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The bioavailability, absorption characteristics and formulation of four commercially-available controlled-release theophylline products

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Summary

The multiplicity of sustained-release preparations of theophylline, the variety of formulations used and the efficacy claims for the products led to the need for a comparative bioavailability study. Direct in vivo methods were applied to 4 products and a standard preparation. The extent of bioavailability of the 4 products examined, measured relative to a standard solution of theophylline, varied from (mean ± S.D.): 78% ± 40% to 123% ± 23%. Cumulative absorption profiles determined using the Wagner-Nelson method also showed large differences among products. The results are discussed with reference to formulation of the products. Older methods of controlling the release of drugs from solid oral forms performed relatively poorly compared with modern systems.

Introduction

One of the current major effective approaches to the treatment of asthma is by the oral administration of theophylline. The drug's action, kinetics and toxicity have been reviewed (Skinner and Summers, 1983). The relationship between plasma concentrations of 10–20 μg/ml and optimal bronchodilating activity is well established (Jenne et al., 1972; Mitenko and Ogilvie, 1973; Paifsky and Ogilvie, 1975; Jacobs et al., 1976). The introduction of sustained-release preparations has encouraged the use of the drug and enhanced its performance in clinical practice by reducing the fluctuation in plasma levels which often occurs in treatment with conventional tablets. Many prolonged-action products are now available internationally, albeit under different proprietary names in different countries. It is not surprising, therefore, that numerous studies have been performed to establish the bioavailability and pharmacokinetic properties of various preparations (Weinberger et al., 1977; Spangler et al., 1978; Andersen et al., 1983; Edwards et al., 1983; Varagic et al., 1983; Kotzan et al., 1984). The most comprehensive and detailed study to date concentrated on products available on the American market (Kotzan et al., 1984). Descriptions of the physical form of the products were generally absent in the above studies. The purpose of this present study then was to investigate and compare the bioavailability and absorption characteristics of 4 sus-

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TABLE 1

PROPRIETARY NAMES AND COUNTRIES WHERE MARKETED FOR FOUR PROLONGED-ACTION THEOPHYLLINE PREPARATIONS

Proprietary brand investigated and active ingredient	Other proprietary names *	Countries where marketed *
Euphyllin Retard (Byk Gulden) Aminophylline		South Africa Zimbabwe West Germany Spain
Micro-Phyllin ** (Rona) Theophylline		South Africa
	Slo-Phyllin **	United Kingdom Ireland India
	Theo-Pexine **	France
	Theophylline retard ratiopharm **	West Germany
	Durophyllin **	Yugoslavia
	Elixine **	Chile
Phyllo-Contin (Mundipharma) Aminophylline		South Africa United Kingdom Others
Theo-Dur (Rio Ethicals) Theophylline		South Africa United Kingdom United States of America Others

* These lists are not complete. The authors would welcome further details.

** Under licence to Pharmatec.

tained-release theophylline preparations which are available in Western Europe and elsewhere (see Tables 1 and 2). We also describe the physical form of the products and attempt to correlate this with their performance.

Experimental

Subjects

The 7 subjects were healthy Caucasian males with an average age of 28.4 (range 25–37) years and an average body mass of 74.9 (range 63–85) kg. Their blood counts, liver function, ECGs, urea and electrolytes were all normal. All subjects were non-smokers and they were not taking other medication. They refrained from ingesting xanthine-containing beverages and alcohol for 48 h prior to and during each study and fasted for 12 h prior to drug administration. They received a standard breakfast, lunch and supper on each day of the study. The breakfast was given 30 min after ingestion of the drug, rather than before or with it, to minimize the effect of food on bioavailability (Welling et al., 1975; Lagas and Jonkman, 1983).

TABLE 2

PHYSICAL FORM OF FOUR PROLONGED-ACTION THEOPHYLLINE PREPARATIONS

Preparation	Form
Euphyllin retard	bi-convex film-coated ovoid tablet
Micro-Phyllin	encapsulated microspheres of uniform size and specific gravity, each covered individually with a polymeric insoluble controlled diffusion membrane
Phyllo-Contin	film-coated granulate round tablet
Theo-Dur	ovoid tablets containing free drug and multi-layered pellets of cellulose acetate phthallate and drug

Method

On successive Tuesdays the following procedure was performed on each of the 7 subjects:

(1) A blood sample was taken.

(2) The appropriate dose of a particular preparation was swallowed with 200 ml of water (see Table 3 for doses of products administered).

(3) Blood samples were taken at 1, 2, 3, 4, 6, 8, 10, 12, 24 and 30 h after zero time.

(4) The samples were centrifuged in batches within 1 h of the last sample for each time being taken.

(5) Drug plasma concentrations were immediately determined on a Beckman ICS II (Immuno-Chemistry System) instrument, which has been shown to give comparable results to EMIT and HPLC (ICL Scientific, 1982).

