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Steady-State Pharmacokinetics of a Multiparticulate Matrix Sustained-Release Theophylline Preparation

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ABSTRACT

A novel multiparticulate matrix sustained-release theophylline preparation was evaluated in comparison with a reference product, Neulin-SR®, in a multiple-dose administration study, conducted according to a randomized, two-way crossover design involving 12 healthy volunteers. Comparison was made using the parameters, area under the serum concentration–time curve from time 0 to 12 hr (AUC_{0-12}), time to reach peak serum concentration (T_{max}), peak serum concentration (C_{max}), trough serum concentration (C_{min}), average drug concentration (C_{av}), degree of fluctuation (DF), percentage of time serum drug concentrations lie within the therapeutic range (occupancy time) and time for 50% of dose absorbed ($T_{50\%}$). The parameters, C_{max}, C_{min}, AUC_{0-12}, C_{av}, and DF were logarithmic transformed prior to statistical analysis. A statistically significant difference was obtained between the values of the two preparations in the T_{max}, C_{min}, DF, and $T_{50\%}$; but not in the C_{max}, AUC_{0-12}, C_{av}, and occupancy time. These findings suggest that the novel preparation has a more sustained rate but equivalent extent of absorption compared to Neulin-SR, leading to a more uniform steady-state serum profile.

INTRODUCTION

Sustained-release formulations can greatly enhance the safe and efficacious use of theophylline in chronic therapy of reversible airway obstructive disease, through providing a more uniform serum level profile (1) and decreased frequency of dosing (2). However, for such formulations, in vitro data alone may not be an adequate proof of their in vivo performance. Validation of their sustained-release characteristics is best achieved through in vivo studies using human volunteers (3).

While single-dose studies are usually sufficient to establish the validity of sustained-release dosage form designs, multiple-dose administration studies, on the

other hand, are useful for establishing the optimum dosing regimen, particularly with drugs of narrow therapeutic indices (3). Hence, the present multiple-dose administration study was conducted to evaluate the steady-state pharmacokinetics of a multiparticulate sustained-release formulation of theophylline, in comparison with a reference product, Neulin-SR®. The design and composition of the preparation (4) as well as its in vivo performance after a single-dose administration (5) have been described previously.

MATERIALS

Neulin-SR 250-mg tablets (3M, Australia) were purchased commercially. Anhydrous theophylline and β-hydroxyethyltheophylline (BHET) standards were obtained from Sigma Chemical Co. (USA). All analytical solvents used were either HPLC or AR grade.

METHODS

In Vivo Study Design

The study protocol was approved by an Ethics Committee on Bioavailability Studies. Twelve healthy nonsmoking adult male volunteers between 29 and 43 years old (mean = 36 years, *SD* = 5 years) and weighing from 52 to 82 kg (mean = 68 kg, *SD* = 11 kg), participated in the study after providing written informed consent. The protocol used for this bioequivalency study was a conventional, two-way, split groups, crossover study with six subjects in each of the two treatment groups and a washout period of 1 week. During each trial period, the volunteers were administered the preparations containing an equivalent of 250 mg theophylline twice daily (at 10:00 a.m. and 10:00 p.m.) for 4 days. The last dose was given at 10:00 a.m. in the morning on day 5 after an overnight fast. Food and drinks were withheld for at least 2 hr after the last dose. Standard lunch and dinner, comprising chicken with rice, were served at 4 and 9 hr after dosing, and water was given ad libitum. The volunteers were to refrain from alcohol and xanthine-containing food or beverages 24 hr before and during both study periods.

Venous blood samples of 5 ml volume each were drawn via an in-dwelling cannula from the forearm into plain vacutainers at 0 (before dosing), 0.5, 1, 2, 3, 4, 6, 8, 10, 14, 18, and 24 hr after the last dose. A 36-hr blood sample was taken by direct venipuncture. After standing for 2 hr, the blood samples were centrifuged at 3500 rpm for 15 min; the serum was separated and kept frozen until analysis.

