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Release and Rectal Absorption of Aminophylline Suppositories Prepared in a Hospital Pharmacy

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In vitro release and in vivo rectal absorption of suppositories containing aminophylline and various bases prepared in our hospital pharmacy were investigated. The release tests were conducted using three methods: the cylindrical filter paper method, the Sartorius solubility simulator method and the disintegration test in J.P. IX. In all cases, release from PEG-containing suppositories was better than that from Witepsol-containing products. However, this tendency was not reflected in the blood level of theophylline after rectal absorption of these suppositories.

(Key Words: Aminophylline Suppositories, Rectal Absorption, Blood Level of Theophylline, Release Test)

INTRODUCTION

In our previous report (1), we described the stability of aminophylline suppositories and observed that the suppository using PEG base, a water-soluble base, was the most stable. The PEG base is different in pharmaceutical characteristics from an oil base, Witepsol, which is prepared in our hospital pharmacy and now used clinically. Since drug absorption from the rectum is largely influenced by the base, careful attention should be paid to the selection of the optimal base. There are many reports on rectal absorption of aminophylline in western countries, but only a few reports are available in Japan (2, 4, 5, 6, 7, 11, 12). In the present report, we examined the influence of the base on rectal absorption of aminophylline by three release test methods and by measuring the level of aminophylline in rabbit blood.

MATERIALS AND METHODS

I. Materials

1. According to the same methods described in our previous report (1), suppositories containing 100mg of aminophylline were prepared using various bases. The bases used were as follows: Witepsol H-15, Witepsol W-35, a combination of Witepsol H-15 and E-75 (50;50) (H-15 + E-75), and PEG base (PEG 6000:PEG 1540:water = 53:32:15)
2. Aminophylline tablets: Neophylline tablets (Aminophylline content: 100mg/tablet, Eizai, D10AB)
3. Aminophylline injections: Neophylline injections (Aminophylline content: 250mg/10ml, Eizai, A12AB)

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PEG: Polyethylene Glycol

4. Suppositories containing 80mg of theophylline using various suppository bases. Bases used: Witepsol H-15 + E-75 (50:50), PEG base (PEG 6000: PEG 1540: water = 53:32:15).

II. Release test of the main ingredient from the suppositories

In vitro releases of aminophylline from the bases were examined using three methods: the cylindrical filter paper method, the disintegration test in J.P. IX and the Sartorius solubility simulator method. In each method, the test sample was diluted to the optimal concentration and its absorbance was determined at a wave length of 272nm by a Hitachi model 124 spectrophotometry. The concentration of the drug was calculated from the calibration curve.

a) Cylindrical filter paper method: The test was performed according to the method described by Kakemi and coworkers (3). A beaker which contained 100ml of saline was kept at 37 ± 0.5°C, and the stirrer at the bottom was rotated at 200rpm. One tablet of the suppository was placed in a cylindrical filter pater No. 84 and immersed in the beaker. An aliquot of 1ml was taken from a constant site at constant intervals to serve as the test sample. The same volume of saline was supplemented.

b) Disintegration test in J.P. IX: To the equipment for the disintegration test of tablets and capsules specified in J.P. IX, 740ml of water was added, and it was kept at 37.5°C. One tablet of the suppository was placed in a glass tube (29 to 30 reciprocating vertical movements, amplitude of the movements: 50mm). An aliquot of 5ml was taken from a constant site at constant intervals using a pipette with a cotton plug to obtain test samples. The same volume of water was supplemented.

c) Sartorius solubility simulator method: For this test, a Sartorius solubility simulator was used (8, 9). In the bath for the solubility test with the temperature regulated at 37°C, 100ml of saline, 72g of beads and one tablet of the suppository were placed and it was rotated at 1.2 rpm around the horizontal axis. A test sample of 2.5ml was obtained through a filter at constant intervals.

In each test (a to c), the measurement was repeated four times.