The process was repeated for each of the test preparations as well as with 180 mg of anhydrous

TABLE 3

PRODUCTS, ACTIVE INGREDIENTS AND DOSES OF FOUR PROLONGED-ACTION THEOPHYLLINE PREPARATIONS

Product	Active ingredient	Labelled strength (mg)	Theophylline equivalent (mg)	Dose administered
Euphyllin retard	Aminophylline (stated as theophylline monohydrate)	350 (281)	256	2 × 350 mg tablets (512 mg)
Micro-Phyllin	Theophylline (anhydrous)	250	250	2 × 250 mg capsules (500 mg)
Phyllo-Contin	Aminophylline	225	180 *	2 × 225 mg tablets (360 mg)
Theo-Dur	Theophylline (anhydrous)	200	200	2 × 200 mg tablets (400 mg)

* Theophylline equivalent = aminophylline strength ×80%.
B.P. 1980: the anhydrous theophylline content of aminophylline is required to be between 78.0 and 84.0%.

theophylline in 200 ml of water as a standard for bioavailability and to determine whether there were any abnormalities in drug absorption by the subjects.

The mean plasma levels for each time period were calculated for each product.

The area under the curve of plasma theophilline concentration versus time (AUC) was calculated using the trapezoidal rule up to the time of the last sample (30 h). To prevent any bias in the estimate of the terminal rate constant due to continuing absorption, the value obtained from the test dose data was used to extrapolate the area to time-infinity.

The bioavailability F for the test batches for each subject was then calculated using the equa-

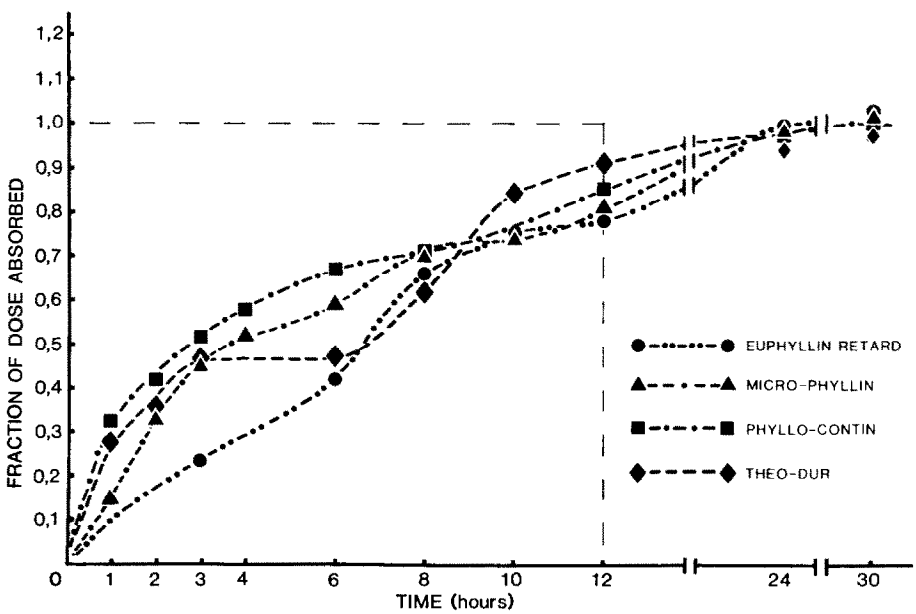

Fig. 1. Absorption data (mean fraction of dose absorbed) for theophylline from four prolonged-action preparations.

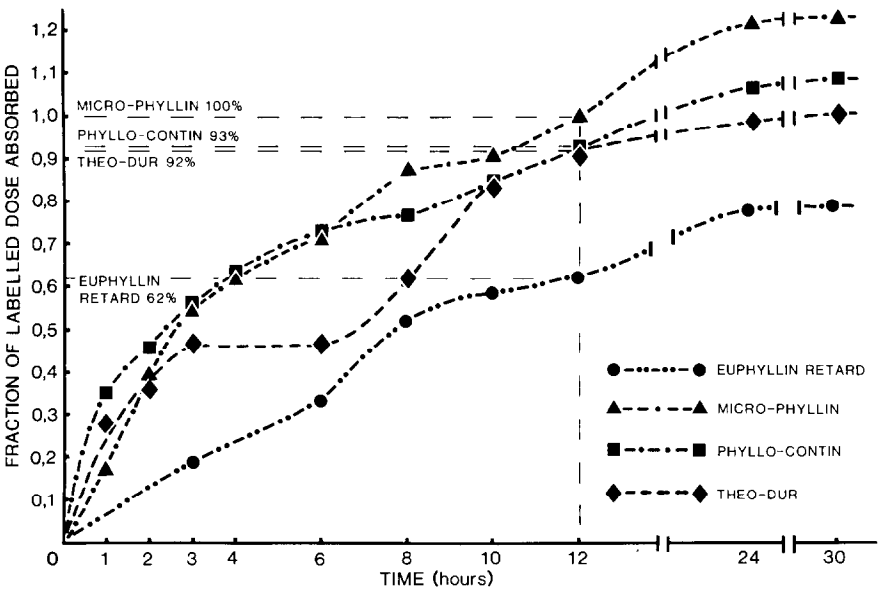

Fig. 2. *Corrected* absorption data (mean fraction of *labelled* dose absorbed) for theophylline from four prolonged-action preparations.

tion:

$$F = \frac{D^{std} \cdot AUC_{\infty}^{prod}}{D^{prod} \cdot AUC_{\infty}^{std}}$$

where $D^{std} = 180$ mg and D^{prod} in each case was taken as the theophylline equivalent of the labelled amount of drug, as the preparations would be prescribed on this basis.

