[Chem. Pharm. Bull. 32(5)2026—2029(1984)]

Effect of Environmental Temperature on the Elimination of Theophylline

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(Received September 9, 1983)

The effect of environmental temperature on the elimination of theophylline was examined by using four male rabbits kept at 15 or 30 °C. The rabbits kept at 30 °C showed a decrease in the elimination of plasma theophylline compared with those at 15 °C. The elimination rate of theophylline from rabbits at 30 °C was about 1.5 times slower than that at 15 °C. However, no difference was observed in the volume of distribution.

Keywords——temperature effect on elimination; theophylline; elimination rate; distribution volume; therapeutic equivalence

In the previous work,[1] the effect of environmental temperature on the metabolism of aminopyrine was examined by using five male rabbits kept at 30 or 15 °C for 14 d. The rabbits kept at 30 °C for 14 d showed a decrease in elimination of plasma aminopyrine compared with those at 15 °C. Furthermore, the total urinary excretion of aminopyrine and its metabolites at 30 °C was larger than that at 15 °C.

As regards the effect of environmental temperature on drug metabolism, Furner and Stitzel demonstrated that the metabolic rate of aniline or ethylmorphine was significantly increased by subjecting rats to a cold environment for several days.[2] Furthermore, according to Lockwood's report, cold stress following both acute and chronic exposure resulted in enhanced rates of demethylation of both aminopyrine and its monomethyl metabolite.[3] On the other hand, Kaplanski and Ben-Zvi demonstrated that the chronic exposure of rats to high environmental temperature caused a significant reduction in both hepatic *N*-demethylation of *p*-chloro-*N*-methylaniline and aniline hydroxylation.[4]

In the present work, theophylline, which is frequently used clinically, was chosen for examination.

Experimental

Materials——Theophylline was purchased from Nakarai Chemical Ind. Co., Ltd., and 8-chlorotheophylline was obtained from Tokyo Chemical Ind. Co., Ltd.

Animal Experiment——Male albino rabbits weighing 2.6 to 3.0 kg were kept in a cool room (15 ± 1 °C at 60% relative humidity) or in a warm room (30 ± 1 °C at 60% relative humidity) for 14 d. In both rooms, the light (2000 lux) was on from 6 a.m. to 6 p.m. At each temperature, a crossover test was performed. Rabbits A and B were first placed in a room at 30 °C for 14 d in order to examine the effect of high environmental temperature on the kinetics of theophylline elimination. After the experiment, they were moved to a room at 15 °C for the examination as a control. Rabbits C and D were first placed in a room at 15 °C and then moved to a room at 30 °C. The rabbits, which had been kept on a commercial diet (Oriental Yeast Co., Ltd.), were fasted for 12 h prior to intravenous administration of 3.8 mg/kg of theophylline. Blood samples were taken at 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0 and 12 h after the drug administration.

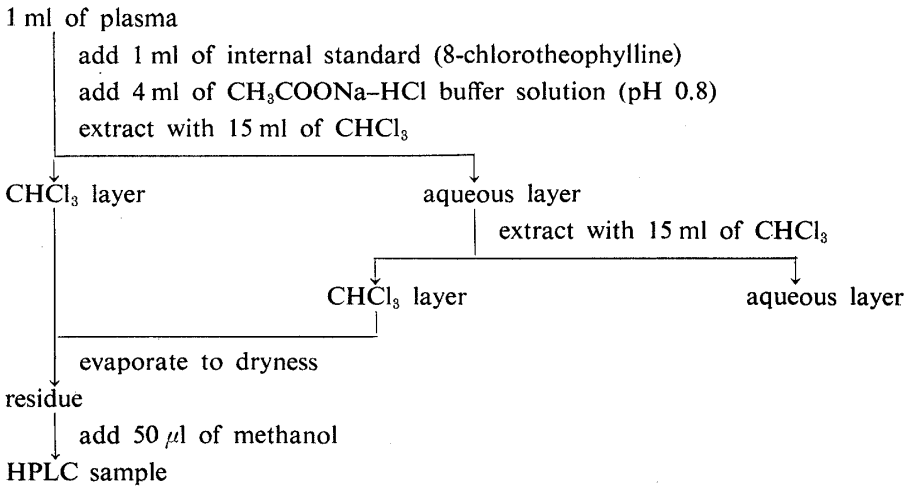

Chart 1. Sample Preparation for HPLC Determination of Theophylline from Rabbit Plasma

