[Chem. Pharm. Bull. 22(3) 500—504 (1974)]

UDC 615.31.014.033.076.9

Pharmacological Effect and Absorption of Ethylphenylephrine in Two Different Dosage Forms[1]

Takashi Hiraoka and Jun Serizawa

Products Development Laboratories, Sankyo Co., Ltd.[2]

(Received April 3, 1973)

A correlation between the ear temperature-lowering effect and blood level was investigated in rabbits and dogs after oral administration of two different dosage forms of ethylphenylephrine; an uncoated tablet which showed a rapid dissolution rate *in vitro* test and a sustained release capsule that showed a gradual dissolution rate. The urinary excretion was also examined in dogs and men after the oral administration of two dosage forms. Absorption of the drug from the uncoated tablet was more rapid than that from the sustained release capsule in rabbits, dogs, and men. Absportion from the sustained release capsule extended over a long period. The ear temperature-lowering effect was well correlated with the blood level after the oral administration of two dosage forms in rabbits. No correlation was observed between the effect and the blood level in dogs; the effect was weak in spite of the fast rise of the blood level in early stage after the administration of both dosage forms.

About 70% of the dose during 48 hr period in dogs and 80% of the dose during 24 hr period in men were recovered in the urine after the administration of either the uncoated tablet or the sustained release capsule. About 60% of the total amount excreted in the urine was recovered as free ethylphenylephrine in dogs, but no free ethylphenylephrine was detected in human urine.

An oral administration of ethylphenylephrine quantitatively decreased the ear temperature in intact rabbits and dogs.[3] By using the ear temperature-lowering effect as a criterion of its pharmacological activity an evaluation on two oral dosage forms of ethylphenylephrine was investigated in rabbits and dogs. The absorption profile of these dosage forms was simultaneously examined in rabbits, dogs, and men.

Material and Method

An uncoated tablet, containing 5 mg of ethylphenylephrine, and a sustained release capsule, containing 15 mg of ethylphenylephrine, were used. The dissolution rate of the drug from two dosage forms used in the present study by means of the *in vitro* procedure of NF XIII is shown in Table I.

Twenty-four healthy, male rabbits weighing 2.5 to 2.8 kg were used after fasting for about 18 hr. The rabbits were orally administered the uncoated tablet or the sustained release capsule in doses equivalent

Table I. Dissolution Rate of Ethylphenylephrine from Uncoated Tablet and Sustained Release Capsule by *in Vitro* Procedure of NF XIII

Dosage form	Dissolution rate (%)					
	1	2	3.5	5	7	hr
Uncoated tablet	99.8	—a)	—	—	—	
Sustained release capsule	34.8	38.9	48.9	67.1	92.1	

a) not determined

1) A part of this report was presented at the 44th Kanto Regional Meeting of the Japanese Pharmacological Society, Yokohama, June 1971.
2) Location: *Hiromachi 1-chome, Shinagawa-ku, Tokyo.*
3) T. Hiraoka and J. Serizawa, *Chem. Pharm. Bull.* (Tokyo), **22**, 248 (1974).

to 60 mg of ethylphenylephrine with 100 ml of water. The ear temperature was measured with a thermistor-thermometer (Natume Seisakusho, Type NS-3P) in 12 of the animals at intervals of 30 min during a 6 hr period after administration of the drug. In other 12 rabbits the blood was drawn from the aural vein 1, 2, 4, 6, and 8 hr after the administration for assay of ethylphenylephrine in plasma.

Twelve healthy, mongrel dogs weighing 10 to 13 kg were used after fasting for about 18 hr. They were orally administered the uncoated tablet or the sustained release capsule in doses equivalent to 60 mg of ethylphenylephrine. In 6 of them the ear temperature was measured at intervals of 30 min during an 8 hr period after administration of the drug. The blood was drawn from the front paw vein 1, 2, 4, 6, and 8 hr later for the assay of ethylphenylephrine in plasma and the urine was collected for a 48 hr period from 6 other dogs for the assay of urinary excretion after administration. After a rest period of 1 week, the dogs were given either the sustained release capsule or uncoated tablet in reverse of the former and the measurement of ear temperature and the assay of ethylphenylephrine in plasma and urine were performed.