III. Blood concentrations in rabbits

White male rabbits weighing about 3kg (four rabbits in each group) were given 20mg/kg of aminophylline through an ear vein, the anus or orally after fasting for 24 hours. To prevent expulsion of suppository, cotton was placed in the anus and fixed with an adhesive bandage. Two milliliters of blood was taken from the ear vein 15, 30, 60 and 90 minutes, and 2, 4, 6 and 8 hours after drug administration. The blood concentration of the drug was determined according to the method of Schack and Waxler (12). Heparinized blood was extracted with 20ml of a mixture of chloroform and isopropanol (20:1) and centrifuged. The organic layer of 15ml was removed extracted with 5ml of 0.1N-NaOH, and centrifuged. The drug concentration per milliliter of the blood was determined by measuring the absorbance of the water phase at a wavelength of 273nm and calculating based on the standard curve.

J.P. IX: Japanese Pharmacopoeia 9

IV. Comparison with theophylline suppositories

Aminophylline is a highly water-soluble derivative of theophylline. Since it is expected that theophylline does not necessarily need to be water-soluble when it is used in a suppository, we used a PEG base and the combined base of Witepsol H-15 and E-75 (50:50) to investigate the release and blood concentration of theophylline suppositories. Suppostories containing 80mg of theophylline (equivalent to 100mg of aminophylline) were prepared. The rabbit was given 16mg/kg of theophylline (corresponding to 20mg/kg of aminophylline).

EXPERIMENTAL RESULTS

I. Release test

a) Cylindrical filter paper method

T_{50} (time required for 50% dissolution of the main drug) was 13 minutes for the H-15 base and 14 minutes for the PEG base. There was 100% drug release within 30 minutes from both bases. However, less than 10% of the drug was released from the H-15 + E-75 base or W-35 base even after 90 minutes. When the drug in the PEG base was kept for 6 months in either a cool place or at room temperature, there was no significant change in its release properties.

However, when the drug in H-15 base was kept in a cool place, the T_{50} value of the drug was 40 minutes. When the drug in H-15 base was kept at room temperature, the release was delayed and only 23% of the drug was released after 90 minutes.

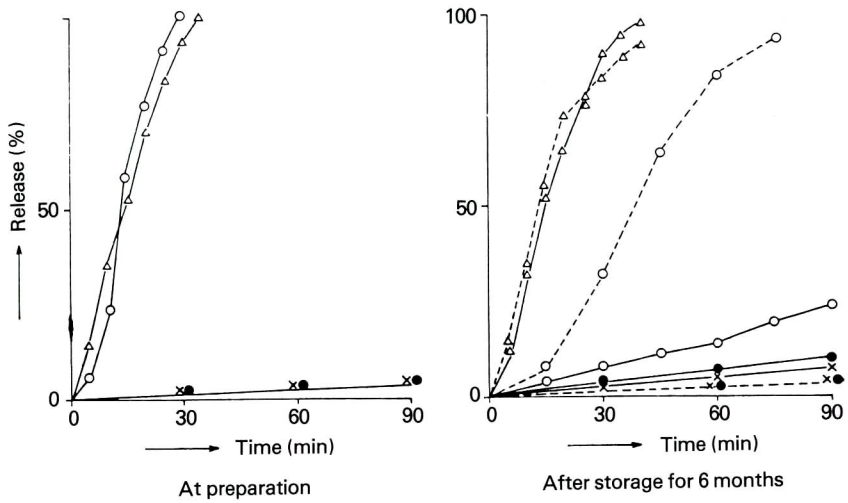

Fig. 1 Release test f aminophylline suppository by the cylindrical filter method.
○H − 15 base × W − 35 base ●H + E base △P.E.G. base
····Storage in a cool place ——Storage at room temperature

b) Disintegration method (JP IX)

There was 100% of drug release from the PEG base and H-15 base in 20 minutes and from the H-15 + E-75 base and W-35 base in 30 to 60 minutes. T_{50} was 4 minutes for the H-15 base, 6 minutes for the PEG base, 15 minutes for the H-15 + E-75 base and 32 minutes for the W-35 base. Thus, these

observations showed that there is a significant difference among the various types of Witepsol oil bases. When the drug in PEG base was kept for 6 months, the drug release was not changed either in a cool place or at room temperature. When the drug in Witepsol base was kept in a cool place, drug release was not changed. When the drug was stored at room temperature, the release was decreased; T_{50} was 24 minutes for the H-15 base, and over 90 minutes for the H-15 + E-75 base and W-35 base.

