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Abstract

Effects of acute (15h) and chronic (15h x 7 days) immobilization (IM) stress on plasma levels of nicorandil [N-(2-hydroxyethyl) nicotinamide nitrate (ester)] administered orally were examined in rats. The maximum plasma level was reached 30 min after administration. Acute IM stress significantly reduced plasma nicorandil levels both in the absorption and elimination phases (15 min and 2-6h after administration, respectively). Chronic IM stress further intensified the reduction of nicorandil levels in the absorption phase, but attenuated the influence of acute stress in the elimination phase. No significant difference was observed one day after removal of chronic IM stress. These results suggest that chronic IM stress markedly inhibits the absorption of nicorandil, but the distribution, metabolism and excretion were influenced more by acute IM stress.

KEYWORDS: immobilization stress, nicorandil, plasma level, absorption, elimination, rat

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— Brief Note —

Effect of Acute and Chronic Immobilization Stress on Plasma Levels of Nicorandil Administered Orally to RatsMOTOO YAMORI, RYOZO OISHI^a, YUTAKA GOMITA^{b*} AND KIYOMI SAEKIDepartment of Pharmacology and ^bDepartment of Hospital Pharmacy, Okayama University Medical School, Okayama 700, Japan

Effects of acute (15h) and chronic (15h × 7 days) immobilization (IM) stress on plasma levels of nicorandil [N-(2-hydroxyethyl) nicotinamide nitrate (ester)] administered orally were examined in rats. The maximum plasma level was reached 30 min after administration. Acute IM stress significantly reduced plasma nicorandil levels both in the absorption and elimination phases (15 min and 2-6 h after administration, respectively). Chronic IM stress further intensified the reduction of nicorandil levels in the absorption phase, but attenuated the influence of acute stress in the elimination phase. No significant difference was observed one day after removal of chronic IM stress. These results suggest that chronic IM stress markedly inhibits the absorption of nicorandil, but the distribution, metabolism and excretion were influenced more by acute IM stress.

Key words: immobilization stress, nicorandil, plasma level, absorption, elimination, rat

Various factors such as body temperature, food intake, age, environment and stress, affect the action of drugs. Such influences may be due to changes in bioavailability resulting from alteration of the absorption, metabolism and excretion of drugs.

Nicorandil [N-(2-hydroxyethyl) nicotinamide nitrate (ester)], a vasodilator, is used clinically as an antianginal drug (1-3). Anginal attacks are often caused by various stress (4,5), and the patients feel fear or anxiety in anticipation of unpredictable attacks. The coronary vasodilatory action of nicorandil is related to its plasma levels, although some interindividual variation exists (6).

We have shown that the bioavailability of nicorandil after oral, subcutaneous and intravenous administration is reduced by footshock stress in rats (7). In the present study, we examined the effects of acute and chronic immobilization (IM) stress on plasma levels of nicorandil after oral administration in rats. We also studied the duration of the effect of chronic IM stress on plasma levels.

Male Wistar strain rats weighing 210-260 g were housed in a room maintained on a 12h light/dark cycle (lights on at 06:00) and at 22 ± 2°C. IM stress was given by restraining rats in a wire net from 19:00 to 10:00 (15h). Rats were given food and water *ad libitum* from 10:00 to 19:00. Rats were divided into five groups as follows, (a) control (intact) group, (b) acute (1 day) IM stress group, (c) chronic (7 consecutive days) IM stress group, (d) 1 day after removal of chronic IM stress group and (e) 3 days after removal of chronic IM stress group. Five rats were used for each group. Nicorandil (donated by Chugai Pharmaceutical Co. Tokyo, Japan) was administered orally at 10:00, and the blood was collected in 60 μl heparinized capillary tubes by cutting the tip of the tail 15 min, 30 min, 1 h, 2 h, 4 h and 6 h after drug administration. In the case of the immobilized rats, IM continued until the last blood collection. After centrifugation at 11,500 rpm for 3 min with a hematocrit centrifuge, 20 μl each of plasma was applied to a Bond Elut cartridge (C18) with N-(2-hydroxypropyl) nicotinamide nitrate (ester) as the internal standard and the amount of nicorandil was determined using high performance liquid chromatography with UV detection as described previously (7). The half-life ($T_{1/2}$) value was estimated from the

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pharmacokinetic parameters, using a personal computer program for nonlinear least squares regression analysis (MULTI). Data obtained were statistically evaluated by analysis of variance followed by Dunnett's test.

The plasma nicorandil levels in the control group reached the maximum value of $9.8 \mu\text{g/ml}$ 30 min after administration, and thereafter gradually decreased to $1.3 \mu\text{g/ml}$ at 6 h after administration (Fig. 1). There were significant differences between the control group and the acutely IM stressed group ($F=24.0$, $p<0.01$) or the chronically IM stressed group ($F=26.3$, $p<0.01$). The plasma levels were significantly lowered by acute IM stress 15 min, 2 h, 4 h and 6 h after nicorandil administration. Significant reduction was observed in the chronically IM stressed group 15 min, 30 min and 2 h after administration, but no effect was seen at 4 h or 6 h after. The $T_{1/2}$ values in the control, acute IM stress group and chronic IM stress group were 1.81 ± 0.11 , 1.32 ± 0.07 and 1.61 ± 0.11 h (mean \pm SEM), respectively. The $T_{1/2}$ value in the acute IM stress group was significantly lower than in the control ($P<0.01$).

