Majalah Farmasi Indonesia, 14(1), 233-237 , 2003

PHARMACOKINETIC PROFILE AND COMPARATIVE BIOAVAILABILITY OF PENTOXYPHYLLINE FROM TWO SUSTAINED-RELEASE PENTOXYPHYLLINE TABLETS IN INDONESIAN HEALTHY VOLUNTEERS

PROFIL FARMAKOKINETIK DAN KETERSEDIAAN HAYATI KOMPARATIF PENTOKSIFILIN DARI DUA SEDIAAN TABLET LEPAS LAMBAT PENTOKSIFILIN PADA SUKARELAWAN SEHAT INDONESIA

Yeyet C. Sumirtapura*, Wibawati Sulistyo, Herwanto Suhalim****
*Department of Pharmacy, Bandung Institute of Technology, Bandung, Indonesia.
**Sanbe Farma, Bandung, Indonesia.

ABSTRACT

In order to assess the quality of a sustained-release pentoxyphylline tablet formulated and produced by a domestic company (PLTF-400), a comparative bioavailability study was carried out in twelve healthy Indonesian volunteers in two-way crossover design. TRTL-400, innovator's product, was taken as reference product. Plasma sample was used and unchanged pentoxyphylline compound was analyzed using HPLC method.

It was found that PLTF-400 was bioequivalent to the reference product (TRTL-400) with 90 % confidence intervals of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ ratio (Test/Reference) of 93.1%-132.0%, 90.6% - 123.5%**,** and 84.2% - 116.2%, respectively. The pharmacokinetic parameters (C_{max}, AUC, half-life) of the drug found in this study were comparable to those obtained previously by the other authors in differrent ethnics.

Keywords: Pentoxyphylline, sustained-release, bioavailability, pharmacokinetics.

ABSTRAK

Dalam rangka penilaian mutu sebuah sediaan tablet pentoksifilin yang dihasilkan oleh sebuah industri farmasi nasional (PLTF-400), telah dilakukan uji ketersediaan hayati komparatif pada 12 sukarelawan sehat Indonesia dengan cara silang lengkap. TRTL-400 digunakan sebagai produk pembanding. Sampel yang digunakan adalah plasma dan senyawa yang dianalisis adalah senyawa utuh pentoksifilin, yang ditentukan secara kromatografi cair kinerja tinggi.

Hasil yang diperoleh menunjukkan bahwa PLTF-400 bioekivalen terhadap sediaan pembanding dengan nilai 90% *confidence interval* rasio $C_{maks,}$ AUC_{0-t} dan $AUC_{0-\infty}$ masing-masing secara berurutan 93,1% - 132,0%, 90,6% - 123,5%, dan 84,2% - 116,2%. Harga parameter-parameter farmakokinetik (C_{maks}, AUC, waktu paro eliminasi) yang dihasilkan dalam penelitian ini berdekatan dengan yang diperoleh para peneliti lain sebelumnya pada etnik yang berbeda.

Kata kunci: pentoksifilin, lepas lambat, ketersediaan hayati, farmakokinetik.

INTRODUCTION

Pentoxyphylline [l -(5-oxohexyl)-3,7-dimethylxanthine] is a xanthine derivative used as a vasodilator in the treatment of peripheral and cerebral vascular disorders (Parfitt, 1999). The drug is widely used in

Indonesia and up to now there are about 12 pentoxyphylline drug preparations marketed in the country as sustained-release tablets (Wai Fun, 2002).

Pentoxyphylline is almost completely absorbed from the gastro-intestinal tract after oral administration but undergoes first-pass hepatic metabolism; its major metabolites are [1-(5-hydroxyhexyl)-3,7-dimethylxanthine] and [1-(3-carboxypropyl)-3,7-imethylxanthinel. The plasma half-life of the compound following bolus intravenous administration is reported to be 0.4 to 0.8 hours. Due to its short elimination half-life, the drug is formulated as sustained-release preparation in tablet dosage form.

Pentoxyphylline has a low and variable systemic availability. Following oral administration of pentoxyphylline in sustained-release tablet dosage form, the absolute bioavailability was found to be about 19%. This is due to the fact that pentoxyphylline undergoes extensive metabolic transformation intrahepatically and extrahepatically.

