Theophylline dose prediction

D T BESWICK, R E CULLEN, AND G W RYLANCE
Children’s Hospital, Birmingham

SUMMARY Two methods of predicting the optimal dose of theophylline in children aged 2 to 13 years were assessed. The observed plasma concentration was within 95% confidence limits of that predicted on eight of 14 occasions using a traditional multiple point pharmacokinetic method. Using a nomogram derived from the plasma concentration 6 hours after dosing and the logarithm of the calculated dose, which were significantly correlated, there was a significant relation between the dose predicted and the actual dose required to produce a concentration of 55 \( \mu \text{mol/l} \).

Theophylline is an effective bronchodilator drug for both acute medical treatment and prophylaxis of asthma. Both the bronchodilator effect and toxicity are closely related to the concentrations of drug in plasma and optimum treatment is usually achieved when the plasma theophylline concentration is maintained within the range 55 to 110 \( \mu \text{mol/l} \).

Because of the large variations in theophylline pharmacokinetics between children, optimum plasma concentrations cannot be achieved predictably by the administration of usual doses. Some clinicians, therefore, monitor plasma concentrations two to three weeks after the start of treatment and subsequently make dose adjustments where indicated. Further asthma symptoms or the onset of drug toxicity in the period before the establishment of individualised treatment may cause distress to the child and family, and this ‘run in’ period should therefore be as short as possible.

Clear benefits may be expected when treatment is individualised at its onset. Calculation methods based on kinetic parameters derived from single dose studies may be employed, but these have the disadvantage that multiple blood sampling is required. More recently, another method based on a hypothesis by Koup et al has been described and assessed in adults. This method depends on the existence of a close relation between the oral maintenance dose required to produce a particular mean steady state plasma concentration and the plasma concentration at 6 hours after a test dose of aminophylline given intravenously. The value of the single point prediction method has recently been substantiated in adults.

The aim of this study was to validate the relation between the plasma concentration at 6 hours after a single drug dose and the logarithm of the oral maintenance dose, and to test the usefulness of a nomogram based on this relation.

Patients and methods

Seven children aged 2 to 13 years were included in the study which had been approved by our local research ethical committee. Informed parental consent was obtained. None of the children had liver or kidney disease and none were receiving drugs known to affect theophylline disposition.

An intravenous dose (approximately 4 mg/kg) of aminophylline (79% theophylline, 21% ethylene diamine) was injected into a peripheral vein as a single dose constant rate infusion over 20 minutes. Venous blood samples (1 ml) were obtained through an indwelling heparinised catheter before and at hourly intervals for 10 hours after completion of the infusion.

Each child was then started on an oral sustained release aminophylline or theophylline preparation given in equal 12 hourly doses at 8 am and 8 pm. Six children received Phyllocontin Continus (Napp, UK) and one received Theodur (Fisons, UK). Within two weeks and after at least five days of oral treatment, samples to allow dose (dose A—see Table) interval theophylline plasma concentrations profiles to be determined were collected at hourly intervals through an indwelling catheter between the morning and evening doses. Subsequently, a change of dose was made in each patient after comprehensive assessment of each child, its symptoms, and the drug concentrations. Samples to allow a further dose (dose B) interval profile to be determined for each child on the new steady state dose schedule were collected after the same time period criteria and practice as on the previous occasion.
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The samples were centrifuged at −20°C until assayed for theophylline by EMIT (Syva, USA). The within and between run coefficients of variation were 4.7 % and 2.7 %, respectively.