Six healthy men weighing 58 to 68 kg were administered the uncoated tablet or the sustained release capsule in a dose equivalent to 15 mg of ethylphenylephrine with 180 ml of water 2 hr after a light breakfast. The whole urine was collected periodically 2, 4, 6, 8, 12, and 24 hr after administration of the drug for assay of ethylphenylephrine in urine. The cross-over test was carried out after one week.

The change in ear temperature was measured by means of the method described in the previous report.[3] Ethylphenylephrine in 2 ml of the plasma sample was determined by fluorometry according to the procedure described by Danneberg, *et al.*[4] Ethylphenylephrine in the urine sample was determined in the same way as the plasma sample (free ethylphenylephrine). The urine sample, after heating in a boiling water bath for 30 min with 2 ml of distilled water and 0.5 ml of 6 N HCl, was treated in the same way as the plasma sample (total ethylphenylephrine).

Result

Decreases in Ear Temperature and Plasma Levels in Rabbits

The mean decreases in ear temperature after administration of two dosage forms of ethylphenylephrine are shown in Fig. 1. The decrease in ear temperature by the uncoated tablet was larger than that by the sustained release capsule during the first 2 hr period after the administration and returned to the initial level 4 hr later. The lowered of ear temperature after administration of the sustained release capsule was maintained from 1 to 4.5 hr.

Fig. 2 shows the mean plasma levels of ethylphenylephrine in rabbits. The plasma level of ethylphenylephrine after oral administration of the uncoated tablet was higher up

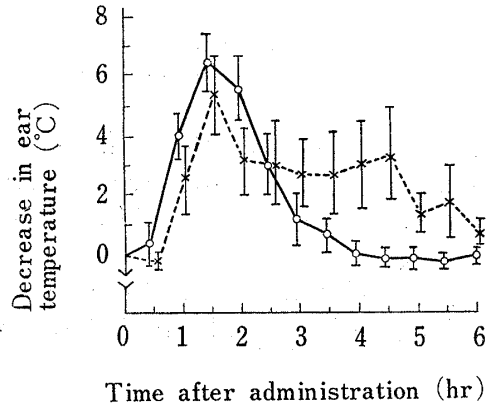

Fig. 1. Means Decrease in Ear Temperature after Oral Administration of Two Different Dosage Forms of Ethylphenylephrine in Rabbits

—○—: uncoated tablet in a dose equivalent to 60 mg of ethylphenylephrine, $n=6$
---×---: sustained release capsule in a dose equivalent to 60 mg of ethylphenylephrine, $n=6$
Vertical lines indicate the standard error of the mean.

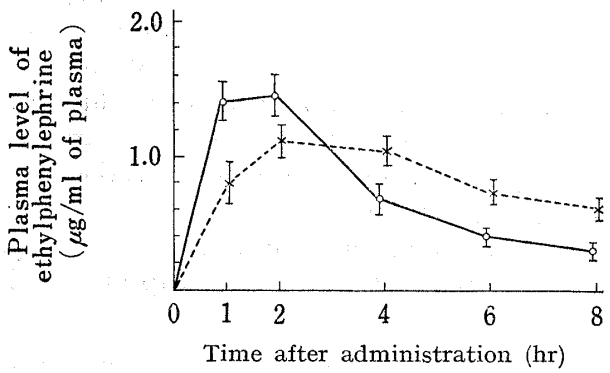

Fig. 2. Mean Plasma Levels of Ethylphenylephrine after Oral Administration of Two Different Dosage Forms in Rabbits

—○—: uncoated tablet in a dose equivalent to 60 mg of ethylphenylephrine, $n=6$
---×---: sustained release capsule in a dose equivalent to 60 mg of ethylphenylephrine, $n=6$
Vertical lines indicate the standard error of the mean.

4) P. Danneberg, E. Hasse, R. Hahn, and R. Stalb, *Arzneimittelforsch.*, **15**, 207 (1965).

to 2 hr and conversely lower from 4 to 8 hr than that after administration of the sustained release capsule.