Analysis of Serum Theophylline Concentration

The serum theophylline concentration was quantitated using a reversed-phase high-performance liquid chromatographic (HPLC) method described previously (5). However, in the present study, a standard curve covering a wider concentration range of 1–20 μg/ml was used in the quantitation. Detector response was found to be linear over a concentration range of 1–64 μg/ml. Recovery, within-day and between-day accuracy, and precision studies ($n = 6$) were performed using drug-free serum spiked with theophylline at the following concentrations: 1.0, 4.0, 8.0, 14.0, and 20.0 μg/ml. Within-day and between-day coefficients of variation for the precision studies were all less than 5% at these concentrations. Likewise, the percentage error values for the accuracy studies were all less than 8%. Recovery values of the internal standard, BHET, and theophylline were greater than 90%. The sensitivity of the assay method was approximately 0.1 μg/ml.

Pharmacokinetic Analysis

The two preparations were compared using the parameters, area under the serum concentration–time curve from time 0 to 12 hr (AUC_{0-12}), time to reach peak serum concentration (T_{max}), peak and trough serum concentration (C_{max}, C_{min}), average drug concentration (C_{av}), degree of fluctuation (DF), and percentage of time serum drug concentrations lie within the therapeutic range (*occupancy time*). The AUC_{0-12} was calculated using a trapezoidal rule, while T_{max}, C_{max}, and C_{min} were obtained directly from the serum concentration data. The *occupancy time* (6) was estimated from individual serum concentration–time curves, whereas C_{av} was calculated as $AUC_{0-12}/12$, and DF as 100% $(C_{max} - C_{min})/C_{av}$.

The elimination rate constant, k_e, was estimated from the terminal slope of the serum concentration–time curve through logarithmic transformation and application of linear regression (7). The elimination half-life, $t_{1/2}$, was calculated using $\ln 2/k_e$, and the apparent volume of distribution, V_d, as $dose/(AUC_{0-12} \cdot k_e)$.

The individual steady-state in vivo absorption–time profiles of the volunteers were estimated using the modified Wagner–Nelson method (8). The time for 50% of dose absorbed, $T_{50\%}$, was then estimated from these profiles.

Statistical Analysis

The parameter values of AUC_{0-12}, C_{max}, C_{min}, C_{av}, *occupancy time*, *DF*, $T_{50\%}$, k_e, $t_{1/2}$, and V_d were analyzed statistically using an analysis of variance procedure appropriate for the study design (9). The AUC_{0-12}, C_{max}, C_{min}, C_{av}, and *DF* values were logarithmic transformed prior to the analysis. On the other hand, the T_{max} values were analyzed using the Wilcoxon signed-rank test for paired samples. A statistically significant difference was considered at $p < 0.05$.

RESULTS AND DISCUSSION

The mean steady-state serum theophylline concentration-time profiles for Neulin-SR and the novel preparation are depicted in Fig. 1. While both preparations produced a relatively small fluctuation in peak-trough serum levels, the serum profile of the novel preparation appeared to be more uniform, indicating that the rate of drug absorption was more sustained.

The numerical values of the pharmacokinetic parameters, AUC_{0-12}, C_{max}, C_{min}, T_{max}, C_{av}, *DF*, and *OT* (occupancy time), obtained with Neulin-SR and the novel preparation, are presented in Table 1 and 2, respectively. For the first parameter, AUC_{0-12}, which is related to the extent of absorption, the novel preparation has a mean value of 116.3 ± 34.1 μg·hr/ml, which is close to the value of 110.0 ± 31.1 μg·hr/ml obtained with Neulin-SR. There was no statistically significant difference between these values ($p = 0.3451$), suggesting that the two preparations are comparable in the extent of absorption. In accord with this finding, no statistically significant difference was also observed between the C_{av} values of the two preparations. In addition, the 90% confidence interval for the ratio of the logarithmic transformed AUC_{0-12} values of the novel preparation over those of Neulin-SR was calculated to lie between 0.95 and 1.17, which is within the acceptable bioequivalence limit of 0.80–1.25 (10,11).

In the case of T_{max}, however, which is related to the rate of absorption, a statistically significant difference ($p = 0.0015$) was observed between the values of the two preparations. The novel preparation showed a more sustained rate of absorption with a larger mean T_{max} value of 4.1 ± 1.2 hr, compared to 3.2 ± 0.9 hr for Neulin-SR.

