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Influence of exposure to new circumstances on pharmacokinetics of plasma drugs concentrations in rats.

Yasuhiko Hashimoto* Hiromu Kawasaki†

Yutaka Gomita‡

*Okayama University,

†Okayama University, kawasaki@pheasant.pharm.okayama-u.ac.jp

‡Okayama University,

Influence of exposure to new circumstances on pharmacokinetics of plasma drugs concentrations in rats.*

Yasuhiko Hashimoto, Hiromu Kawasaki, and Yutaka Gomita

Abstract

The influences of emotional changes induced by being exposed to a new environment on the pharmacokinetics of plasma drug concentration were studied in male Wistar rats. Transfer from a familiar home cage to a new home cage was considered to induce psychological (non-physical) emotional changes. First, nicorandil and zonisamide, drugs that act on the peripheral system and central nervous systems, were used, respectively. Immediately after oral administration of nicorandil (10 mg/kg) or zonisamide (50 mg/kg), the animals were transferred to new home cages. Plasma nicorandil and zonisamide concentrations were determined by high-performance liquid chromatography at 1 and 4 h after administration. Plasma nicorandil concentration in the group transferred to new home cages was significantly decreased relative to levels in the non-transferred control group. However, zonisamide concentrations were unchanged. These findings suggest that the pharmacokinetics of nicorandil, but not those of zonisamide, tend to be influenced by non-physically induced emotional changes.

KEYWORDS: psychologically induced emotional changes, drug plasma concentration, nicorandil, zonisamide

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Brief Note

Influence of Exposure to New Circumstances on Pharmacokinetics of Plasma Drugs Concentrations in Rats

Yasuhiko HASHIMOTO*, Hiromu KAWASAKI and Yutaka GOMITA

Department of Hospital Pharmacy, Okayama University Medical School, Okayama 700-8558, Japan

The influences of emotional changes induced by being exposed to a new environment on the pharmacokinetics of plasma drug concentration were studied in male Wistar rats. Transfer from a familiar home cage to a new home cage was considered to induce psychological (non-physical) emotional changes. First, nicorandil and zonisamide, drugs that act on the peripheral system and central nervous systems, were used, respectively. Immediately after oral administration of nicorandil (10 mg/kg) or zonisamide (50 mg/kg) , the animals were transferred to new home cages. Plasma nicorandil and zonisamide concentrations were determined by high-performance liquid chromatography at 1 and 4 h after administration. Plasma nicorandil concentration in the group transferred to new home cages was significantly decreased relative to levels in the non-transferred control group. However, zonisamide concentrations were unchanged. These findings suggest that the pharmacokinetics of nicorandil, but not those of zonisamide, tend to be influenced by non-physically induced emotional changes.

Key words: psychologically induced emotional changes, drug plasma concentration, nicorandil, zonisamide

In general, patients in a clinical setting are exposed to continuous stress, and medication is taken or administered under stressful conditions. It is known that drug action is influenced by various stresses, including environmental circumstances, smoking, overall physical condition, and so on (1, 2). Certain effects of some drugs have been shown to be altered by changes in the sensitivity of the site of drug action, while the pharmacokinetics of the drug itself have also been changed (3).

It may be possible to divide the stress into the categories of physical stress caused by direct aversive stimulation such as foot-shock and immobilization, and non-physical stress caused by solely psychological stimulation such as sociopsychological stress.

In experiments concerning stress, laboratory techniques including immobilization, foot-shock, or exposure to cold environments have often been used. We have previously reported that severe stress, such as foot-shock or immobilization in animals, decreases the plasma concentration of drugs such as nicorandil, isosorbide dinitrate, and theophylline when administered orally (4-6). However, these reports do not separate the effects induced by psychological factors from those induced by physical factors (7, 8).

In the case of humans, sources of stress may include the complexity or density of human society, interaction in the context of relationships, and so on. Therefore, for animal research to be relevant to human subjects, submitting animal subjects to situation is required. Psychological stress may cause hormonal changes in an absence of rapid neural changes, and implicate a higher level of expression of adaptation syndrome in the central nervous system; *i.e.*, the changes may differ from those induced by physical stress.

