The bioavailability of a paediatric sustained-action theophylline capsule

RS Summers

Curriculum Vitae
Robert Summers was born in 1940 in Rhodesia (now Zimbabwe) and obtained his BSc and MSc (Pharmacy) at Rhodes University, Grahamstown. In 1973 he obtained the PhD at the Postgraduate School of Studies in Pharmacy, University of Bradford. He worked for several years at the University of the North where he was appointed Professor in 1974. From 1978 to 1983 he was Head of the Department of Pharmacy, University of Zimbabwe during which time he was also Deputy Dean in the Faculty of Medicine. Since 1983 he has been Professor and Head of the Department of Pharmaceutics, MEDUNSA where he is also serving as Assistant Dean since 1984. Professor Summers has served on many academic, research and examining bodies and has published quite extensively in the field of pharmacy.

Summary

A controlled study was done on a new paediatric sustained-action theophylline capsule as a new form of therapy for asthma in children, especially to test the pattern of bioavailability and the appropriate prolonged release curve. The results demonstrated that the test product performed better than the standard.

KEYWORDS: Biological Availability; Availability Equivalency; Delayed-Action Preparations; Theophylline; Drug Therapy; Drug Evaluation; Pediatrics; Pharmacology.

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INTRODUCTION

The introduction of a ***paediatric*** sustained-action theophylline capsule* has re-awakened interest in this form of therapy for asthma in children. Previously, solid, oral sustained-action theophylline (and aminophylline) dosage forms contained a minimum of approximately 182 mg of active drug (*ie* of theophylline itself). This quantity may be too large for some children. By contrast, the new capsule contains 60 mg of active substance, so gives a choice of dosage in multiples of this quantity.

Note: * **Micro-Phyllin 60 mg Capsules (also marketed in some countries as Slo-Phyllin).**

The bioavailability of a paediatric sustained-action theophylline capsule

It is generally accepted that the optimum bronchodilating activity of theophylline is obtained at plasma levels from 10-20 mcg/mℓ. In adults, the recommended oral maintenance dose, for acute symptoms, to achieve these levels, is approximately 10 mg/kg/day. In children from 1-9 years this dose may need to be much higher, up to 20 mg/kg/day[1]. This latter recommendation is due to the dose-dependent kinetics of theophylline in children in the therapeutic range[2], which is rarely observed in adults.

It should be noted, however, that steady state therapeutic plasma levels have been achieved in children with dosages below 10 mg/kg/day, although the 18 patients in the study had an average age of twelve (range 7-16 years)[3]. One result of the more rapid kinetics is the shorter half-life of the drug in young children (3-5 hours), compared with that in adults (non-smokers 3-16 hours; average 8 hours)[1]. Hence, under normal circumstances, young patients would require more frequent dosing than adults.

The development of a ***prolonged-action*** capsule for paediatric use is therefore an event of some importance. Whilst kinetics will be more rapid between each 'pulsed' dose from the encapsulated beads of drug, provided sufficient is given, maintenance of therapeutic levels should be assured, rather than the marked peak and valley effect seen with normal short-acting tablets and oral liquids. The initial determining factor will be the bioavailability of theophylline in the product. The performance of drug studies, including the investigation of bioavailability, in children is however fraught with difficulties. We therefore investigated the relevance of adult studies in this context. Although it cannot be stated categorically that the bioavailability of drugs is identical in children and adults, it has been shown to be similar for some (groups of) drugs. These include sulphonamides, phenobarbitone, digoxin and the test substances of D(+)-xylose and L(+)-arabinose[4]. The ***amount*** of drug absorbed showed no age dependence, whereas the ***rate*** of absorption was low at birth and reached adult values after the ***neonatal*** period. Changes in bioavailability occurred during that period and in early infancy, whereafter there was little difference between children and adults. Overall then, there was a ***similar pattern of bioavailability***, particularly with increasing age of the child. We therefore investigated the bioavailability of Micro-Phyllin 60 mg Capsules in adult subjects, with the proviso that the data obtained could not be applied to ***young infants*** without further investigation.

SUBJECTS

The 7 subjects in this study 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. They were not taking other medication. They refrained from ingesting xanthine-containing beverages and alcohol for 48 hours prior to and during the study and fasted for 12 hours prior to drug administration. They received a standard breakfast, lunch and supper on each day of the study. The breakfast was given 30 minutes after ingestion of the drug.

METHOD

The 7 subjects were given 7 x 60mg capsules of Micro-Phyllin with 200 mℓ of water at zero time, after initial blood samples had been taken. Further samples were taken at one hour, 2, 3, 4, 6, 8, 10, 12, 24 and 30 hours after zero time. The samples were centrifuged in batches within one hour of the last sample for each time being taken. Drug plasma concentrations were immediately determined on a Beckman I.C.S. II (Immuno-Chemistry System) instrument, which gives comparable results to EMIT and HPLC[5]. The whole process was repeated using 180 mg of Anhydrous Theophylline in 200 mℓ of water as the bioavailability standard.