<table>
<thead>
<tr>
<th>Case No</th>
<th>Elimination rate constant (Ke) (hour)</th>
<th>Volume of distribution (Vd) (l/kg)</th>
<th>$D_{	ext{M,calc}}$ from Eq 4 (mg/kg/day)</th>
<th>$C_{	ext{PSS}}^*$ (µmol/l)</th>
<th>$D_{	ext{M,pred}}$ from nomogram of Koup et al (mg/kg/day)</th>
<th>$D_{	ext{M,pred}}$ from nomogram derived from study data (mg/kg/day)</th>
<th>$\text{Obs}(C_{\text{PSS}})$ (µmol/l)</th>
<th>$D_{\text{M,act}}$ (mg/kg/day)</th>
<th>$D_{\text{M,act}}'$ (mg/kg/day)</th>
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</table>

*Cp*: linearly corrected plasma theophylline concentration 6 hours after intravenous dose of 4.0 mg/kg aminophylline.

$D_{\text{M,pred}}$ = maintenance dose predicted; $\text{Obs}(C_{\text{PSS}})$ = observed mean steady state plasma concentration; $D_{\text{M,act}}$ = actual maintenance dose.

The actual oral maintenance dose to produce a mean steady state plasma concentration of 55 µmol/l was calculated from the equation:

$$V_{d} = \frac{C_{p}}{C_{l}} \times \frac{D_{\text{M,act}}}{1000}$$

Where $C_{l}$ is the total body clearance of theophylline; $C_{p}$ is the apparent oral maintenance dose to produce a mean steady state plasma concentration of 55 µmol/l; $V_{d}$ is the apparent volume of distribution, and $D_{\text{M,act}}$ is the actual oral maintenance dose.

The predicted mean steady state plasma concentration (pred $C_{\text{PSS}}$) was estimated from the relation:

$$V_{d} = \frac{C_{p}}{C_{l}} \times \frac{D_{\text{M,calc}}}{1000}$$

Where $C_{l}$ is the total body clearance of theophylline; $C_{p}$ is the apparent oral maintenance dose to produce a mean steady state plasma concentration of 55 µmol/l; $V_{d}$ is the apparent volume of distribution, and $D_{\text{M,calc}}$ is the actual oral maintenance dose.

The results are shown in the Table. The linearly corrected plasma theophylline concentration at 6 hours after a single dose (Cp) and the logarithm of Cp were significantly correlated ($r = 0.98$, P < 0.001) as shown in Fig. 1. The correlation was linearly correlated with substitution of 55 µmol/l for $C_{p}$.

The actual oral maintenance dose to produce a mean steady state plasma concentration of 55 µmol/l was calculated from the equation:

$D_{\text{M,act}} = \frac{C_{p}}{C_{l}} \times \frac{D_{\text{M,calc}}}{1000}$

Assuming theophylline is eliminated by a first order process, the oral daily maintenance dose (DM,calc) to produce a mean steady state plasma concentration of 55 µmol/l was calculated from the equation:

$DM_{\text{calc}} = (Cp) \times \frac{1}{k \times V_{d} \times 24 \text{ mg/kg/24 h}}$  

Where $C_{l}$ is the total body clearance of theophylline and $V_{d}$ is the apparent volume of distribution.

$\Delta$ The predicted mean steady state plasma concentration (pred $C_{\text{PSS}}$) was estimated from the relation:

$$V_{d} = \frac{C_{p}}{C_{l}} \times \frac{D_{\text{M,calc}}}{1000}$$

The predicted maintenance oral dose was derived area under the plasma concentration time curve (AUC) for the dose interval, thus:

$$AUC = \frac{V_{d}}{k} \times C_{p} \times t_{0}^{6 \text{ h}}$$

The observed, mean steady state plasma concentration at 6 hours after a single dose ($C_{p}$) and the logarithm of $C_{p}$ were significantly correlated ($r = 0.98$, P < 0.001) as shown in Fig. 1. The correlation was linearly correlated with substitution of 55 µmol/l for $C_{p}$.
significant correlations between the plasma concentrations at other times and log $D_{M,calc}$ ($C_p^2$: $r = 0.94$, P<0-01; $C_p^3$: $r = 0.95$, P<0-01; $C_p^4$: $r = 0.98$, P<0-001; $C_p^5$: $r = 0.95$, P<0-01; $C_p^6$: $r = 0.91$, P<0-01). In addition there was a highly significant correlation between the dose predicted from the nomogram based on the relation between $C_p^6$ and log $D_{M,calc}$ in our study and that derived from the observations of Koup et al \(^4\) as shown in Fig. 2 ($r = 0.99$, P<0-001).

