma NTG levels, a marked and statistically significant increase in the plasma levels was still observed during exercise with both routes of administration.

The kinetics of intravenous NTG were characterized by a short half-life (4 to 6 min) due to rapid and extensive metabolism by the liver and to uptake into red blood cells and the vascular endothelium. The absorption of transdermal NTG is dependent upon the physical properties of the membrane in the delivery system and cutaneous blood flow. Exercise modifies several of the major physiological parameters involved in NTG pharmacokinetics. Exercise-induced reduction in hepatic blood flow (Dossing, 1985) can decrease clearance, prolong the half-life and increase plasma levels of high clearance, hepatic blood flow dependent, drugs such as NTG.

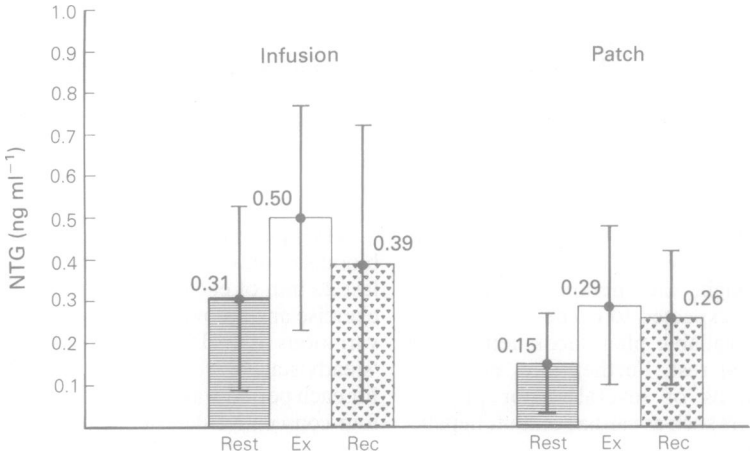

Figure 1 Mean (± s.d.) NTG plasma concentrations during rest (■), exercise (□) and recovery (□).

Moderate exercise increases cutaneous blood flow and therefore has the potential to increase transdermal NTG absorption. The exercise-induced reduction of hepatic blood flow and thus of NTG clearance may provide an explanation for the increase in plasma NTG levels seen with both routes of administration. The conceivable exercise-induced enhancement of cutaneous blood flow may increase transdermal NTG absorption; but the contribution of this phenomenon to the overall rise in plasma NTG would be small, since the increase in plasma levels during exercise with transdermal NTG, did not differ significantly from that with the intravenous drug.

Curry & Kwon (1985) in their recent study of the influence of posture on plasma NTG showed that after sublingual NTG, the mean maximum plasma concentration was over three times higher in the supine than in a subsequent sitting position. In the present study the volunteers were lying supine during rest and recovery, but sitting on a bicycle during exercise. If the results of Curry & Kwon (1985) can be applied to the intravenous and transdermal administration, the effect of exercise in the upright position on NTG plasma levels should be even greater than demonstrated. However, extrapolation of these data is of doubtful significance since the difference between sitting and supine NTG concentration may be due to posture-induced changes in sublingual venous pressure in addition to modifications of cardiac output and liver blood flow.

The observed exercise-induced increase in plasma NTG level does not imply any concurrent increase in pharmacodynamic or therapeutic effects of NTG since a plasma level-activity relationship has not yet been established. However it does indicate a possible need for pharmacokinetic studies to be carried out under those circumstances during which drugs are seen to have their therapeutic effects i.e.: during exercise in the case of NTG. Furthermore, sustained moderate exercise tests may be of value in the study of those antianginal drugs whose pharmacokinetics are possibly affected by physical activity.

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Nizatidine (300 mg nocte) does not interfere with diazepam pharmacokinetics in man

The discovery of the histamine H_2-receptor-antagonists signalled an important breakthrough in medicinal chemistry. They decrease basal and stimulated acid production and promote healing of acid related diseases. Today H_2-receptor blocking agents are among the most widely used drugs. The same applies to diazepam which is also the hypnotic frequently used for sedation during endoscopy.

However, cimetidine has been demonstrated to produce clinically relevant though reversible inhibition of hepatic oxidative metabolism of many drugs including diazepam, while ranitidine in therapeutic doses does not show this unwanted effect.

Nizatidine too is a new and potent specific H_2-receptor blocker. A prominent feature of nizatidine is its high bioavailability in man (about 95%).

In this journal Secor *et al.* (1985) reported that nizatidine does not inhibit the hepatic metabolism of three probe drugs: chlordiazepoxide and theophylline which are like diazepam metabolized in part by *N*-demethylation by the hepatic cytochrome P-450 system and lorazepam which is conjugated to lorazepam glucuronide.

In our study we investigated the influence of nizatidine on diazepam pharmacokinetics. It was a double-blind, two-way, crossover study with the treatments (nizatidine 300 mg nocte or placebo) administered in a latin square design. Nine healthy male subjects (age 22–32 years, body weight 57–80 kg) received each study drug for 6 days during each of the two treatment periods, separated by 8 days when no medication was given. Diazepam 10 mg p.o. was given on day 3 of each treatment period at 21.00 h. Venous heparinized blood samples (5 ml) for assay of diazepam and desmethyldiazepam were taken at 0, 0.5, 1, 3, 6, 12, 18, 24, 36, 48, 60, 72, 84 h after each diazepam dose on days 3 and 17.

Diazepam and its major metabolite desmethyldiazepam were measured by a specific and sensitive g.l.c.-assay as described elsewhere (Klotz *et al.*, 1975). From the monitored plasma levels pharmacokinetic data of diazepam were individually analyzed according to the two compartment open model by the iterative curve fitting computer program NONLIN (e.g. elimination half-life $t_{½}$ from the terminal slope and total plasma clearance CL by the ratio dose to area under the concentration time curve (AUC) from zero to infinity based on complete bioavailability for diazepam). The area under the plasma concentration time curve for desmethyldiazepam was calculated according to the trapezoidal rule. The pharmacokinetic results of the cross-over study were compared by ANOVA.

Table 1 shows no differences in $t_{½}$ (h), CL (ml h^{-1}) of diazepam and the AUC (ng ml^{-1} h) of