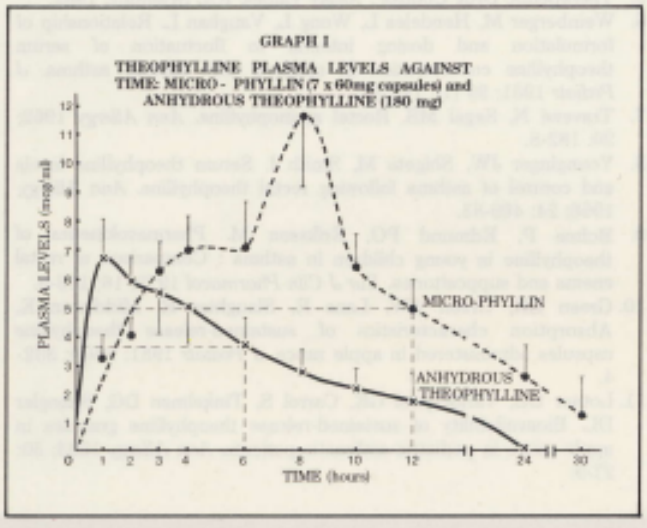
The data pairs of time and plasma concentration of each subject for the test and standard preparations were recorded. The mean values and standard deviations are tabulated in TABLE 1 and graphically drawn in GRAPH 1. The data pairs for each time and

TABLE 1: THEOPHYLLINE PLASMA LEVELS (mcg/mℓ) AGAINST TIME:
MICRO-PHYLLIN (7 x 60 mg capsules) AND ANHYDROUS THEOPHYLLINE (180mg)

Time (hours)	Micro-Phyllin (7 x 60 mg)			Anhydrous Theophylline (180 mg)		
	mean plasma level	standard deviation	coefficient of variance	mean plasma level	standard deviation	coefficient of variance
0	0	-	-	0	-	-
1	3,3	0,74	22,4	6,7	1,41	21,0
2	4,1	0,63	15,4	5,7	1,13	19,8
3	6,3	0,98	15,6	5,6	1,50	26,8
4	7,1	1,28	18,0	5,1	1,33	26,1
6	7,0	1,65	23,6	3,7	1,06	28,6
8	11,7	2,52	21,5	2,8	0,76	27,1
10	6,4	1,24	19,4	2,2	0,73	33,2
12	5,0*	0,95	19,0	1,7	0,95	55,9
24	2,6	1,10	42,3	0	-	-
30	1,3	1,26	96,9	0	-	-

NOTE: * mean of 6 determinations

Young patients normally require more frequent dosing than adults.



concentration for each subject were fed into a computer programme* which calculated AUC (inf) in each case. The terminal rate constant in the equation for AUC (inf) for the test preparation for each subject was taken as the slope from the calculation for the standard preparation. The bioavailability F for the test preparation for each subject was calculated using the equation:

$$F = \frac{D^{std}\ AUC^{prod}\ (inf)}{D^{prod}\ AUC^{std}\ (inf)}$$

where $D^{std} = 180$ mg

$D^{prod} = 420$ mg (*ie* the capsules were assumed to contain the labelled amount of drug, as they would be prescribed on this basis). Mean bioavailability for theophylline in the test preparation was calculated from the subject data, as were the standard deviation and the coefficient of variance. The results are tabulated in TABLE 2.

RESULTS

The plasma concentration against time results (TABLE 1 and GRAPH 1) demonstrate an appropriate prolonged release curve for the test product, and the characteristic 'surge' followed by steadily decreasing levels for the standard aqueous preparation of 180 mg of Anhydrous Theophylline. Comparison of the standard deviations and coefficients of variance for the 2 preparations reflects well on the test product. If the expected duration of action for the standard is taken as 6 hours and that for the test products as 12 hours (designed duration) then the test product performs better than the standard. The average coefficient of variance for the test product, at 19,4 is lower than that for the standard, at 24,5 over the respective periods. The bioavailability data (TABLE 2) demonstrate that the theophylline in the test product is readily available, *ie*, it has a mean bioavailability of 112% compared with the standard 100%. The standard deviation and coefficient of variance figures show similar subject-to-subject bioavailability for the test product.

*NOTE: * AUC (KINETICS) programme by Dr Paul Collier, Department of Pharmacy, Queen's University of Belfast.*

TABLE 2: BIOAVAILABILITY(F) OF THEOPHYLLINE FROM A PAEDIATRIC SUSTAINED-RELEASE CAPSULE*

Subject	Bioavailability(F)
1	1,0818
2	1,1509
3	0,9747
4	1,1692
5	1,2275
6	0,9921
7	1,2635
Mean	1,1228
Standard deviation	0,1114
Coefficient of variance	9,92%

NOTE: * Micro-Phyllin 60 mg

DISCUSSION

The results of this study indicate that general practitioners and paediatricians can prescribe the test product with a high level of confidence that the active ingredient will be released well from the dosage form, and in a predictable and uniform fashion over a prolonged period. These characteristics are especially important in paediatric therapy, because in addition to the factors mentioned previously, children tend to sleep for long periods. Hence, in this case, frequent repeat dosage is not required.

Unfortunately, this advantageous situation does not apply to all prolonged-action theophylline preparations[3,6]. Prescribers therefore need to watch the literature rather than rely on promotional material in this area, as in others.

The advantages of a predictable ***oral paediatric*** product also need to be considered against the problems which occur with ***rectal suppositories.*** Theophylline is slowly absorbed and gives low and unpredictable plasma levels by this route[7,8]. In

This test product would eliminate or reduce the fluctuating drug plasma concentration and also patient non-compliance.

particular the absorption of the drug from suppositories was incomplete and highly variable in children ranging from 2 months to 4 years (bioavailability range 8-100%; mean 80%)[9].

Another aspect which causes concern in paediatric therapy is patient non-compliance. This is especially important with solid dosage forms, which the patient may not be able to swallow easily. In the case of Micro-Phyllin capsules this difficulty can be circumvented, as it has been shown that the pellets contained in the capsule may be sprinkled on apple sauce and then ingested, whilst retaining their bioavailability and sustained-release characteristics[10,11], provided they are ***not*** chewed. Using the test product in this way would therefore eliminate or at least reduce the two problems of fluctuating drug plasma concentrations and patient non-compliance.

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