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COMPARATIVE BIOAVAILABILITY OF A NEW SUSTAINED-RELEASE THEOPHYLLINE TABLET

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The bioavailability of a newly designed sustained-release theophylline tablet formulation (NIK-168TX) was investigated in five healthy volunteers after a single oral dose in a cross over study. Another sustained-release theophylline tablet (Theo-Dur) and an immediate-release tablet formulation (Neophylline), both widely used clinically, were used for comparison. We tested the dissolution of the new formulation by the rotating basket method according to the USP XX. The in vitro dissolution rates showed prolonged release of theophylline, with a tendency to increase in the presence of 0.1% polysorbate 80. The mean values of maximum plasma concentration (C_{max}), the peak time (T_{max}) and mean residence time (MRT) were significantly different between the sustained-release formulations and Neophylline, although no significant difference between the new formulation and Theo-Dur was found. On the other hand, these formulations showed no statistically significant difference in the area under the plasma concentration-time curve ($AUC_{0\to\infty}$). The new formulation had good sustained-release characteristics with adequate bioavailability like that of Theo-Dur, which has complete absorption. The new formulation probably has a more sustained action than Theo-Dur.

Key words: bioavailability —— dissolution test —— sustained-release theophylline formulation —— immediate-release formulation —— Theo-Dur —— healthy volunteers

INTRODUCTION

Theophylline is regarded as useful in the treatment of patients with reversible obstructive airway diseases and its effect as a bronchodilator is well established[1)2)]. The efficacy of theophylline in the control of chronic asthma depends on the maintenance of plasma theophylline concentrations between 10 and 20 μg/ml[3)4)].

Many review articles on the bioavailability of sustained-release theophylline formulations have now been published[5)-8)]. However, one of these articles stated that some formulations had a high bioavailability, while others showed erratic and incomplete absorption[6)].

Recently, there has been much interest in sustained-release theophylline formulations with a more sustained action than those now most commonly used. The use of such formulations is advantageous in cases of poor patient compliance in maintaining effective plasma concentration of theophylline.

The aim of the present study was to determine the bioavailability of a newly designed sustained-release theophylline tablet formulation (NIK-168TX), and compare it with a different sustained-release formulation (Theo-Dur) and an immediate-release formulation (Neophylline), both already available for clinical work.

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Abbreviations: CL plasma clearance; C_{max} maximum plasma concentration; K_a apparent absorption rate constant; K_{el} apparent elimination rate constant; **MRT** mean residence time; T_{max} time to reach maximum plasma concentration (C_{max}); **Vd** volume of distribution

MATERIALS AND METHODS

Drug

We tested a newly designed sustained-release theophylline tablet formulation (NIK-168TX), which contains 200 mg of theophylline per tablet (Nikken Chemicals Co., Ltd., Tokyo). Another sustained-release tablet, Theo-Dur (theophylline 100 mg per tablet; Nikken Chemicals Co., Ltd., Tokyo) and an immediate-release tablet, Neophylline (theophylline 80 mg per tablet; Eisai Co., Ltd., Tokyo) were used as the reference drugs.

In vitro dissolution study

The in vitro dissolution rate of theophylline from the test formulation was tested with a USP XX dissolution apparatus by the rotating basket method. The test formulation was submitted to 12 hr dissolution appraisals in the media (JP X 1st fluid and JP X 2nd fluid), and also in the same medium with the addition of 0.01% or 0.1% (w/v) of polysorbate 80, at a stirring rate of 100 rpm at 37°C. The initial medium, JP X 1st fluid (pH 1.2), was kept for 2 hr and the beaker was then removed and the medium replaced by JP X 2nd fluid (pH 6.8). Five ml of the medium was sampled at appropriate time intervals, and the volume was kept constant by adding the same volume of the respective medium. The theophylline content was measured spectrophotometrically.

Procedure used with healthy volunteers

Characteristics of the nonsmoking volunteers tested are given in Table 1. We obtained informed consent from each person after full explantation of the procedures. They were judged to be healthy as determined by routine laboratory tests. Each formulation was given in a dose of 400 mg equivalent of theophylline together with 150 ml of water 2 hr after a light breakfast (a slice of bread with 100 ml of milk). The volunteers were not allowed to take xanthine-containing food or drink for 12 hr before and throughout the experiments. Drug administration trials were delivered in Latin-square design. Blood samples were taken at the following times after administration: 0, 2, 4, 6, 8, 10, 12, 14, 24 and 30 hr for the test formulation; 0, 1, 2, 3, 4, 6, 8, 14 and 24 hr for Neophylline; 0, 1, 2, 4, 6, 8, 10, 12, 14 and 24 hr for Theo-Dur. Plasma separated by centrifugation was frozen until subsequent analysis. The concentration of theophylline in the plasma was determined by a high-performance liquid chromatographic method previously reported[9].