c) Sartorius solubility simulator method

The drug was released most rapidly from the H-15 base; i.e. 100% in 15 minutes. There was 100% of drug release from the W-35, PEG and H-15 + E-75 bases within 30 minutes. T_{50} was 8.5 for the H-15 base, 13.3 for W-35, 14.6 for PEG and 13.2 minutes for H-15 + E-75; there was no significant difference among the types of bases. When the drug in W-35 base was stored

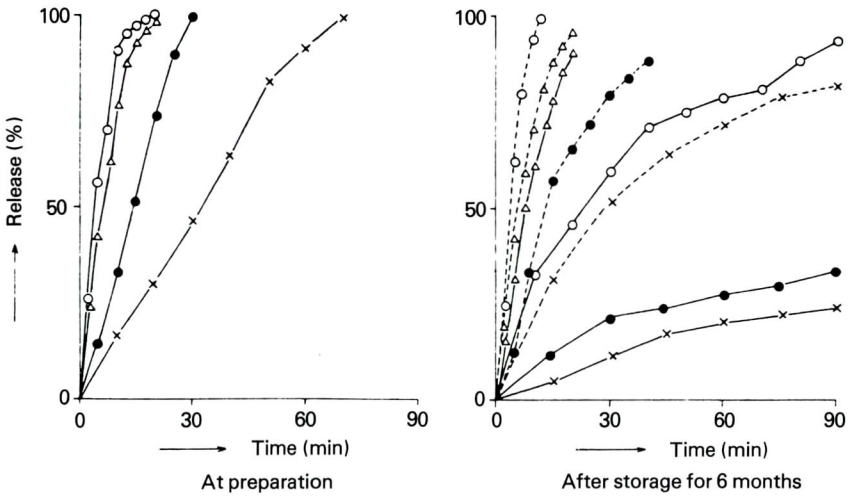

Fig. 2 Release test of aminophylline suppository by the disintegration test in JP IX.
○H − 15 base × W − 35 base •H + E base △P.E.G. base
····Storage in a cool place ——Storage at room temperature

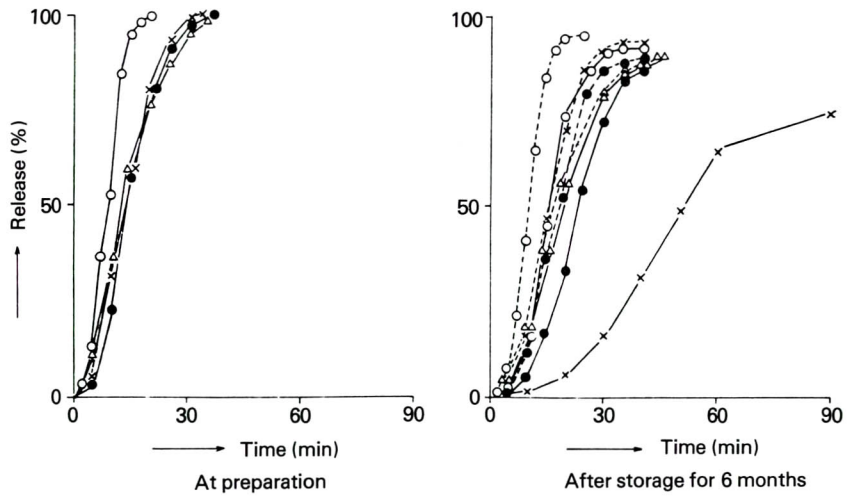

Fig. 3 Release test of aminophylline suppository by the Sartorius solubility test.
○H − 15 base × W − 35 base •H + E base △P.E.G. Base
····Storage in a cool place ——Storage at room temperature

at room temperature for 6 months, T_{50} was significantly prolonged to 50 minutes.

II. Blood concentrations in rabbits

Fig. 4 shows the blood concentrations of the theophylline by types of bases after administration of aminophylline suppositories. At each time interval after drug administration the Witepsol oil base, showed higher blood concentrations than the PEG base. No differences were observed among the various types of Witepsol bases. When the drug in Witepsol oil base was administered, the maximum blood concentration of the drug was attained within 1 hour after the administration. However, when the drug was given in water-soluble PEG base, the drug reached a peak in 30 minutes. Thus, the drug in the latter base was more rapidly absorbed, but, no difference was observed in the peak blood level.

