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Bayesian derived predictions for twice daily theophylline under outpatient conditions and an assessment of optimal sampling times

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1 The accuracy of a computerised method of pharmacokinetic interpretation of a single serum theophylline concentration, employing the statistical technique of Bayesian analysis, has been evaluated for an oral slow release form of theophylline using twice daily dosing.
2 Twenty-four hour steady state serum theophylline concentration-time profiles of one Uniphyllin Continus 400 mg tablet (Napp Laboratories) every 12 h were measured in 15 patients. These profiles demonstrated a diurnal variation of theophylline absorption which was faster during the day.
3 Revised predictions of the profiles were generated by Bayesian analysis using a single serum theophylline concentration taken during a previous outpatient appointment. Comparing the predicted and measured profiles, the accuracy of the Bayesian method is considered more than adequate for clinical purposes.
4 The predictions produced by the revised estimates were statistically less biased and more precise than those derived by a theophylline algorithm using population data.
5 The mean prediction errors of the revised estimates of the day and night-peak drug concentrations were -0.55 mg l^{-1} and -0.21 mg l^{-1} whilst those of the evening and morning troughs were 1.17 mg l^{-1} and 0.41 mg l^{-1}, respectively.
6 Analysis of the predictive and relative performance of the samples drawn during the profile revealed that the sample taken prior to a morning dose produced the most accurate predictions.
7 There was no statistical difference in the relative predictive performance of samples drawn up to 4 h before or 2 h after the morning dose. It is, therefore, recommended that all serum theophylline concentrations to be used in Bayesian analysis, should be drawn within this period.

Keywords theophylline Bayesian analysis outpatient monitoring

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Introduction

When a clinical decision is taken to use oral theophylline in the management of patients with obstructive airways disease, there are frequently problems in achieving the optimal dose and in the interpretation of isolated measurements of serum theophylline concentration (Jenne *et al.*, 1972; Woodcock *et al.*, 1983; Howard, 1987). Many of the difficulties associated with this problem can be overcome by using pharmacokinetic forecasting based on the technique of Bayesian analysis (Peck *et al.*, 1980; Sheiner & Beal, 1982). Using this method it is possible to individualise the dosage regimen from these isolated measurements of serum concentration (Chrystyn *et al.*, 1985). The dosage recommendations made should allow an optimal compromise between the maximal clinical effect and minimal toxicity to be achieved.

We have already measured the accuracy of this technique using a once daily dosing regimen of a slow release form of theophylline (Chrystyn *et al.*, 1987). From this multicentre study, involving 83 patients, it was shown that in routine practice a serum theophylline sample drawn 12 to 24 h post dose could be used in the Bayesian technique. Patients were studied over a limited period of 7 days and, therefore, the long-term accuracy of any Bayesian derived predictions could not be evaluated. We report here an extension of this work with the same theophylline preparation using twice daily administration. In this study the performance of the Bayesian method is assessed over a period of up to 3 months, using a routinely collected sample in the outpatient clinic.

Methods

Outpatients aged 18 years or more were recruited into the study. All patients had obstructive airways disease, were currently being treated with twice daily slow-release theophylline, and on a stable drug therapy. Patients were excluded if they had hepatic or renal disease, viral infection or took erythromycin within 7 days of starting the study or taking the first blood sample. All patients gave their informed consent and the study was approved by the Pontefract Ethics Committee.

The first blood sample was taken for serum theophylline analysis during a routine outpatient appointment. The time for the sample was not set and was taken at the time of attendance. Each patient's demographic details, clinical status, social habits (e.g. smoking), and concurrent drug therapy were recorded using a standard form (see Figure 1). Using this information initial estimates of each patient's pharmacokinetic parameters were obtained using a theophylline algorithm previously derived from population data (Chrystyn *et al.*, 1984). These were then refined into revised estimates by Bayesian analysis, using the patient's dosage history and serum theophylline concentration resulting from the blood sample drawn during the out patient visit (also recorded on the standard form). The standard deviation of the initial estimates of clearance and volume of distribution used in the Bayesian technique were set at 50% and 25% respectively. A weight was also placed on the serum theophylline concentration to allow for assay error (5%) and pharmacokinetic model mis-specification (10%). The use of these weightings has been previously described by Peck *et al.* (1980).

Patients were admitted to hospital between 1 and 3 months (mode 3 months) after this outpatient visit. This time period was not set and depended on bed availability or the need for acute admission. Patients' theophylline treatment consisted of one slow release theophylline 400 mg tablet (Uniphyllin Continus 400 mg—Napp Laboratories Limited, Cambridge, UK) given at 10.00 h and 22.00 h. After 4 days blood samples were drawn via an indwelling heparinised cannula at 10.00 h immediately before the morning dose and subsequently at two hourly intervals until the same time on the following day. A 10 ml blood sample was drawn and placed in an appropriately labelled tube.

