Product-to-product differences in plasma concentration-time curves from recommended doses of prolonged-action preparations of theophylline

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Summary

The author conducted drug plasma level determinations on four slow-release theophylline products using doses which would be recommended for adult patients. The study demonstrated an inequivalence amongst the preparations in drug levels achieved and in predictability.

KEYWORDS: Product Surveillance, Postmarketing; Theophylline.

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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 1978-1983 he was Head of the Department of Pharmacy, University of Zimbabwe, and also Deputy Dean in the Faculty of Medicine. Since 1983 he has been Professor and Head of the Department of Pharmaceutics, Medunsa, where he has also been the 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.

INTRODUCTION

Oral prolonged-action theophylline preparations are playing an increasingly important part in the effective treatment of asthma. The drug's optimal bronchodilating activity occurs at plasma levels of 10-20 mcg/mℓ^{-1}. One problem is that the drug has a narrow therapeutic window, with a lack of effect being

CHART I
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	350	280	2 x 350 mg tablets (560 mg)
Micro-Phyllin	Theophylline	250	250	2 x 250 mg capsules (500 mg)
Phyllocontin	Aminophylline	225	180	2 x 225 mg tablets (360 mg)
Theo-Dur	Theophylline	200	200	2 x 200 mg tablets (400 mg)

demonstrated below 8 mcg/mℓ, and toxicity appearing from levels sometimes as low as 15mcg/mℓ. It is therefore important that prescribers have confidence that appropriate levels will be achieved from their prescribed doses, no matter which preparation they use.

Currently, there is a variety of prolonged-action theophylline and aminophylline single active ingredient preparations on the market. For the above reasons, we conducted drug plasma level determinations on four products* using doses which would be recommended for adult patients.

SUBJECTS

The 8 subjects in the study were healthy Caucasian males with an average age of 28,4 (range 25-37 years) and an average body mass of 75,1 (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 each 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

On successive Tuesdays the following procedure was performed on each of the 8 subjects:

1. A blood sample was taken
2. The appropriate dose of a particular preparation was swallowed with 200 mℓ of water (See Chart 1 for doses of products administered)
3. Blood samples were taken at one hour, 2, 3, 4, 6, 8, 10, 12, 24 and 30 hours after zero time
4. The samples were centrifuged in batches within one hour 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 results comparable to EMIT and HPLC[2].

The process was repeated for each of the test preparations as well as with 180 mg of Anhydrous Theophylline in 200 mℓ of water as a standard to determine whether there were any abnormalities in drug absorption by the subjects.

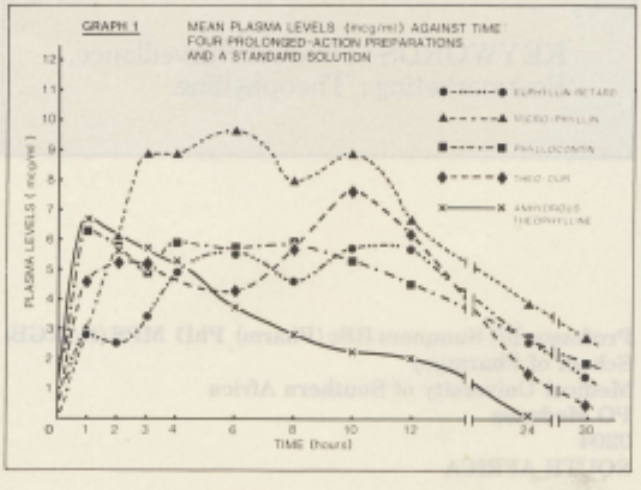
The mean plasma levels for each time period were calculated for each product, as were the 90% confidence limits.

RESULTS

The results are graphically represented in GRAPHS 1-6. GRAPH 1 contains the plasma level *vs* time curves for the 4 test preparations and standard. GRAPHS 2-6 show the plasma concentrations and the 90% upper and lower confidence limits for the standard solution and the respective products.

A. CONCENTRATION CURVES

The difference among products and the short duration of action of the standard solution are clearly shown in GRAPH 1.