The aim of the study was to investigate the comparative bioavailability of a sustained-release pentoxyphylline tablet produced by a domestic company available in Indonesia (PLTF-400). As up to that moment there was still no data about pentoxyphylline pharmacokinetics in Indonesian subjects, this study was also valuable to provide the pharmacokinetic characteristics of the drug in this ethnic.

METHODS

Drug preparations

Two commercial sustained-release pentoxyphylline 400-mg tablets available in Indonesia were used in the study. The tested product was PLTF-400 (BN BB5810205) and the reference product was TRTL-400 (BN 079W135).

Experimental design and drug analysis

Twelve healthy male Indonesian volunteers, aged 21 - 45 years, weight 55 - 84 kg, and height 158 - 181 cm, participated in this study. Each subject gave a written informed consent before participating in the study. The subjects took no drugs at least one week before and during the study. Each volunteer received one tablet of each drug (with two weeks interval) in a two-way crossover design. The drug was administered at about 8 a.m. with about 150 ml of water following overnight fasting. A standard breakfast was given 2 hours after drug intake. Venous blood samples were collected into heparinized vacuum blood collector tubes just before, and 0.5, 1, l.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours after drug intake. Plasma was separated by centrifugation and stored frozen at -20°C until being analyzed.

The concentrations of pentoxyphylline in plasma samples were assayed by HPLC. The method was validated before being used.

Bioavailability parameters calculation and statistical analysis

Plasma concentration-time data for each subject and each drug were analysed by model-independent method. Area under the plasma level curve from 0 to infinity ($AUC_{0\text{-inf}}$ or $AUC_{0\text{-}\infty}$) was calculated as follow:

$$AUC_{0\text{-inf}} \text{ or } AUC_{0\text{-}\infty} = AUC_{0\text{-t}} + Ct/\beta$$

$AUC_{0\text{-t}}$ was calculated by trapezoidal rule, where *t* is the time of last measurable point (in this case t = 12 hours; at t = 24 hours the drug concentrations were below the quantification limit of the method) and β is the slope of the elimination phase which was estimated from the elimination phase by usual regression analysis of semi-logarithmic drug concentrations-time data. Time to peak (T_{max}) and peak plasma concentration (C_{max}) were taken from the experimental data without pharmacokinctic modelisation. Confidence limit of interval was used for statistical analysis of the main bioavailability parameters. All statistical analysis were carried out with 10% significant level ($\alpha = 0.1$).

The test drug preparation was considered bioequivalent to standard preparation if the 90% confidence interval (90% CI) of ratio (Test/Reference) of bioavailability parameters fell inside the interval of 80% - 125% for AUC parameters, and between 75% - 133% for C_{max} parameter (wider interval was used for C_{max} as a great variation was observed on C_{max} parameter, and it was accepted). The value of C_{max} $AUC_{0\text{-t}}$ and $AUC_{0\text{-}\infty}$ were log-transformed before statistical analysis (Anon., 1995; Bolton, 1990; Steinijans and Diletti, 1983). T_{max} parameter was analysed by Wilcoxon signed rank test (Bolton, 1990).

RESULTS AND DISCUSSION

The mean plasma levels versus time of pentoxyphylline obtained in a 12 subjects after administration of each tablet are reported in Figure 1 and the corresponding bioavailability parameters are summarized in Table I.

There were a great interindividual variation of the pharmacokinetic parameters of the drug observed during the study (Table I). After administration of PLTF-400 and TRTL-400, C_{max} obtained were respectively 134.2 $\pm$ 63.6 and 122.7 $\pm$ 72.7 ng/ml; AUC_{0-t} (t = 12 hours) were 642.3 $\pm$ 414.7 and 621.3 $\pm$ 372.6 ng/ml.hr.; $AUC_{0-\infty}$ were 716.6 $\pm$ 471.1 and 735.5 $\pm$ 414.6 ng/ml.hr. Time to peak (T_{max}) were found to be 2.0 $\pm$ 1.1 and 3.0 $\pm$ 2.3 hours for PLTF-400 and TRTL-400, respectively.