Fig. 5 shows the changes of the blood concentrations after intravenous,

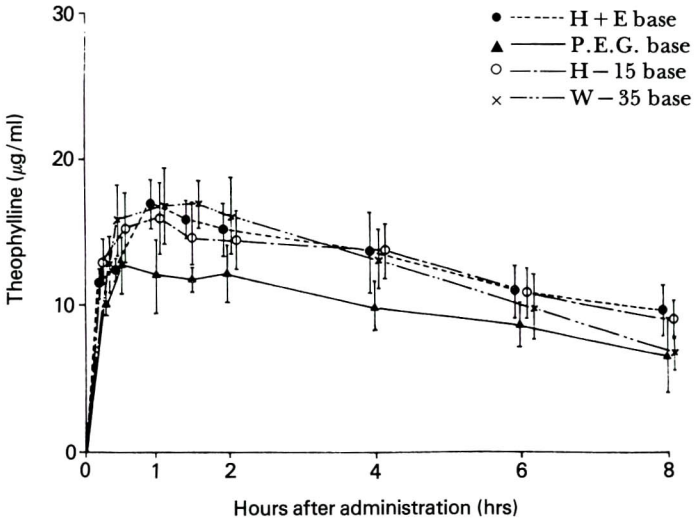

Fig. 4 Blood concentrations of theophylline in rabbits (20 mg/kg of aminophylline)

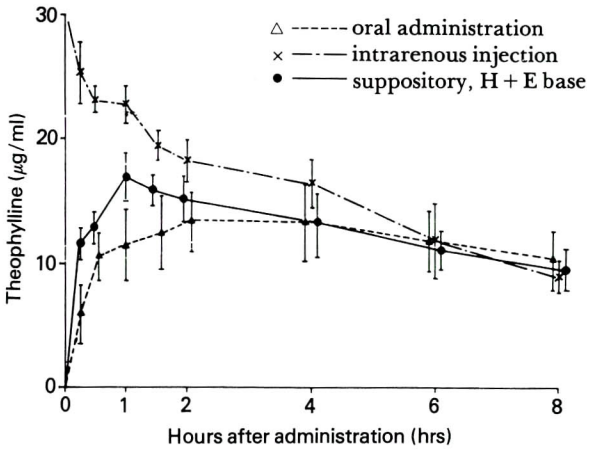

Fig. 5 Blood concentrations of theophylline in rabbits (administration of 20 mg/kg of aminophylline)

oral and rectal administration of the drugs. Witepsol H-15 + E-75, which we now employ in our hospital pharmacy, was used for the suppository test base. When the drug was given intravenously, it reached a level of 25 μg/ml after 15 minutes and decreased thereafter.

The maximal blood level was observed 1 hour after rectal administration and 2 hours after oral administration. No difference was seen in the peak blood level between rectal (suppository) and oral administration.

However, higher blood levels were attained after 15 and 60 minutes and also after 30 and 90 minutes when the drug was given as a suppository.

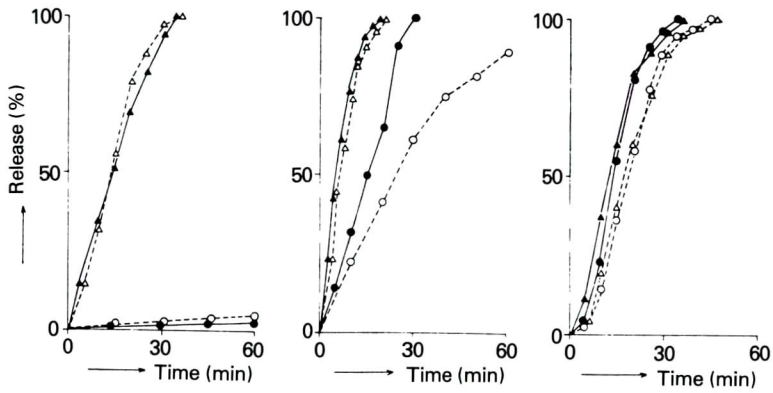

Fig. 6 Release tests of suppositories
1. Cylindrical filter paper method
2. Disintegration test in J.P. IX
3. Sartorius solubility test method