A portion of plasma (4 ml) was gently shaken by hand in a stoppered centrifuge tube for 10 s after the addition of 4 ml of sodium acetate–HCl buffer (pH 0.8) solution containing 8-chlorotheophylline (5 μg) as an internal standard. The mixture was extracted twice with 15 ml of chloroform. The combined extracts were evaporated to dryness (Chart I).

HPLC Assay——one μl of sample was injected into a high performance liquid chromatograph (HPLC). Elution was carried out with a 2-component, 2-phase system, consisting of acetonitrile and 10 mM potassium dihydrogen phosphate solution (1 : 9) on an octadecylsilane-bonded silica column (4 mm i.d. × 15 cm: Unisil C_{18}, Gasukuro Kogyo Inc.) at a flow rate of 1.5 ml/min. The apparatus used was a Shimadzu LC-3A liquid chromatograph with a ultraviolet detector (SPD-2A, Shimadzu) set at 275 nm.

Statistical Treatment——The statistical significances of differences between group means were determined by analysis of variance.

Results and Discussion

Figure 1 shows the effect of environmental temperature on the elimination of theophylline in rabbit plasma after the intravenous administration of theophylline. In all cases, a crossover test was performed. The rabbits kept at 30 °C showed a lower elimination rate of plasma theophylline than the rabbits kept at 15 °C. The result is very similar to that of previous work using aminopyrine as the test drug.[1] The pharmacokinetic parameters are listed in Table I. A significant difference in the elimination rate of theophylline was observed between rabbits kept at 30 and 15 °C ($p < 0.02$). The rate was about 1.5 times slower in the rabbits kept at 30 °C than in those at 15 °C. In addition, significant differences were observed in elimination half-life, AUC and total body clearance. However, in the case of volume of distribution, there was no significant difference between them. The effect of environmental temperature on the kinetics for theophylline, digoxin, propranolol and phenytoin was examined by Albin *et al.*[5] using rats kept at 35 and 22 °C for 30 d. The chronic hyperthermia diminished total body clearance of theophylline, digoxin and propranolol. They speculated that the reduction in total body clearance was due to a decrease in the content of cytochrome P-450.[5] However, in the previous paper, it was observed that exposure to a temperature of 30 °C for 14 d resulted in a significant reduction of the activity of nicotinamide adenine dinucleotide phosphate (NADPH)–cytochrome c reductase, though the content of cytochrome P-450 was not changed.[6] Considering that the elimination of theophylline is mainly due to metabolism,[7,8] the decrease in the elimination of theophylline after exposure to 30 °C for 14 d is thought to be dependent on the reduction of the activity of NADPH–cytochrome c reductase.