Clotted blood samples were centrifuged and frozen at −20° C. The serum theophylline assays were carried out in duplicate by EMIT.

Data analysis

Predictions of the 24 h steady state serum theophylline concentration-time profile were made from both the initial and revised pharmacokinetic parameters. An open one compartmental model was used to describe the kinetics of theophylline with a zero order release rate of 9 h representing the absorption process and 100% bio-availability of the slow release theophylline. The predicted profile was compared with the measured profile. For each individual, a prediction error was calculated by subtracting the measured serum theophylline concentration from that of the revised estimated serum theophylline concentration at:

(a) Evening trough—using the 22.00 h measured and revised concentration
(b) Morning trough—using the measured and

revised serum concentration of the 10.00 h sample on day 2, (i.e. the last sample).

(c) Day peak—using the highest measured and revised serum concentration between 10.00 and 22.00 h.

(d) Night peak—using the highest measured and revised serum concentration between 22.00 and 10.00 h.

For each set of results the mean prediction error (me) and mean squared prediction error (mse) were calculated along with their standard deviation and 95% confidence limits, as described by Sheiner & Beal (1981). Me and mse are measures of bias and precision respectively.

Additionally each of the 6.00, 8.00, 10.00, 12.00, 14.00, and 16.00 h theophylline serum concentrations were used, separately, in Bayesian analysis to generate a further six sets of revised parameters i.e. one feedback concentration per set. For each of these revised estimates, the 24 h steady state serum theophylline concentration profile was predicted. Prediction errors, me and mse with their 95% confidence intervals were calculated as previously described.

THEOPHYLLINE Tablets - Individualised Dosage Estimator

Demographic Data

Doctor Name .....

Patient Name ..... Hospital No .....

Patient Age ..... years Weight ..... kg. Height ..... m Sex ....

Patient History

Does this patient smoke? ..... How many per day? .....

Associated Illness (please tick where applicable)

Hepatic Cirrhosis ☐ Chronic Alcoholism ☐

Congestive Heart Failure ☐ Severe Congestive Heart Failure ☐

Acute Pulmonary Oedema ☐ Chronic Obstructive Airways Disease ☐

Other - please specify [ ]

Concommitant Medication (please tick where applicable)

Oral Contraceptives ☐ Allopurinol ☐ Cimetidine ☐ Carbamazepine ☐

Erythromycin ☐ Tricyclic Antidepressants ☐ Benzodiazepines ☐ Phenytoin ☐

Other - please specify [ ]

Dosage Information

Steady state dose ..... Dosage times ..... Preparation .....

Last 4 dosage times	Date	Time	Dose
1			
2			
3			
4			

Serum Theophylline Assay Information

Assay Taken Date ..... Time .....

Assay result ..... mg/L (mcg/ml)

Doctors Signature ....

Figure 1 Theophylline monitoring form.

By comparison with the most accurate prediction the relative bias (Δme) and precision (Δmse) were calculated for each sample according to the method of Sheiner & Beal (1981). To determine the degree of any significant difference 95, 99 and 99.9% confidence limits were calculated, as appropriate.

From the measured profiles t_{max}, C_{max}, C_{min} and the area under the curve (AUC) for day and night-time administration were derived. Differences between day and night values of these were tested using the Mann Whitney test and a value of $P < 0.05$ to demonstrate significance.

Results

Fifteen patients (seven females) with a mean (range) age of 60.1 years (39–69) and weight of 72.1 kg (57–102) completed the study.

The mean steady state measured and revised estimates of the serum theophylline concentration-time profiles are shown in Figure 2. The measured profile indicates diurnal differences in the absorption rate reflected in a significantly ($P < 0.01$) faster time to maximum concentration (t_{max}) during the day (mean t_{max} 5.6 h) than during the night (mean t_{max} 7.6 h). Nevertheless, there was no difference between the maximum concentration (C_{max}) measured during the day (mean 14.2 mg l^{-1}) and that measured after night-time administration (mean 13.9 mg l^{-1}). However, there was a small but significant difference ($P < 0.05$) between the measured trough value (C_{min}) during day time (mean 9.5 mg l^{-1}) and night-time administration (mean 10.2 mg l^{-1}). There was no significant difference between the area under the curve during day and night administration with a mean relative availability (pm/am) of 95.1% with 95% confidence limits of 90.1 to 100%.

The close similarity of the two profiles shown in Figure 2 is reflected in Table 1 by the prediction of peak and trough concentrations in terms of bias and precision. This table reveals that all the predictions produced by the revised estimates were less biased and more precise than those obtained using the initial estimated values. Evaluation of the relative performance revealed that these differences in bias and precision were significant ($P < 0.01$ except the precision of the day peak which was $P < 0.05$).