No significant difference in the plasma level was observed as early as 1 day after removal of chronic IM stress ($F=2.0$ and $F=0.1$ for 1 and 3 days after, respectively) (Fig. 2).

The influence of stress on animal responses has been examined by several methods, including electric footshock, IM, exposure to heat or cold, and forced exercise. We examined the influence of acute footshock stress on pharmacokinetics of nicorandil administered to rats by various routes in a previous study, and suggested that footshock stress affects not only the absorption of nicorandil but also its distribution, metabolism and excretion (7). In the present study, we used IM to examine the influence of acute and chronic stress on plasma nicorandil levels after oral administration.

The absorption of drugs from the gastrointestinal tract is affected by such physiological factors as gastrointestinal motility and mucosal blood flow, and these factors are influenced by stress (8-12). Acute IM stress lowered the plasma nicorandil levels both in the absorption and elimination phases in this study. These results agree well with the previous results of footshock stress (7). The reduction in the plasma levels in the absorption phase (15 min and 30 min after administration) was further intensified by chronic IM stress, but the acute IM stress-induced reduction of plasma levels in the elimination phase (2-6 h) appeared to be attenuated by chronic IM stress. These

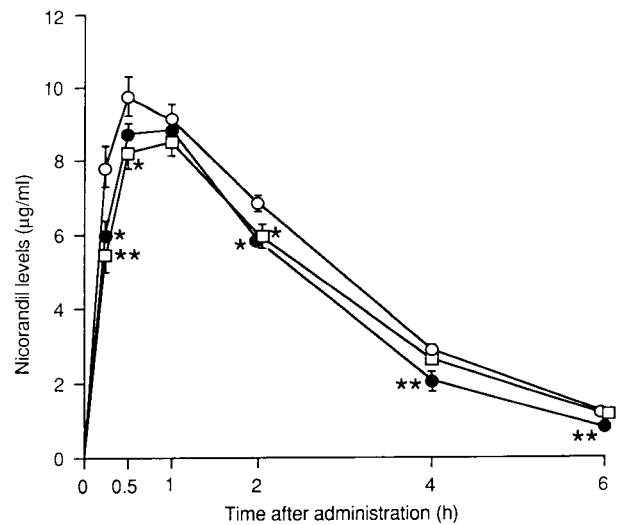


Fig. 1 Effect of acute (15h) and chronic (15h \times 7 days) immobilization (IM) stress on plasma levels of nicorandil in rats. Nicorandil (10 mg/kg) was administered orally. (\circ): control group; (\bullet): acute IM stress group; (\square): chronic IM stress group. Each value is the mean \pm SEM of 5 rats. * $P<0.05$, ** $P<0.01$ as compared with the control group.

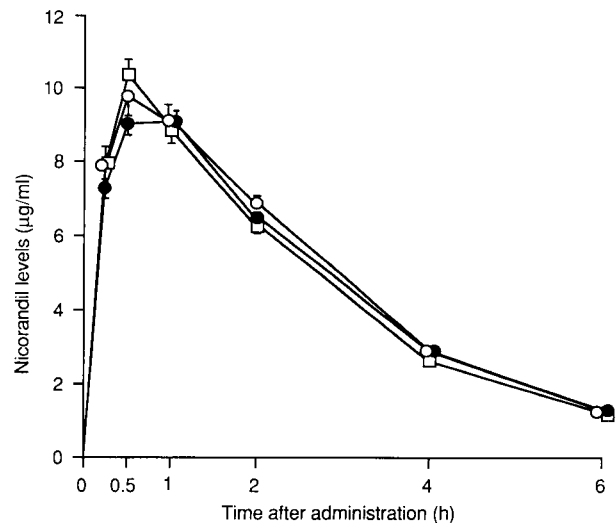


Fig. 2 Time course of plasma levels of nicorandil administered 1 and 3 days after removal of chronic immobilization (IM) stress in rats. Nicorandil (10 mg/kg) was administered orally. (\circ): control group; (\bullet): 1 day after removal of chronic IM stress group; (\square): 3 days after removal of chronic IM stress group. Each value is the mean \pm SEM of 5 rats. There was no significant difference among three groups.

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results suggest that chronic IM stress inhibits nicorandil absorption from the gastrointestinal tract more markedly than acute IM stress. It is also suggested that the elimination phase which reflects processes such as distribution, metabolism and excretion of nicorandil is also influenced by IM stress, but the effect on elimination becomes less marked during chronic exposure to IM stress. The complicated influence of stress on nicorandil pharmacokinetics should be considered during the clinical use of this drug.

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