* Euphyllin Retard (Byk-Gulden) Batch 061 L: 350mg tablet/Micro-phyllin (Rona: Script Intal) Batch 034: 250mg capsule/Phyllocontin (Mundipharma: Script Intal) Batch UF 002: 225mg tablet/Theo-Dur (Rio) Batch B 300 334: 200mg tablet.

Product-to-product differences

1. ***Euphyllin Retard (560 mg theophylline):*** This product gave a fairly consistent curve from ±4-12 hours. Unfortunately the levels of theophylline are particularly low (4,5-6 mcg/mℓ) for the administered dose (N.B: We initially carried out plasma level determinations with a single 350 mg tablet containing 280 mg theophylline. The drug concentrations were so low with the single tablet dose that we repeated the determination as above with 2 tablets.)

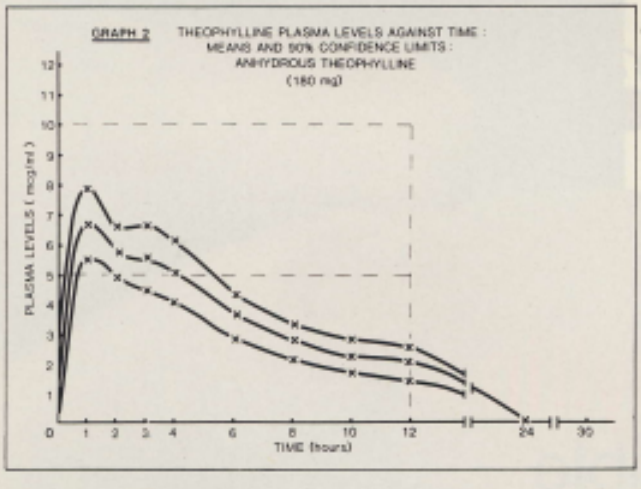
2. ***Microphyllin (500 mg theophylline):*** This preparation manifested the highest consistent plasma levels of drug (between 8 and 10 mcg/mℓ from 3½-11¼ hours) from a fairly high dose of drug.

3. **Phyllocontin (360 mg theophylline):** This tablet exhibited a rapid onset of action with drug level after the first hour (6,3 mcg/mℓ) close to that for the aqueous solution (6,7 mcg/mℓ). Drug concentrations remained consistent, but relatively low, until ± 11 hours from zero time.

4. ***Theo-Dur (400 mg theophylline):*** The concentration curve for this product remained fairly consistent from 1-8 hours, after which it showed a surge.

B. 90% CONFIDENCE LIMITS

We performed this calculation to ascertain whether the levels from the different products would be predictable in similar subjects and hence justify prescriber confidence in general guidelines for dosing, compared with the standard solution (GRAPH 2), where the 'confidence curve' followed the mean fairly closely.