Table 2 details the predictive performance of each of the daytime samples when used separately in Bayesian analysis. This table shows that although the precision of the peak prediction of the 10.00 h sample was one of the worst, overall this sampling time produced the most accurate predictions. Relative performance using Δmse indicated that the poorer level of precision in the prediction of the peak serum theophylline concentration of the 10.00 h revised estimates (Table

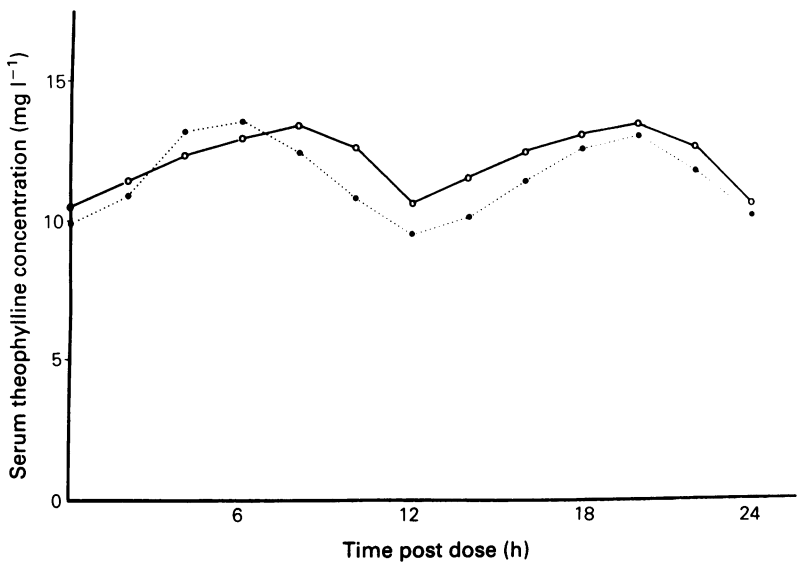

Figure 2 Mean measured (•) and revised (○) estimated steady state serum theophylline concentration-time profiles of one slow release theophylline 400 mg tablet (Uniphyllin Continus 400 mg) taken every 12 h ($n = 15$).

Table 1 Predictive performance of the initial estimates and revised estimates produced by the out-patient clinic sample (n = 15). Upper and lower limits of 95% confidence intervals given in parentheses

Performance indicator	*Day peak*	*Evening trough*	*Night peak*	*Morning trough*
Bias me (mg l^{-1})				
Revised Estimates	–0.55 (0.72, –1.82)	1.17 (1.93, 0.41)	–0.21 (0.76, –1.18)	0.41 (1.26, –0.44)
Initial Estimates	3.12 (5.46, 0.78)	3.14 (5.62, 0.66)	3.46 (5.92, 1.00)	4.02 (5.96, 2.08)
Precision mse (mg l^{-1})^2				
Revised Estimates	5.27 (9.10, 1.44)	3.14 (5.62, 0.66)	2.91 (4.77, 1.05)	2.37 (5.45, –0.71)
Initial Estimates	26.43 (41.79, 11.07)	36.24 (54.26, 18.22)	30.40 (46.48, 14.32)	27.60 (40.43, 14.77)

Table 2 Predictive performance for the revised estimates from the samples taken from the measured profile (n = 15). Upper and lower limits of 95% confidence intervals in parentheses

Performance indicator	*Revised estimates Time (h) 06.00*	*08.00*	*10.00*	*12.00*	*14.00*	*16.00*
BIAS me (mg l^{-1})						
Peak	–0.45 (0.27, 1.17)	–0.50 (0.35, –1.35)	–0.31 (0.54, –1.16)	–0.46 (0.19, –1.11)	0.80 (1.40, 0.20)	0.66 (1.20, 0.12)
Trough	0.67 (1.06, 0.28)	0.57 (1.02, 0.12)	0.64 (1.01, 0.27)	0.58 (1.44, –0.28)	1.83 (2.81, 0.77)	1.70 (2.64, 0.76)
Precision mse (mg l^{-1})^2)						
Peak	3.83 (6.03, 1.83)	5.23 (7.20, 3.26)	5.15 (7.73, 2.57)	3.09 (4.90, 1.28)	3.26 (4.81, 1.63)	2.33 (4.13, 0.53)
Trough	1.53 (2.27, 0.79)	1.90 (2.98, 0.82)	1.36 (2.16, 0.56)	5.53 (8.02, 3.04)	11.13 (16.42, 5.84)	8.86 (12.57, 5.15)

2) is only reflected by a significant difference ($P < 0.05$) between the peak predictions of this sample and that of the 06.00 h sample. The 10.00 h revised estimates were significantly ($P < 0.05$) more precise and less biased than those of the trough 14.00 h revised estimates and more precise than the trough predictions of the 12.00 h and 16.00 h revised estimates. There was no significant difference between all the other comparisons.