Table 1 Characteristics of the healthy volunteers

Subject	Sex	Age (years)	B.W. (kg)	Height (cm)
A	M	25	62	168
B	M	35	54	165
C	M	22	56	166
D	M	22	53	170
E	M	25	63	173
Mean		25.8	57.6	168.4
S.E.M.		2.4	2.1	1.4
CV %[a)]		20.8	8.0	1.9

a) Coefficient of variation.

Pharmacokinetic analysis

The total area under the plasma theophylline concentration-time curve after administration ($ACU_{0\to\infty}$) was calculated as the sum of the area obtained by the trapezoidal rule from time zero to the last data point and the area calculated as an extrapolation from the last data point to infinity by dividing the last data point by the apparent elimination rate constant (k_{el}) calculated by fitting plasma concentration data after administration of Neophylline to a one-compartment model including a first-order absorption process according to Equation [1]. The parameters were analyzed by nonlinear least-squares regression analysis (MULTI[10]). The bioavailability of the test formulation was estimated by the observed maximum plasma theophylline concentration (C_{max}), the time of the C_{max} (T_{max}), $ACU_{0\to\infty}$ and the mean residence time in vivo, MRT[11]. The mean cumulative fraction of the dose absorbed after administration of the three different formulations was calculated by the method of Wagner-Nelson[12].

$$C_t=\frac{F\cdot D\cdot k_a}{Vd\ (k_a-k_{el})}\left(e^{-k_{el}\cdot t}-e^{-k_a\cdot t}\right) \quad \text{.....[Eq·1]}$$

where k_a is the apparent absorption rate constant, Vd is the apparent volume of distribution and F is the fraction absorbed. D is the dose (oral administration). Values of C_t were calculated assuming F=1.0.

Values in this paper are expressed as the mean ± standard error, and the statistical significance of differences in the pharmacokinetic data was

assessed by means of an analysis of variance and Tukey's Q test, with $p<0.05$ taken as the minimum level of significance.

RESULTS AND DISCUSSION

In vitro study

The results of comparison of the dissolution profiles of the test formulation are shown in Fig. 1. The dissolution profiles showed that approximately 90% of the theophylline was released in 12 hr from the test formulation, indicating that the test formulation prolonged the release of theophylline. It is well-known that biological surfactants such as bile salts play an important role in the dissolution and absorption processes. In the present study, 0.01 and 0.1% of polysorbate 80 were used as the surfactant in the dissolution test medium. In the presence of 0.01% polysorbate 80 no increase in the rate of release was observed, but with 0.1% polysorbate 80 approximately 100% of the theophylline was released within 12 hr. It is likely that the dissolution rate of theophylline from the test formulation shows a tendency to increase in the presence of certain surfactants. If it is assumed that the dissolution of theophylline from the test formulation is a first-order process, the dissolution rate constant (k_{dis}) calculated from

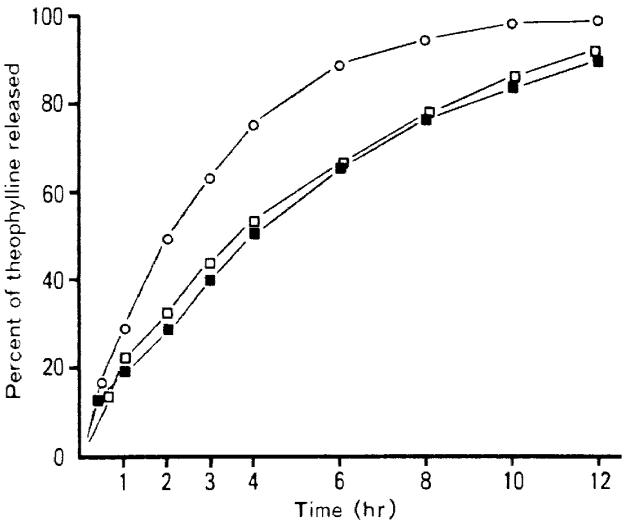

Fig. 1. In vitro dissolution of the test formulation by use of the USP XX apparatus. Each value represents the mean of three determinations. ■, without polysorbate 80; □, with 0.01% polysorbate 80; ○, with 0.1% polysorbate 80.