In the present study, the case in which the animal was exposed to the new environment was assumed to constitute a psychological stress situation, and the pharmacokinetics of drugs occurring in response to transfer from a

* To whom correspondence should be addressed.

familiar home cage to a new home cage were examined. We investigated nicorandil that is clinically used for angina pectoris as a coronary dilator, and zonisamide for epilepsy as an antiepileptic drug. In each case the actions of the respective drug are related to its plasma concentration, although inter-individual variations exist (9, 10).

Materials and Methods

Animals. Male Wistar rats weighing 250–300 g (supplied by Charles River Lab., Japan) were used as subjects. They were housed 3 or 4 animals per plastic animal cage (26 × 36 × 25 cm) in a 12 h light-12 h dark cycle (light on 7:00–19:00) at 22 ± 1 °C in an atmosphere maintained at 60% relative humidity. Rats had free access to food and water, except during the 12 h period before and during the experiment. Drugs and administration nicorandil (Chugai Pharmaceutical Co., Japan) and zonisamide (Dainippon Pharmaceutical Co., Japan) were respectively suspended in 0.5% carboxymethylcellulose and administered orally in a volume of 0.1 ml per 100 g body weight.

Procedures. The animals were housed in group of 4–5 rats for 1 week in a home cage, and divided into 2 separate home cages after drug administration, one for control animals, which were housed in the familiar home cage (control group), the other for experimental animals in which emotional changes were induced by this transfer to new home cages (non-physically stressed group). More specifically, after oral administration of nicorandil at a dose of 10 mg/kg, or zonisamide at a dose of 50 mg/kg, animals in respective control group were returned to their home cage and animals in respective experimental group were returned to new home cages. The wood floor chips in the new home cage of the experimental group were changed every 30 min. At 1 h after adnimistration of nicorandil and 4 h after administration of zonisamide (at Tmax in each drug), blood samples to determine the plasma drug concentrations were collected in capillary tubes (60 μl, Miles-Sankyo Co.) from the tail vein of each rat. The proximal part of the tail vein was carefully incised with a knife (approximately 1 mm) to cause bleeding under local xylocaine jelly anesthesia. Plasma separation was performed by centrifugation for 3 min at 5,400 g (Compur M1100, Miles-Sankyo Co.). Obtained plasma (20 μl) was used to determine the plasma drug concentrations. Nicorandil and zonisamide plasma concentrations were determined according to modified high-performance liquid chromatography methods previously reported by Tanikawa *et al.* (11) and Furuno *et al.* (12), respectively.

Statistics. Data were expressed as the mean ± standard error, analyzed by the Student's *t* test between 2 groups. *P* values smaller than 0.05 were considered significant.

Results and Discussion

After nicorandil or zonisamide was administered, experimental animals were placed in new home cages (the non-physical stressed group), and control animals were returned to their familiar home cages. All animals in the control group exhibited a slightly increased exploratory behavior immediately after being placed in the familiar home cage, but soon sat together in one corner. In both non-physical stressed groups, however, animals manifested a marked exploratory behavior in the new home cages, and continued to maintain high locomotor activity.

As shown in Fig. 1, plasma nicorandil concentration at 1 h after administration in the non-physically stressed

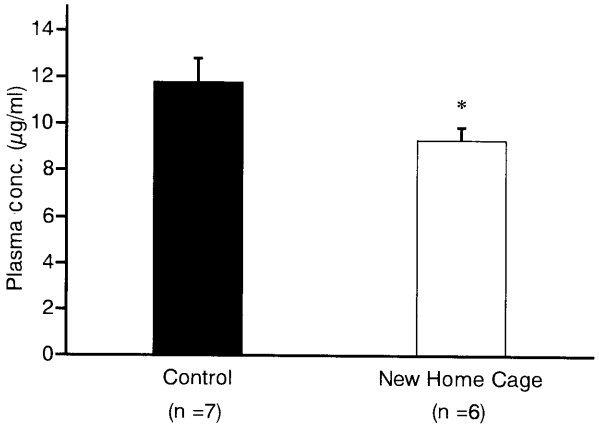

Fig. 1 Influence of emotional changes caused by encountering new environmental circumstances on nicorandil plasma concentration in rats.
Nicorandil was orally administered at a dose of 10 mg/kg, and the rats were transferred to new home cages immediately after administration. At 1 h after administration of nicorandil, blood samples were collected from the tail vein of each rat. Bars indicate the mean value ± standard error. ■, control group (n = 7); □, experimental group (n = 6); conc., concentration. *$P < 0.05$, experimental group compared with the control group.

group was significantly lower than that in control group ($P < 0.05$). On the other hand, plasma zonisamide at 4 h after administration showed no difference between the groups, as shown in Fig. 2.