From these results it was confirmed that the ear temperature-lowering effect correlated well with the plasma level after the oral administration of two different dosage forms in rabbits.

Decreases in Ear Temperature, Plasma Levels, and Urinary Excretion in Dogs

As shown in Fig. 3 a similar decrease in ear temperature was observed after oral administration of either the uncoated tablet or the sustained release capsule during the first 5 hr period in dogs. Thereafter, effect of the sustained release capsule was more potent than that of the uncoated tablet.

The mean plasma levels after oral administration of two dosage forms in dogs are presented in Fig. 4. The mean level of ethylphenylephrine after oral administration of the uncoated

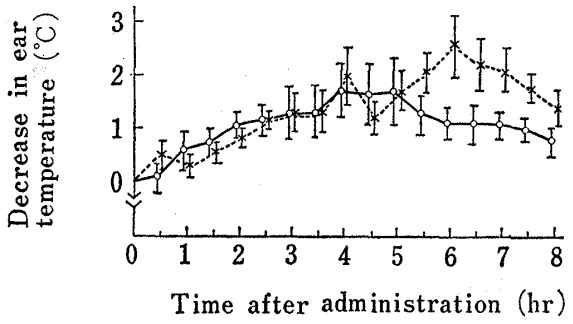

Fig. 3. Mean Decreases in Ear Temperature after Oral Administration of Two Different Dosage Forms of Ethylphenylephrine in Dogs

—○—: uncoated tablet in a dose equivalent to 60 mg of ethylphenylephrine, $n=6$
---×---: sustained release capsule in a dose equivalent to 60 mg of ethylphenylephrine, $n=6$
Vertical lines indicate the standard error of the mean.

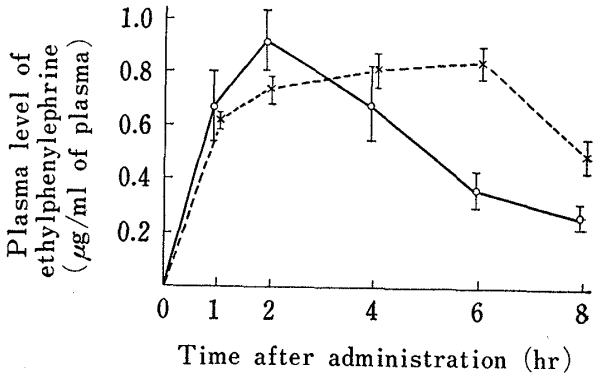

Fig. 4. Mean Plasma Levels of Ethylphenylephrine after Oral Administration of Two Different Dosage Forms in Dogs

—○—: uncoated tablet in a dose equivalent to 60 mg of ethylphenylephrine, $n=6$
---×---: sustained release capsule in a dose equivalent to 60 mg of ethylphenylephrine, $n=6$
Vertival lines indicate the standard error of the mean.

tablet reached the peak level in 2 hr and declined thereafter. The peak plasma level after administration of the sustained release capsule was observed in 6 hr, raising the level gradually during 1 to 6 hr after the administration.

A high plasma level was detected during 1 to 4 hr after the administration of both dosage forms, but the decrease in ear temperature was of a small degree. Thus, the ear tempeature-lowering effect was not correlated with the plasma level after the administration of two different dosage forms in dogs.

The mean excretion in urine for a 48 hr period after oral administration of the uncoated tablet and the sustained release capsule was 70.6 and 71.4% in terms of total, and 42.2 and

Table II. Urinary Excretion of Ethylphenylephrine during a 48 hr Period after Oral Administration of Two Different Dosage Forms in Dogs

Dosage form	% of dose in terms of	
	free	total
Uncoated tablet	42.2±5.9[b]	70.6±6.1
Sustained release capsule	44.4±2.3	71.4±3.9

a) equivalent to 60 mg of ethylphenylphrine
b) mean ± S.E., $n=6$

44.4% in terms of free ethylphenylephrine of the dose given in dogs, respectively. Approximately 60% of the amount excreted was detected as free ethylphenylephrine (Table II).