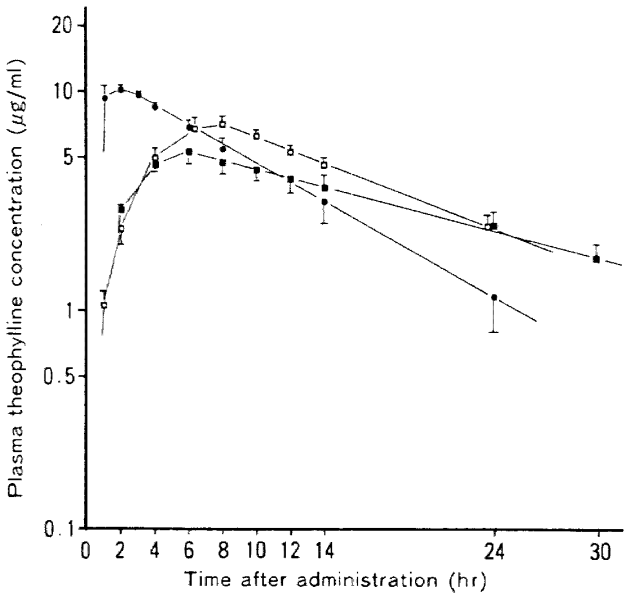

Fig. 2. Semilogarithmic plots of plasma theophylline concentration in five subjects after a single oral administration of the three different formulations. Each value represents the mean ± S.E.M. of five subjects. ■, test formulation; □, Theo-Dur; ●, Neophylline.

the slope of the log residual ratio versus time curve, by least squares regression analysis, was shown to be 0.172 ± 0.008 h^{-1} in the absence and 0.429 ± 0.011 h^{-1} in the presence of 0.1% polysorbate 80. On the other hand, the release property of Theo-Dur in the in vitro study was shown to be an apparent zero-order release process with a release rate of approximately 10% of the dose[13]. From these in vitro data, it may be concluded that there is a difference in the in vitro dissolution behaviour between the test formulation and Theo-

Table 2 Computer estimates of pharmacokinetic parameters following administration of Neophylline

Subject	k_a (1/hr)	k_{el} (1/hr)	Vd (l/kg)	CL (ml/kg/hr)
A	1.534	0.088	0.574	50.51
B	2.093	0.091	0.552	50.23
C	2.441	0.076	0.580	44.08
D	1.852	0.153	0.578	88.43
E	0.621	0.189	0.445	84.11
Mean	1.708	0.119	0.547	63.47
S.E.M.	0.310	0.022	0.026	9.40

Plasma theophylline clearance, CL, was calculated as K_{el}. Vd.

Table 3 Bioavailability parameters of three different theophylline tablet formulations

Formulation	C_{max} (μg/ml)	T_{max} (hr)	$AUC_{0\to\infty}$ (μg · hr/ml)	MRT (hr)
Neophylline	10.65±0.57	1.80±0.37	122.33±17.47	10.38±1.37
Theo-Dur	7.33±0.66[a)]	7.60±0.75[a)]	128.39±13.68	18.65±2.30[a)]
NIK-168TX	5.29±0.54[a)]	6.00±0.00[a)]	116.72±16.63	24.19±2.18[a)]

Values represent the mean±S.E.M. of five subjects.
a) Statistical significance from Neophylline at $p<0.05$.
C_{max}=maximum theophylline concentration.
T_{max}=time which the maximum theophylline concentration is reached.
$AUC_{0\to\infty}$=area under the theophylline concentration-time curve during the period from zero to infinity after administration.
MRT=the mean residence in vivo, calculated by use of moment analysis.

Dur. A detailed examination of the in vitro dissolution behaviour of the test formulation will be reported in the next paper of this series.

Comparative bioavailability of the three different formulations

Fig. 2 shows the comparison of the mean plasma theophylline concentration-time curve after administration of the three different formulations. The mean theophylline concentrations for the test formulation and Theo-Dur showed slower and more prolonged absorption than Neophylline. The mean plasma theophylline concentration-time curve after administration of the test formulation was similar to that of Theo-Dur, but the test formulation exhibits a longer half-life of elimination than Theo-Dur.