Fig. 3 shows the significant relation between the predicted maintenance dose ($D_{M,pred}$) from the study data and $D_{M,act}$ using data for both Dose A and B ($r = 0.78$; P<0-01). Forcing the line through the origin \(^5\) produced a slope of 1.06, and five of the 14 predicted values fell within 95% confidence limits of the line.

Using a Student’s $t$ test for paired data, there was no significant difference between the predicted and the measured ($C_p$) values ($t = 1.17$; DF = 13; P>0.2). Eight of the 14 observations were within 95% confidence limits of predicted values.

**Discussion**

The results show that the relation between $C_p^6$ and log $D_{M,calc}$ was highly significant and similar to the findings of Koup et al. \(^4\) There was also a highly significant correlation between the dose predicted from the study nomogram ($D_{M,pred}$) and that derived from pharmacokinetic data using the traditional approach. Both these observations seem to substantiate the validity of the nomogram and suggest that a simple means of predicting optimal dose based on a single blood test is available.

We tested the potential usefulness of the nomogram in clinical practice by determining the actual dose required to produce a mean, steady state concentration of 55 $\mu$mol/l in each of the seven children, comparing these results with the doses
predicted from the plasma concentrations at 6 hours using the nomogram. Despite the significant correlation between the parameters, the relation was not close enough to satisfy reasonable criteria for clinical use. In only five patients was the nomogram predicted dose ($D_{M,pred}$) within 95% confidence limits of the actual dose ($D_{M,act}$) and the predicted dose exceeded the actual dose by more than 3 mg/kg/day in six of 14 patients and fell short by the same margin in four of 14. Values overestimating actual doses were similar in number to those underestimating dose, suggesting that error in accuracy was not a result of less than 100% compliance with or bioavailability of the preparations. A combination of over and under use of the drug on the day before the study, however, cannot be ruled out.

The results using the nomogram are similar to those obtained using the traditional pharmacokinetic method but their predictive accuracy and therefore usefulness have limitations, and the reason is not clear. The calculations from the results have assumed that plasma theophylline concentrations are related linearly to dosage. Although there is some evidence to suggest that theophylline kinetics may be dose dependent, we found no statistically significant difference between the means of the areas under the plasma concentration time curves adjusted for standard dose on each of the three occasions observed, suggesting that linear kinetics were operative. Any error based on non-linear kinetics would be expected to bias the results towards over prediction of $D_{M,pred}$ compared with $D_{M,act}$.

The degree of error in these methods may reflect variation in the theophylline elimination between individual patients. Individualisation of treatment measurement of specific, timed theophylline plasma concentrations and adjustment of dose during treatment may be no more accurate than prediction methods, as the former approach assumes that these concentrations are reproduced accurately over the same period each day, and there is no evidence to substantiate this. Variation in theophylline elimination between subjects would affect this approach in the same way as for the prediction methods.

The correlation coefficient between $D_{M,act}$ and $D_{M,pred}$ in this study (0.78) is lower than that found in adults (0.90) but reaches a similar degree of statistical significance ($P<0.01$). In this method we have used the mean steady state concentration ($[(Cp)_{ss}]$ for the dose interval as the standard for calculations, unlike the study in adults which used trough concentrations ($[(Cp)_{trough}]$. This reduces the error by excluding that which arises from differences between $(Cp)_{ss}$ and $(Cp)_{trough}$. As all the children were free from renal or hepatic disease, it seems likely that correlation coefficient difference between children and adults arises from the lesser reproducibility of specific timed plasma concentrations from day to day in children, and suggests that difference in absorption and elimination between individuals is greater in children.

References


Correspondence to Dr G W Rylance, Children's Hospital, Birmingham B16 8ET.

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