△ ------ P.E.G. base, theophylline suppository
○ ------ H + E base, theophylline suppository
▲ —— P.E.G. base, aminophylline suppository
● —— H + E base aminophylline suppository

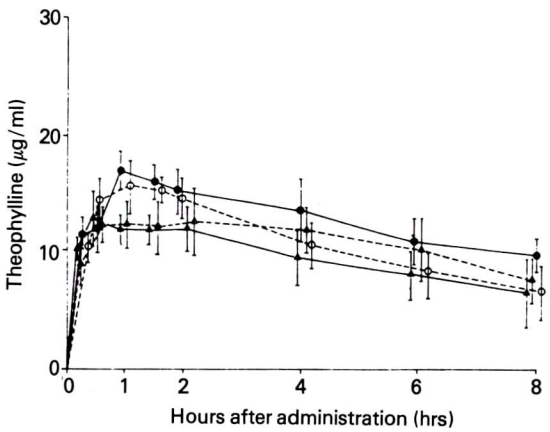

Fig. 7 Blood concentrations of theophylline in rabbits (administration of 20 mg/kg of aminophylline, or 16 mg/kg of theophylline)

△ ------ P.E.G. base, theophylline suppository
○ ------ H + E base, theophylline suppository
▲ —— P.E.G. base aminophylline suppository
● —— H + E base aminophylline suppository

III. Comparison with theophylline suppositories

In the comparison between aminophylline and theophylline suppositories, the results of release tests (three methods) are shown in Fig. 6, and the changes in the blood concentrations in Fig. 7. No difference was observed in the results of release tests of both aminophylline and theophylline suppositories. As already shown in Fig. 4, a difference between PEG base and H-15 + E-75 base aminophylline suppositories was found in the blood concentrations 1 to 4 hours after drug adminstration. In contrast, no difference was seen between the two types of theophylline suppositories (Fig. 7).
The results indicate that a greater difference can be seen when the types of base are different but only a small difference is observed between aminophylline and theophylline suppositories if their bases are identical.

DISCUSSION

We compared three types of release tests for suppositories. The solution volume was 100ml for both the cylindrical filter paper method and the Sartorius solubility simulator method and 740ml for the disintegration test in JP IX. The degree of vibration and agitation was the severest in the Sartorius solubility test and this degree decreased in the order of the disintegration test (JP IX) and the cylindrical filter paper method. The difference in drug release observed in the present study may be due to the degree of vibration and agitation rather than the solution volume in each test. With the cylindrical filter paper method, extremely poor release was observed for Witepsol H-15 + E-75 and W-35 bases when compared with the H-15 base. The poor release of the drug from the H-15 + E-75 base seems to be attributable to the addition of 5% bleached beeswax to the E-75 base. Tanno and coworkers (10) reported that the release of the main drug was inhibited in a cellulose tube method when beeswax was added to cacao butter. In the disintegration test in JP IX, differences could be observed among the types of bases. This disintegration method also allowed us to observe easily the time course changes of drug release. In each of the release test, the drug was released more rapidly from the PEG base than from Witepsol H-15 + E-75. The results of these release tests were inconsistent with the results of the blood concentrations after rectal administration. Therefore, it seems difficult to predict the degree of rectal absorption in vivo based on the results of these release tests. Although the suppository containing PEG base was stable physicochemically, this suppository showed lower blood concentrations than that containing the H-15 + E-75 base which we are now using clinically. Therefore, attention should be directed to the clinical use of the PEG base.

Aminophylline suppositories containing H-15 + E-75 base, which is now clinically employed, show more remarkable absorption than oral aminophylline, and the drug is relatively stable for up to 6 months when kept in a cool place. These observations suggest that the preparation of aminophylline suppositories in H-15 + E-75 base is applicable to clinical use as long as the drug is stored in a cool place. We are planning to examine the rectal absorption of this preparation in subsequent experiments.

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