Mean bioavailability for theophylline in the test batches was calculated from the subject data, as were the standard deviations and the coefficients of variance. The results are summarized in Table 4 and were analyzed statistically by means of the paired *t*-test.

The data pairs were then fed into a computer programme which computed the fraction of dose absorbed over time, according to the Wagner-Nelson method (Wagner and Pernarowski, 1971). The results of this procedure are represented in Fig. 1.

These data do not allow, however, for the influence of bioavailability on the absorption profile, i.e. the Wagner-Nelson method only calculates the fraction of dose absorbed over time from the *quantity* of drug actually *absorbed*, and takes no account of the amount of drug present in the *dosage form*. This can be rectified by incorporating the bioavailability factor F, i.e. each calculated fraction of dose absorbed is multiplied by F to give a value for the *fraction* of *labelled* drug absorbed. The corrected data are drawn in Fig. 2.

Results

The bioavailability data for the 4 products (see Table 4) showed marked product-to-product differences, both in actual values and in subject-to-subject spread. The lowest bioavailability (78%) was shown by Euphyllin retard.

On the other hand, the value obtained for Micro-Phyllin (123%) is high. Phyllo-Contin and Theo-Dur exhibit bioavailability closest to the standard (109% and 100%, respectively). Statistical analysis of the bioavailability data demonstrates that only the Euphyllin retard/Micro-Phyllin ($P < 0.1$) and the Micro-Phyllin/Theo-Dur ($P < 0.05$) differences are significant. The coefficients of variance for both Micro-Phyllin (19%) and Theo-Dur (13%) show satisfactory subject-to-subject consistency.

The uncorrected absorption profiles (Fig. 1)

TABLE 4

BIOAVAILABILITY OF THEOPHYLLINE FROM FOUR SUSTAINED-RELEASE PRODUCTS

Subject	Product			
	Euphyllin retard	Micro-Phyllin	Phyllo--Contin	Theo-Dur
1	1.192	1.149	0.862	1.153
2	1.175	1.012	1.519	1.130
3	0.260	0.917	0.723	0.785
4	0.689	1.321	1.067	0.998
5	0.357	1.612	1.422	1.047
6	1.198	1.256	1.019	0.888
7	0.641	1.357	1.035	1.059
Mean	0.787	1.232	1.092	1.007
Standard deviation (±)	0.404	0.232	0.286	0.133
Coefficient of variation	51.24%	18.85%	26.15%	13.19%

Statistical comparison	*P*
Euphyllin retard/Micro-Phyllin	< 0.10
Euphyllin retard/Phyllo-Contin	< 0.20
Euphyllin retard/Theo-Dur	< 0.20
Micro-Phyllin/Phyllo-Contin	< 0.30
Micro-Phyllin/Theo-Dur	< 0.05
Phyllo-Contin/Theo-Dur	< 0.40

also demonstrate differences among the products. Euphyllin retard shows slow initial release (absorption), with a slight surge from 6 h. The profiles for Micro-Phyllin and Phyllo-Contin are not dissimilar. That for Theo-Dur exhibits initial release, followed by a 'pulse' of drug at 6 h.

The respective similarities and differences among the products are more apparent in Fig. 2 (corrected profiles).

Discussion

Although there will be some intra- and inter-subject variability, the differences in absorption observed among the products will be due largely to their formulation.

Euphyllin retard

This product has been marketed for a longer period than the other brands. It performed poorly in bioavailability, subject-to-subject consistency and in absorption characteristics. Poor bioavailability for this preparation has been demonstrated in other studies (Mangues et al., 1984; Stanislaus, 1984). The formulation may now be outdated in terms of current technology for controlled drug release.

Micro-Phyllin

This new preparation is based on recent technology. It exhibited high bioavailability and satisfactory subject-to-subject uniformity and absorption. Although patients who commence treatment with this product can be titrated to appropriate levels, caution should be exercised when a patient is transferred from a preparation of lower bioavailability to this product. An equivalent *labelled* dose of Micro-Phyllin to the previous preparation could well result in levels high enough to produce toxic effects.

Phyllo-Contin

Although this product has a more traditional formulation it performed satisfactorily.

Theo-Dur

This product combines free drug in the bulk of the tablet with retarded-release pellets. These features are illustrated by the absorption profile(s). They may lead, however, to relatively poor control in the 4–6 h period before significant amounts of drug are released from the pellets. The preparation performed satisfactorily in bioavailability and well in subject-to-subject consistency.

Conclusion

This study has shown the continued value of comparative bioavailability studies particularly in controlled-release formulations where technological advances are the order of the day. We have demonstrated that more efficacious preparations are one result, the corollary being that the performance of more traditional formulations may be poor in comparison. The question therefore arises as to their continued presence on the market as

standards improve, especially for drugs like theophylline which have a narrow therapeutic window, and where low drug levels lead to inadequate clinical control.

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