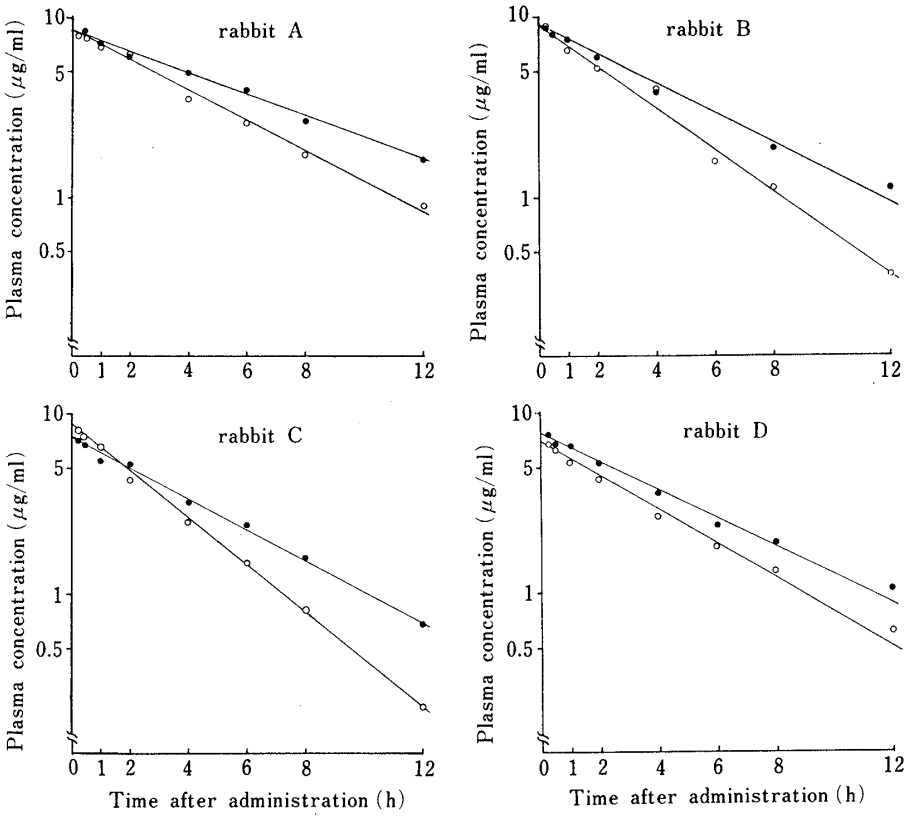

Fig. 1. Effect of Environmental Temperature on Theophylline Elimination in Rabbit Plasma (3.8 mg/kg, *i.v.*)
—●—, 30 °C; —○—, 15 °C.

TABLE I. Pharmacokinetic Parameters of Theophylline after Intravenous Administration (3.8 mg/kg) to Rabbits ($n=4$)

Parameters	15 °C	30 °C
Body weight (kg)	2.84±0.23	2.47±0.20 (NS)
K (elimination) (h^{-1})	0.251±0.034	0.178±0.019[a]
$T_{1/2}$ (h)	2.80±0.39	3.96±0.42[a]
AUC (μg·h/ml)	32.7±4.8	44.8±5.5[b]
Total body clearance (ml/kg/h)	117.3±15.8	84.6±9.3[a]
V_d (ml/kg)	486±69	478±35 (NS)

Values are means±S.D.
a) $p<0.02$, *b*) $p<0.01$ by analysis of variance.
NS: Not significant.

The therapeutic serum concentration ranges of theophylline is relatively narrow (5—20 μg/ml).[9] If the metabolism of theophylline in man is influenced by change of the environmental temperature as is the case in rabbits, therapeutic equivalence throughout the year is not assured. The present results suggest that an appropriate dosage regimen should take account of the season. The effect of seasonal change on the metabolism of theophylline in man is now under examination.

References

1) K. Matsuyama, S. Takenaka, A. Noda and S. Iguchi, *Chem. Pharm. Bull.*, **31**, 1404 (1983).

2) R. L. Furner and R. E. Stitzel, *Biochem. Pharmacol.*, **17**, 121 (1968).
3) G. F. Lockwood and J. B. Houston, *J. Pharm. Pharmacol.*, **34**, 777 (1982).
4) J. Kaplanski and Z. Ben-Zvi, *Life Sci.*, **26**, 639 (1980).
5) H. Albin, G. Vincon, D. Ploux and J. Dangoumau, *J. Pharmacol.*, **12**, 229 (1981).
6) K. Matsuyama, H. Sawahara, A. Noda, S. Goto, T. Tanaka and S. Iguchi, *J. Pharm. Dyn.*, **6**, 1005 (1983).
7) J. Jenne, H. Nagasawa, R. McHugh, F. MacDonald and E. Wyse, *Life Sci.*, **17**, 195 (1975).
8) P. A. Mitenko and R. I. Ogilvie, *Clin. Pharmacol. Ther.*, **14**, 509 (1973).
9) P. A. Mitenko and E. I. Ogilvie, *N. Engl. J. Med.*, **289**, 600 (1973).