On the other hand, the other parameters, C_{max}, C_{min}, and *DF* are influenced by both the rate and extent of drug absorption. Given that the novel preparation has a slower rate but comparable extent of absorption to Neulin-SR, its *DF* and C_{max} values can be expected to

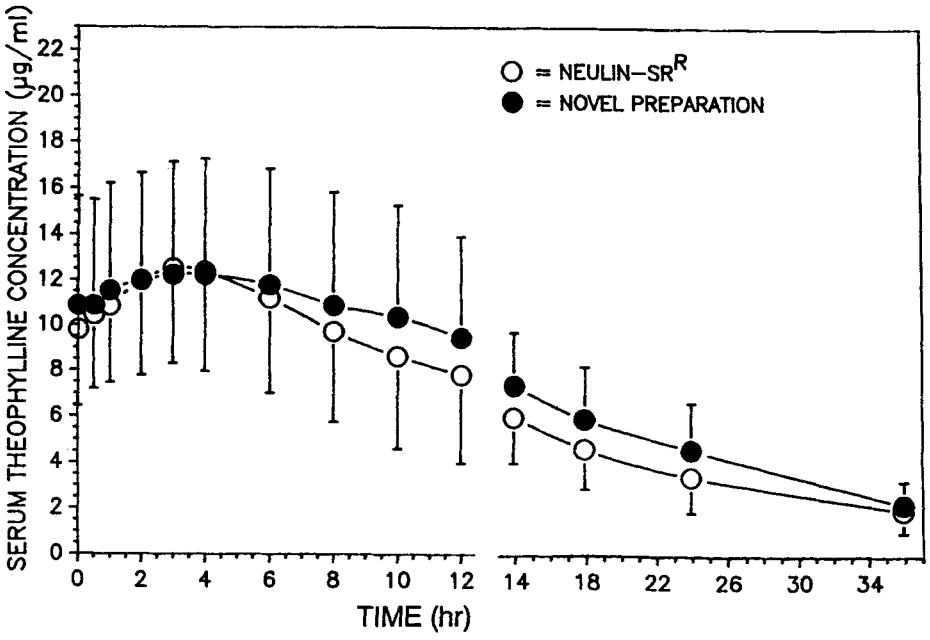

Figure 1. Mean serum theophylline concentration versus time profiles of Neulin-SR and the novel preparation. Mean ± *SD*; $N = 12$.

Table 1

Individual Numerical Values After Dosing with Neulin-SR

	Neulin-SR						
Subject	AUC_{0-12} (μg·hr/ml)	C_{max} (μg/ml)	C_{min} (μg/ml)	T_{max} (hr)	C_{av} (μg/ml)	*DF* (%)	*OT* (%)
1	127.2	13.6	7.2	4.0	10.6	60.4	100
2	108.6	10.3	7.5	4.0	9.1	30.8	100
3	106.8	10.2	8.1	4.0	8.9	23.6	100
4	161.0	16.4	9.9	2.0	13.4	48.5	100
5	153.7	14.8	9.9	4.0	12.8	38.3	100
6	80.3	9.0	4.5	3.0	6.7	67.2	80
7	104.1	10.6	7.0	3.0	8.7	41.4	100
8	120.3	14.6	5.8	3.0	10.0	88.0	100
9	101.9	10.5	5.6	1.0	8.5	57.6	100
10	124.7	12.9	7.5	3.0	10.4	51.9	100
11	49.1	5.0	3.1	3.0	4.1	46.3	0
12	81.9	8.8	3.6	4.0	6.8	76.5	79
Mean	110.0	11.4	6.6	3.2	9.2	52.2	88
SD	31.1	3.2	2.2	0.9	2.6	18.7	29

be smaller, while the C_{min} values are larger than those of Neulin-SR, as observed in Tables 1 and 2. However, a statistically significant difference was obtained between the values of the preparation only in the *DF* ($p = 0.0001$) and C_{min} ($p = 0.0006$), but not in C_{max} ($p = 0.4778$).