Urinary Excretion in Men

During the first 24 hr period after oral administration of the uncoated tablet and the sustained release capsule, 11.7 and 12.2 mg, respectively, of ethylphenylephrine in average was recovered in the urine of men (Fig. 5). Free ethylphenylephrine was not detected in human urine. The excretion of ethylphenylephrine after administration of the uncoated tablet was large during the first 2 and 4 hr period, whereas the rate of excretion after administration of the sustained release capsule became large 6 to 12 hr later.

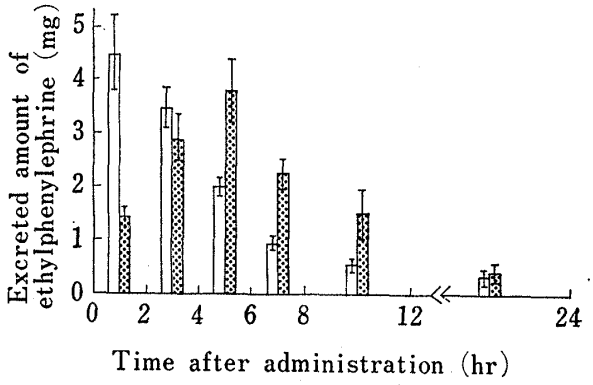

Fig. 5. Urinary Excretion of Ethylphenylephrine after Oral Administration of Two Different Dosage Forms in Men

□: uncoated tablet in a dose equivalent to 15 mg of ethylphenylephrine, $n=6$
▨: sustained release capsule in a dose equivalent to 15 mg of ethylphenylephrine, $n=6$
Vertical lines indicate the standard error of the mean.

Discussion

The absorption of ethylphenylephrine in rabbits, dogs, and men was rapid after oral administration of the uncoated tablet which rapidly released the drug and was slow after administration of the sustained release capsule which gradually released the drug by *in vitro* test. The peak plasma level (rabbits and dogs) or the peak excretion (men) after administration of the uncoated tablet was reached 1.5 hr faster (rabbits) and 4 hr faster (dogs and men) than after administration of the sustained release capsule. It might be suggested that the absorption pattarn of two different dosage forms in men is rather similar to that in dogs than in rabbits.

An interesting observation was that there was no correlation between the plasma level of ethylphenylephrine and its pharmacological effect (ear temperature-lowering effect) in dogs. For its reason, it is speculated that the onset of the lowering of ear temperature is essentially slow in spite of a high plasma level in dogs, as already shown in the previous report.[3] If this speculation were true, it is quite natural that similar plasma level by both dosage forms during the first 1 to 4 hr period after the administration should causes a similar effect. More detailed studies will be necessary to clarify this problem. Longer duration of the effect was also observed by the used sustained release capsule in dogs, same as in rabbits.

During a 48 hr period in dogs and a 24 hr period in men after administration of the sustained release capsule, the total amount of ethylphenylephrine excreted in the urine was equal to that after administration of the uncoated tablet, indicating an equal bioavailability of both dosage forms in dogs and men. It is interesting that approximately 60% of the total amount excreted in the urine of dogs was found to be free ethylphenylphrine, but no free ethylphenylephrine was found in the urine of men. Danneberg, *et al.*[4] have postulated the formation of glucuronic acid or sulfuric acid conjugate of ethylphenylephrine as a possible metabolite in dogs. The difference in the amount excreted between free and total ethylphenylephrine in the present study also suggests the possibility of conjugations.

The determination of blood concentration of ethylphenyleprine in men receiving 15 mg of the drug was impossible because of the low drug levels. Therefore, only urinary excretion was determined in the present study according to the proposal of Beckett[5] with regard to

5) A.H. Beckett, *Pharm. J.*, **201**, 425, (1968).

the evaluation for absorption of the sustained release dosage forms. A more sensitive technique for determining the low concentration of ethylphenylephrine in blood must be found for further experiments.

Acknowledgement The authors express their deep gratitude to Dr. Y. Aizawa, Professor of Tokyo College of Pharmacy, for his kindness in publishing of this manuscript, and also to Dr. H. Negoro, Director of this Laboratories, for his encouragement and permission for publication of this work. Thanks are given to Mr. K. Sasahara and Mr. T. Yoshizaki for the useful discussion and technical assistance during this work.