With the sampling times used in the study, the half-life parameters could not be obtained in all subjects. In some subjects, until 12 hours after drug administration, the plasma level-time course did not reach the elimination phase with adequate data points. For these subjects the $AUC_{0-\infty}$ parameter was then estimated using average β value (0.3). The half-life value of (which could be calculated in some subjects) 2.6 $\pm$ 1.1 and 2.3 $\pm$ 0.9 hours were obtained after administration of PLTF-400 and TRTL-400, respectively. The mean value of half-life parameter for all subjects and all products was 2.5 $\pm$ 1.0 hours.

The pharmacokinetic parameters of pentoxyphylline found in this study were within the range reported previously by several authors. The AUC parameter was very close to those obtained by Rames *et al.* (1990) and Mauro *et al.* (1988) but lower than that obtained by Yuen *et al.* (2000). Rames *et al.* (1990) and Mauro *et al.* (1988) found AUC value of about 500 to 700 ng/ml.hr. while Yuen *et al.* (2000) found $AUC_{0-\infty}$, value of about 1000 ng/ml.hr. It is supposed that higher $AUC_{0-\infty}$ value obtained by Yuen *et al.* (2000) was due to higher elimination half-life (smaller elimination rate constant). Yuen *et al.* (2000) found elimination half-life value of about 2.9 - 3.5 hours which is higher than that obtained in the study (2.5 $\pm$ 1.0 hours).

On the other hand, relatively prolonged absorption of the drug was observed during the study, resulted in lower $_{Cmax}$ value compared to the data obtained by Yuen *et al.* (2000). They found mean C_{max} value of about 170 ng/ml.

The difference in the prolongation of pentoxyphylline absorption (especially for TRTL-400 which was the same reference product used in both study) might be due to the effect of food and/or the other causes. Yakatan *et al.* (1981) observed that concomitant administration of food delayed absorption of pentoxyphylline and lowered peak plasma concentration. Two hours periode of food intake after a sustained release drug administration did not guarantee the absence of food interference to drug absorption process. In this study and the study of Yuen *et al.*,(2000) the food was administered two hours after drug intake but the nature of food was different. Chicken and rice were given as lunch (about 10.00 a.m.) during the study of Yuen *et al.* (2000), while in this study the standard breakfast (given at about 09.30 a.m., drug was administered at about 07.30 a.m.) which was given to the volunteers composed of two boiled eggs, instant noodles and fresh milk. The difference of food nature might result in different effect to drug absorption process (i.e. transit time) and might also affect the first-pass effect (extra-hepatic metabolism) of pentoxyphylline.

Statistical analysis of the main bioavailability parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) showed that PLTF-400 was bioequivalent to the reference product (TRTL-400). Confidence interval of ratio (T/R) of the three parameters fell inside the acceptance limits (Table II). C_{max} ratio lay between 75% and 133% (93.1% - 132.0%), and 90% confidence interval of the ratio of AUC_{0-t} and $AUC_{0-\infty}$, lay between 80% and 125% (90.6% - 123.5% for AUC_{0-t} and 84.2% - 116.2% for $AUC_{0-\infty}$). The C_{max} ratio on subject no. 9 was not included in calculation of confidence interval as the ratio value was considered to be outlier which was proved by Dixon Test.

Tabel I. Bioavailability parameters of pentoxyphylline obtained after administration of each product

Subject No	C_{max}(ng/ml)	T_{max}(hrs)	AUC_{0-t}(ng/ml.hr)	$AUC_{0-\infty}$(ng/ml.hr)	$T_{1/2}$(hrs)

	I	II	I	II	I	II	I	II	I	II
1	118.0	85.4	3	10	692.2	789.7	744.8	1065.5	2.4	-
2	99.5	180.5	1	2	541.7	569.7	640.9	617.6	4.2	2.9
3	122.9	104.2	3	1	572.8	401.9	623.0	543.1	2.5	-
4	118.7	67.0	1.5	3	498.1	347.2	592.2	448.0	-	-
5	92.9	71.2	4	3	502.5	524.6	517.0	650.3	1.1	-
6	163.9	221.4	3	1.5	392.9	694.1	411.6	713.5	1.6	1.3
7	317.5	273.8	1	3	1912.0	4668.5	2165.9	1860.5	3.4	2.6
8	166.7	166.5	1	3	552.3	633.7	599.6	654.3	2.3	1.1
9	72.6	22.0	2	3	263.3	159.1	327.0	178.0	4.2	2.6
10	103.5	100.0	1	3	589.4	703.8	689.1	866.8	-	-
11	121.4	97.5	3	1	588.1	452.6	637.4	540.2	-	3.1
12	112.3	83.2	1	3	602.2	511.0	650.4	687.7	2.1	-
Mean	134.2	122.7	2.0	3.0	642.3	621.3	716.6	735.5	2.6	2.3
S.D.	63.6	72.7	1.1	2.3	414.7	372.6	471	414.6	1.1	0.9