Discussion

The finding of a longer t_{max} at night and higher trough serum concentrations in the morning reflecting circadian variation in theophylline absorption is similar to that reported in children (Scott *et al.*, 1981) and adults (Lesko *et al.*, 1980; Taylor *et al.*, 1983; Isles *et al.*, 1984). There was no significant difference in the area under the curve between day and night time administration suggesting that bioavailability and clearance were unchanged, a finding previously reported (Birkett *et al.*, 1983; Taylor *et al.*, 1983; Taylor *et al.*, 1984; Isles *et al.*, 1984; Watanabe *et al.*, 1984), but in contrast to a decrease in theophylline elimination at night found by others (Jonkman, 1983; St Pierre *et al.*, 1985).

In accordance with a recently published study (Chrystyn *et al.*, 1988a) it was found that the technique of Bayesian analysis using slow release theophylline 400 mg tablets is accurate for twice daily dosing, and for use in the outpatient clinic over a period of 3 months. However it should be noted that detailed and precise patient demography was obtained during the clinic visit and

therefore the use of a suitably designed form is mandatory (see Figure 1). The predictive performance of the theophylline algorithm in that the concentrations were all over-predicted, is similar to that previously published (Chrystyn *et al.*, 1984, 1988a) and emphasises the need for careful measurement and interpretation of the serum theophylline concentrations in order to optimise the dose.

Overall, the sample drawn immediately before the morning dose when used in Bayesian analysis, provided the most accurate predictions. The closer a sample was drawn to the peak or trough then the greater was the degree of precision in the prediction of the respective value. This we have previously demonstrated (Chrystyn *et al.*, 1987) using once daily dosing.

The large improvement in the bias and precision of the revised estimates reflects how Bayesian analysis refines the population derived pharmacokinetic parameters into ones of a more individualised nature. Although there was some difference in the bias and precision of the revised estimates derived from various sampling times, during a dosage interval, they were only small. These do not necessarily give estimates of variability of serum drug concentration within individual subjects since they can reflect variability in the population values of bias.

Nevertheless, despite some slight differences in bias and precision estimates, any sample would be more than adequate for clinical purposes in the optimisation of theophylline dosage using Bayesian analysis, with the possible exception of the 14.00 and 16.00 h samples. The serum theophylline concentration of these two samples (i.e. 4 h and 6 h post dose) are the most likely to be affected by pharmacokinetic mis-specification or variability in absorption should it occur and therefore should be avoided. If such samples are used in Bayesian analysis then this should be borne in mind and the results carefully checked by a person with extensive clinical pharmacokinetic experience before any dosage recommendations are made. The samples drawn between 2 h after and 4 h before the morning dose underestimated the peak serum theophylline concentration. Since the lower limit of the 95% confidence interval of peak predictions was as much as 1.35 mg l^{-1} (Table 2, 08.00 h revised estimate) less than the overall mean measured peak serum theophylline concentration of 14.2 mg l^{-1} then all dosage recommendations, when using these samples with Bayesian analysis, should not exceed a peak concentration of 17.5 mg l^{-1}. It is doubtful whether improved clinical benefit would occur if the peak serum theophylline concentrations were increased above this value and keeping levels below 17.5 mg l^{-1} should minimise the possibility of side effects.

From our experience we have found that when used on a routine day to day basis it is possible to make individualised dosage recommendations in this way. However, interpretation of data should be carried out by an experienced person with pharmacokinetic knowledge (both theoretical and clinical) so that variabilities due to absorption, non-compliance, pharmacokinetic mis-specification and other factors which may alter the theophylline pharmacokinetic parameters can be identified. The individualised pharmacokinetic parameters produced by the Bayesian technique are used to generate computer print outs of the estimated serum concentration-time profiles of any dosage regimen (Chrystyn *et al.*, 1987). These profiles enable once daily, twice daily or assymetric dosing (smaller dose at midday and larger dose at night) recommendations to be made meeting with the clinical needs of each individual. The availability of these visual displays of serum concentration profiles are more convenient than attempting to interpret isolated serum drug concentrations. No clinical assessment of these patients was carried out during this study. However in another study we have recently demonstrated linear dose-response relationships to theophylline in irreversible chronic obstructive airways disease when the dose was individualised using Bayesian analysis (Chrystyn *et al.*, 1988b).

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The computer program used is available to run on Amstrad PC1512, Apricot F2, BBC, IBM, Opus and Sirius micro-computers, and can also provide similar interpretation of aminoglycoside antibiotics, digoxin and phenytoin serum concentrations.

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