Although a serum concentration between 10 and 20 μg/ml has generally been accepted as the therapeutic range for theophylline (12,13), concentrations as low as 5 μg/ml have been shown to produce impressive clinical responses (14,15). Hence, a therapeutic range of 5–20 μg/ml was chosen in the estimation of *occupancy*

Table 2

Individual Numerical Values After Dosing with Novel Preparation

	Novel Preparation						
Subject	AUC_{0-12} (μg·hr/ml)	C_{max} (μg/ml)	C_{min} (μg/ml)	T_{max} (hr)	C_{av} (μg/ml)	*DF* (%)	*OT* (%)
1	101.9	9.9	6.3	3.0	8.5	42.4	100
2	124.0	11.0	8.9	4.0	10.3	20.4	100
3	121.0	10.8	9.1	4.0	10.1	16.8	100
4	170.9	14.9	12.8	6.0	14.2	14.8	100
5	168.4	15.7	11.1	6.0	14.0	32.9	100
6	83.8	7.9	5.9	4.0	7.0	28.6	100
7	127.7	11.5	9.1	3.0	10.6	22.6	100
8	91.2	9.4	6.1	3.0	7.6	43.4	100
9	137.2	13.0	9.1	4.0	11.4	34.2	100
10	130.2	12.1	9.3	3.0	10.9	25.7	100
11	68.6	6.6	4.6	3.0	5.7	35.1	83
12	70.6	6.6	4.9	6.0	5.9	28.8	98
Mean	116.3	10.8	8.1	4.1	9.7	28.8	98
SD	34.1	2.9	2.5	1.2	2.8	9.37	5

time in the present study. The mean values obtained for the novel preparation and Neulin-SR were 98 ± 5% and 88 ± 29%, respectively, but they were not significantly different ($p = 0.1777$). Based on this therapeutic range, only two subjects consistently had serum drug concentrations lower than 5 μg/ml for both preparations, suggesting a faster clearance rate of the drug in these two individuals. On the other hand, none of the subjects achieved a serum concentration above the upper limit of 20 μg/ml.

The mean in vivo theophylline absorption–time profiles of the two preparations are presented in Fig. 2. Inspection of the two plots revealed that absorption from both preparations was sustained, but the novel preparations had a relatively slower rate of absorption, which is in good agreement with our earlier analysis of the data. The novel preparation had a larger mean $T_{50\%}$ value of 2.9 ± 0.9 hr and was significantly different ($p = 0.0074$) from the value of 2.0 ± 0.8 hr obtained with Neulin-SR.

The numerical values of the pharmacokinetic parameters, k_e, $t_{1/2}$, and V_d, are shown in Table 3. The values of all three parameters obtained with the novel preparation were almost the same as those of Neulin-SR and were not significantly different statistically. Moreover, the values obtained are in good agreement with those obtained in our previous single-dose administration study (5) and also with those reported in the literature (16,17).

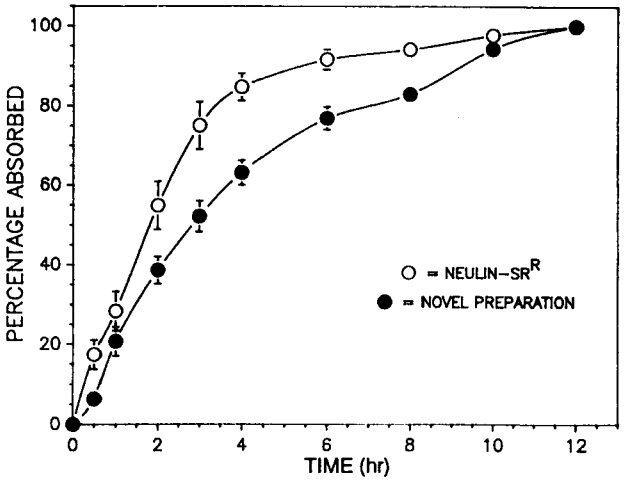

Figure 2. Mean in vivo theophylline absorption versus time profiles of Neulin-SR and the novel preparation. Mean ± *SD*; $N = 12$.