I=PLTF-400 (Tested product); II = TRTL-400 (Reference product)

Tabel II. Summary of statistical analysis of bioavailability parameters

Statistics	C_{max} (ng/ml)*		AUC_{0-t}(ng/ml.hr)**		$AUC_{0-\infty}$(ng/ml.hr)**	
	I	II	I	II	I	II
Arithmetic mean	139.8	131.9	642.3	621.3	716.6	735.5
S.D.	63.5	68.6	414.7	372.6	471.1	414.6
Variation coefficient	45.4%	52.0%	64.6%	60.0%	63.1%	56.4%
Geometric mean	131.0	118.2	571.9	540.8	638.0	645.0
Minimum	92.9	67.0	263.2	159.1	327.0	178.0
Maximum	317.5	273.8	1912.0	1668.5	2165.9	1860.5
Median	118.7	100.0	562.6	547.2	630.2	652.3
90% Confidence interval of the ratio (Test/Reference)	93.1% - 132.0%		90.6% - 123.5%		84.2% - 116.2%	

*) n = 11; **) n = 12; I = PLTF-400 (tested product); II = TRTL-400 (reference product)

Figure 1. Plasma level-time courses of pentoxifylline following administration of each product (mean in 12 subjects)

CONCLUSION

Based on the results obtained, it was found that the PLTF-400 was bioequivalent to the reference product (TRTL-400) (90% confidence intervals of C_{max} and AUC ratio lie inside the acceptance limits). The pharmacokinetic parameters of the drug in Indonesian volunteers were comparable to those obtained previously by the other authors in different ethnics.

REFERENCES

Anonim, 1995, *The United States Pharmacopoeia 23, Supplement 4*, U.S. Pharmacopoeial Convention, Rockville, MD, 3223.

Bolton, S. , 1990, *Pharmaceutical Statistics Practical and Clinical Applications*, 2nd ed., Marcel Dekker, New York, 347-351, 498.

Mauro, V.F., Mauro, L.S., and Hageman, J.H., 1988, Alteration of pentoxyphylline pharmacokinetics by cimetidine, *J. Clin. Pharmacol.*, 28 (7), 649-654.

Parfitt, K. (Ed.), 1999, *Martindale The Complete Drug Reference*, 32nd ed., 925926.

Rames, A., Poirier, J-M., LeCoz, F., Midavaine, M., Lecocq, B., Grange, J-D., Poupon, R., Cheymol, G., Jaillon, P., 1990, Pharmacokinetics of intravenous and oral pentoxyphylline in healthy volunteers and in cirrhotic patients, *Clin. Pharmacol. Ther.*, 47 (3), 354-359.

Steinijans, V.W. and Diletti, E., 1983, Statistical analysis of bioavailability studies: parametric and nonparametric confidence intervals, *Eur. J. Clin. Pharmacol.*, 24, 127-136.

Wai Fun, L., 2002, *Indonesia Index of Medical Specialities (IIMS)*, vol. 31 (2), MediMedia, Singapore, 71-72.

Yakatan, G.J., Ho, I., Wills, R.J., Puri, S.K., and Waller, E.S., 1981, Influence of food on the bioavailability of Trental pentoxyphylline in man, *Drug dev. Ind Pharm.*, 7 (4), 385-396.

Yuen, K.H., Wong, J.W., Peh, K.H., Julianto, T., and Choy, W.P., 2000, Comparative bioavailability study of two controlled-release pentoxyphylline tablet preparations, *Drug Dev. Ind Pharm.*, 26 (7), 803-807.