Pharmacokinetic parameters of theophylline after single oral dosing of Neophylline are listed in Table 2. Bioavailability parameters such as $AUC_{0\to\infty}$, maximum plasma concentration (C_{max}), the peak time (T_{max}) and MRT for each formulation are also listed in Table 3. The C_{max}, T_{max} and MRT values were significantly different between the sustained-release formulations and Neophylline, although no significant difference between the test formulation and Theo-Dur was found. On the other hand, there was no statistically significant difference among these formulations with regard to the area under the plasma concentration-time curve ($AUC_{0\to\infty}$). The results show that the extent of absorption calculated from the ratio of the $AUC_{0\to\infty}$ of the test formulation to that of the completely absorbed reference drugs[1)7)14)] is nearly equal among these formulations. Moreover,

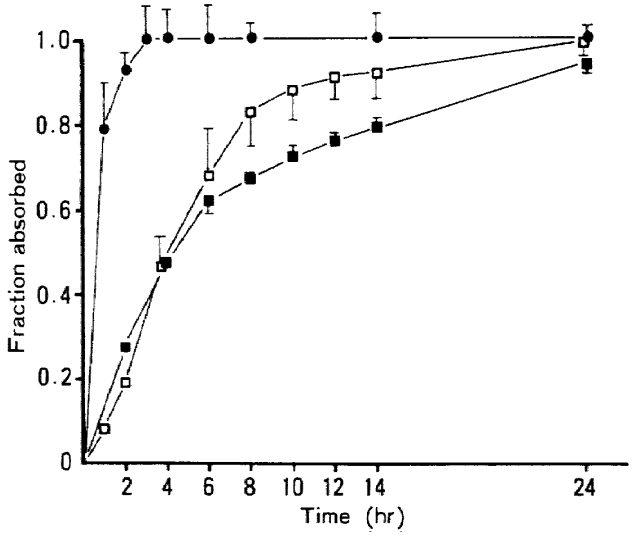

Fig. 3. The cumulative fraction of the dose absorbed over time after a single oral administration of the three different formulations. Each value represents the mean ± S.E.M. of five subjects. ■, test formulation; □, Theo-Dur; ●, Neophylline.

Fig. 3 shows the mean cumulative fraction of the dose absorbed after administration of the three different formulations. The result shows that the test formulation is slowly absorbed, with a more sustained release than Theo-Dur. These results obtained in the bioavailability test indicate that the test formulation and Theo-Dur are equivalent in the extent of bioavailability and show a tendency to differ in the rate of bioavailability between the test formulation and Theo-Dur, although there was no statistically significant difference in the MRT. In addition, the mean absorption profile of theophylline during 24 hr in the test formula-

tion did not show a correlation with in vitro dissolution behaviour obtained from the in vitro dissolution test. Previously, we found that the in vitro sustained-release characteristics of Theo-Dur were confirmed to be reflected in the plasma concentration-time behaviour and that the gastrointestinal absorption is best described as an apparent zero-order rather than a first-order process[12)14)]. From the result shown in Fig. 3, it may be thought that the test formulation is a preparation disigned with a slow-absorption phase followed by a slower-absorption phase.

Recently, Uchida et al.[15)] have reported that the values of C_{max} and T_{max} were observed to be 6.3 μg/ml and 6 hr, respectively in patients with bronchial asthma after once-a-day administration of the test formulation in the early morning and that clinical efficacy was also found. Their results were nearly equal to those obtained in the present study.

On the basis of these observations, it is concluded that the test formulation, NIK-168TX, has good sustained-release properties with a bioavailability as good as that of Theo-Dur. Moreover, the test formulation seems to offer advantages in cases of poor patient compliance and for the purpose of maintaining effective plasma theophylline concentrations. However, in the clinical use of sustained-release formulations we must take into consideration the effect of food on absorption and bioavailability[16)17)]. In the case of Theo-Dur, there were no significant decreases in absorption and bioavailability after administration with food[18)]. In the present study, the volunteers received the formulations 2 hr after a light breakfast. Further study of the test formulation is needed to determine the reproducibility in plasma concentration, and also to determine whether the absorption and bioavailability of the test formulation are affected by food. Later, we will investigate the comparative advantages of the test formulation from a clinical point of view.

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新しい徐放性テオフィリン錠の Bioavailability

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新しく開発された徐放性テオフィリン製剤(NIK-168TX)の bioavailability 評価を，健常成人5名を対象として対照徐放製剤（Theo-Dur）及び即放性製剤（Neophylline）と比較検討した．NIK-168TX の in vitro 放出挙動は十分な徐放性を示した．この製剤の薬物放出速度は消化管内の界面活性様物質(ポリソルベート80使用)によって速くなる傾向を示した．各製剤投与後の最高血中濃度（C_{max}），最高血中濃度到達時間（T_{max}）及び平均滞留時間（MRT）は両徐放性製剤と即放性製剤との間で有意な差が認められたが，両徐放性製剤間では有意な差はなかった．一方，血中濃度曲線下面積（AUC）は各製剤間で差は認められなかった．このことより，NIK-168TX は Theo-Dur とほぼ同等の bioavailability を有し，かつ十分な徐放特性を有する製剤であることが明らかとなった．