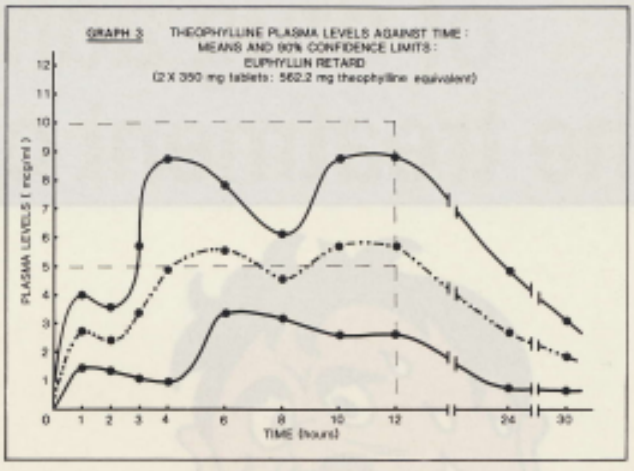


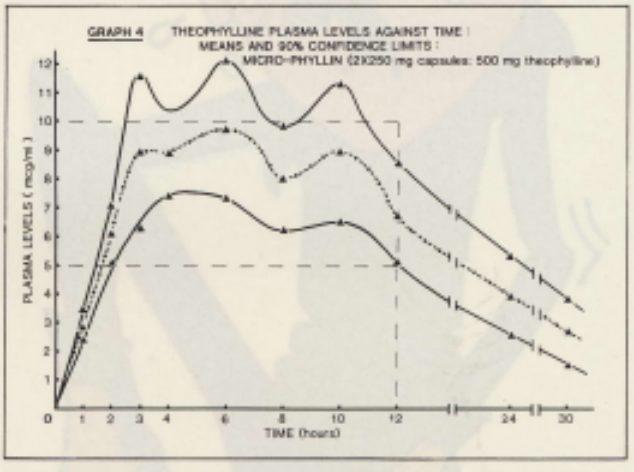
1. ***Euphyllin Retard*** (GRAPH 3): The confidence limits are extremely wide and variable around the mean, which demonstrates lack of uniformity from subject to subject.

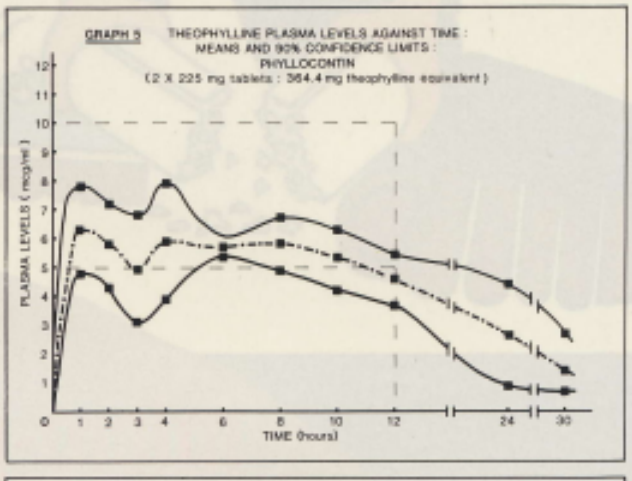
2. ***Microphyllin*** (GRAPH 4): The confidence curve followed the mean but was fairly wide.

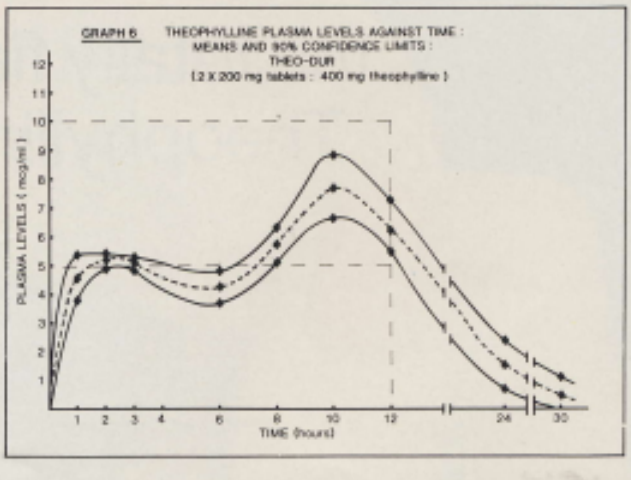
3. ***Phyllocontin*** (GRAPH 5): The curve was variable, but closer to the mean than in the 2 previous cases.

4. ***Theo-Dur*** (GRAPH 6): A slight mid-period dip is illustrated in this case. The confidence curve follows the









mean and remains close to it, which exhibits uniformity among subjects.

DISCUSSION

This study has clearly demonstrated an inequivalence among prolonged-action theophylline preparations, in both drug levels achieved and predictability. In general terms Micro-Phyllin exhibited high levels with the lower doses of Phyllocontin and Theo-Dur giving expected lower levels. Hence, therapeutic drug monitoring and appropriate dosage adjustments could be expected to produce a favourable response with these 3 products. The situation is entirely different with Euphyllin Retard which showed great variation around generally unacceptably-low mean drug levels (in relation to dose), *ie* the product did not exhibit satisfactory plasma concentrations or predictability.

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