CONCLUSION

From the above findings, it can be concluded that the novel preparation is comparable to Neulin-SR in the extent of bioavailability but has a more sustained rate of drug absorption, being consistent with the results of our previous single-dose administration study (5). The serum level profile of the novel preparation was more uniform, with less fluctuation in the peak and trough serum lev-

Table 3

Numerical Values of k_e, $t_{1/2}$ and V_d

	Neulin-SR			Novel Preparation		
Subject	k_e (hr^{-1})	$t_{1/2}$ (hr)	V_d (liter/kg)	k_e (hr^{-1})	$t_{1/2}$ (hr)	V_d (liter/kg)
1	0.13	5.4	0.29	0.11	6.3	0.42
2	0.06	11.5	0.50	0.06	11.7	0.45
3	0.06	11.9	0.24	0.06	11.9	0.22
4	0.07	9.5	0.26	0.06	11.3	0.29
5	0.06	12.0	0.42	0.06	12.2	0.39
6	0.06	12.2	0.92	0.06	11.4	0.82
7	0.06	11.6	0.40	0.06	11.0	0.31
8	0.07	9.0	0.40	0.06	10.9	0.63
9	0.07	9.8	0.66	0.06	11.6	0.58
10	0.06	11.5	0.47	0.06	11.7	0.46
11	0.06	12.0	1.08	0.08	9.1	0.58
12	0.07	10.1	0.54	0.07	9.6	0.60
Mean	0.07	10.5	0.52	0.07	10.7	0.48
SD	0.02	2.0	0.26	0.01	1.7	0.17

els. Except for two subjects, a twice daily dose of 250 mg, given 12 hourly, was found sufficient to produce a serum profile within 5–20 μg/ml. In addition, the values of k_e, $t_{1/2}$, and V_d were comparable between the two preparations and found to be in good agreement with those reported in the literature for healthy non-smoking male adults.

REFERENCES

1. J. Urquhart, Drugs, 23, 207 (1982).
2. D. G. Tinkelman, G. E. Van deer Pool, M. Scott-Caroll, G. E. Page, and D. L. Sprangler, Ann. Allergy, 44, 283 (1980).
3. N. G. Lordi, in *The Theory and Practice of Industrial Pharmacy* (L. Lachman, H. A. Lieberman, and J. L. Kanig, eds.), Lea and Febiger, Philadelphia, 1986, p. 430.
4. K. K. Peh and K. H. Yuen, Drug Dev. Ind. Pharm., 21(13), 1545 (1995).
5. K. K. Peh and K. H. Yuen, Drug Dev. Ind. Pharm., 22(4), 349 (1996).
6. J. P. Skelly, *Division Guidelines for the Evaluation of Controlled Release Products*, Division of Biopharmaceutics, Food and Drug Administration, 1984.
7. M. Gibaldi and D. Perrier, in *Pharmacokinetics*, 2nd ed., Marcel Dekker, New York, 1982, p. 145.
8. J. G. Wagner and E. Nelson, J. Pharm. Sci., 72, 578 (1983).
9. J. G. Wagner, in *Fundamentals of Clinical Pharmacokinetics*, 1st ed., Drug Intelligence, Hamilton, IL, 1975, pp. 129, 285.
10. V. W. Steinijans and E. Dilleti, Eur. J. Clin. Pharmacol., 24, 127 (1983).
11. W. J. Westlake, in *Biopharmaceutical Statistics for Drug Development* (K. E. Peace, eds.), Marcel Dekker, New York, 1988, p. 329.
12. L. Hendeles, R. P. Lafrate, and M. Weinberger, Clin. Pharmacokinet., 9, 95 (1984).
13. M. Weinberger and L. Hendeles, N. Engl. J. Med., 308, 760 (1983).
14. R. I. Ogilvie, Clin. Pharmacokinet., 3, 267 (1978).
15. R. J. Dockhorn, A. W. Green, and E. Green, Ann. Allergy, 55, 658 (1985).
16. Y. Horai, T. Ishizaki, T. Sasaki, M. Watanabe, and J. Kabe, Eur. J. Clin. Pharmacol., 23, 111 (1982).
17. S. Valenti, P. Crimi, and V. Brusasco, Respiration, 52, 195 (1987).