It is well known that drug actions are influenced by various factors (13), one of which is emotional stress. We have already reported in experimental animals, physical emotional stress such as that of foot-shock or immobilization decreases the plasma concentrations of orally administered nicorandil and isosorbide (5). However, those stresses seemed to be much more intense and included both physical and psychological factors. For experimental findings on animals to be applicable to human stress, an experimental situation based on psychological factor is required. Therefore, in this study, a method to induce psychological stress was used that was considered to approximate a quotidian aspect of human life. That is, in this study, emotional changes in rats induced by being transferred from an adapted home cage to new home cage were used to represent human emotional responses to an unstable or changing environment.

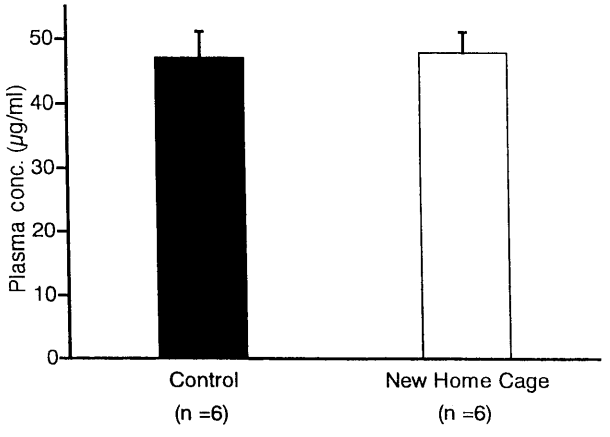

Fig. 2 Influence of emotional changes caused by encountering new environmental circumstances on zonisamide plasma concentration in rats.

Zonisamide was orally administered at a dose of 50 mg/kg, and the rats were transferred to new home cages immediately after administration. At 4 h after administration of zonisamide, blood samples were collected from the tail vein of each rat. Bars indicate the mean value ± standard error. ■, control group (n = 7); □, experimental group (n = 6); conc., concentration.

In nicorandil experiment, the drug plasma concentrations in animals which an unstable emotional state had been induced were lower than those in animals which were returned to their home cages. Generally, the high locomotor activity is observed in unstable situation. It can not be said that all drug metabolisms are facilitated by the increased locomotor activity.

On the other hand, it is known that blood flow in the gastrointestinal tract decreases under stress and that gastrointestinal absorption of drugs is consequently inhibited. Yamori *et al.* (14) and Gomita *et al.* (5) reported that the plasma levels of orally administered nicorandil and dinitrate isosorbide were markedly decreased by physical and emotional stress induced, for example, by foot-shock, and considered that the inhibition of gastrointestinal absorption induced by stress loading might be one of the causes. Foot-shock stress caused very strong aversive stimulation to subjects; *i.e.*, both physical and psychological emotional factors were involved. However, we found a difference between the new home cage group and the control group despite the relative weakness of the stimulation applied in this experiment. These findings show that the phamacokinetics of nicorandil are likely to be influenced by psychological stress.

In the experiment with zonisamide, no change similar to that recognized in nicorandil plasma concentration was observed. We previously determined in animal experiments that plasma concentrations of drugs that act on the central nervous system, such as orally administered caffeine (6) and lithium (in preparation), were not particularly influenced in the term of plasma concentration by induction of emotional stress. The explanation for this finding may be that the central action of the drug suppressed stress response in the brain. Zonisamide, at an oral dose of 100 mg/kg, was found to slightly lower the pelvic and tail positions, and the body temperature. Higher doses were necessary for inducing ataxia and sedation. Specifically, zonisamide has an inhibitory action on the central nervous system, but not a sedation action (15). Thus the influence of zonisamide might not be apparent in psychologically stressed animals. Further research on other central nervous acting drugs is necessary.

In conclusion, our findings indicate that the pharmacokinetics of nicorandil, which acts on peripheral sites, tends to be influenced by psychological emotional changes caused by exposure to new environmental circumstances, whereas the pharmacokinetics of zonisamide, which acts on central sites, tends to be unchanged.

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