PREDICTION OF MAINTENANCE ORAL THEOPHYLLINE DOSAGE USING SINGLE ORAL DOSES IN PATIENTS WITH OBSTRUCTIVE AIRWAYS DISEASE

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1 This study was designed to test whether single oral doses of theophylline, rather than the specified single intravenous infusions, could be used with a nomogram designed to predict the maintenance oral dose necessary to establish plasma theophylline concentrations of $10 \mu\text{g ml}$ (Koup *et al.*, 1979) in patients with obstructive airways disease.

2 A test dose of theophylline (5 mg kg) was administered on two separate occasions as an oral elixir and as an intravenous infusion. Exactly 6 h after each test dose, plasma theophylline concentration was measured, and the result used to predict daily maintenance dose requirements. During subsequent oral administration, a sustained-release preparation was given in equally divided 12-hourly doses, and 'steady-state' concentrations were measured at trough.

3 Nineteen patients completed the study, and on doses ranging from 4.2 to $21.1 \text{ mg kg}^{-1} \text{ day}^{-1}$, trough concentrations of 5.4 to $15.8 \mu\text{g ml}$ (mean $10.0 \pm 0.7 \mu\text{g ml}$) were achieved. No significant differences were noted between the dose predictions made following either the oral or the intravenous test doses, and the predictive accuracy using the oral route was not compromised.

4 This would suggest that the test dose of theophylline may be administered orally, instead of intravenously, with this nomogram without reducing its efficiency.

Keywords theophylline nomogram obstructive airways disease

Introduction

The use of theophylline in the overall management of obstructive airways disease has been enhanced not only by recognizing that its bronchodilator action is related to plasma drug concentrations (Mitenko & Ogilvie, 1973) but also by the advent of sustained release preparations affording the opportunity to maintain constant plasma drug concentrations (Riegelman, 1980). It is generally accepted that optimal effect is achieved within the 'therapeutic' range of 10 – $20 \mu\text{g/ml}$, but dose selection in the individual patient to ensure concentrations within this range is difficult because wide inter-individual variation in the elimination half-life of the drug results in a four-fold variation in drug levels achieved on a fixed dose (Jenne *et al.*, 1972). Furthermore, the advent of toxicity may occur at drug concentrations within the therapeutic range in some patients (Ramsay *et al.*, 1980) although adverse symptoms are less common when plasma levels remain below $15 \mu\text{g/ml}$ (Jacobs *et al.*, 1976). For these reasons, the minimum recom-

mended dose is frequently prescribed by clinicians and because of practical difficulties, further adjustment based on monitoring plasma concentrations may be neglected (McDevitt *et al.*, 1979). Therefore, a simple means of predicting the optimum dose would increase the practical usefulness of this drug in clinical practice.

Recently a nomogram for predicting oral maintenance theophylline dosage based on a single plasma drug assay has been reported (Koup *et al.*, 1979): this depends on the observed correlation between the plasma drug concentration 6 h after the administration of intravenous theophylline 5 mg/kg and the logarithm of the oral maintenance dose necessary to establish a mean plasma concentration of $10 \mu\text{g/ml}$. In a previous study the validity of this correlation has been confirmed and the potential usefulness of the nomogram for dose selection examined in 14 patients (Taylor *et al.*, 1983).

This present investigation was undertaken to

evaluate, in patients with obstructive airways disease, whether the plasma theophylline concentration used to predict oral dose requirements could be obtained 6 h after a single oral dose instead of the recommended intravenous one, in view of the rapid absorption and almost complete bioavailability of some liquid theophylline preparations (Ogilvie, 1978).

Methods

Patients with bronchial asthma or chronic airways disease without evidence of hepatic or cardiac dysfunction were studied. While maintaining all other bronchodilator treatment, theophylline was withdrawn for 48 h prior to each of two study days. In randomized order, theophylline (5 mg/kg) was administered on one occasion as aminophylline injection BP by constant rate intravenous infusion over 30 min, and on the other as theophylline sodium glycinate oral elixir (Nuelin liquid, Riker Laboratories) given with 100 ml of water. Before the oral dose, a 12 h fast was observed and each patient was permitted a light breakfast 1.5 h after drug administration. Venous blood samples were obtained immediately before and exactly 6 h following both the commencement of the infusion and the administration of the oral dose. After centrifugation plasma samples were stored at -20°C until assayed. Plasma theophylline concentrations were determined using a high performance liquid chromatography technique (Kelly & Leahey, 1976), for which the coefficient of variation at $4.8\text{ }\mu\text{g/ml}$ was 8.8% and at $16.8\text{ }\mu\text{g/ml}$ was 3.3%.

Using the nomogram (Koup *et al.*, 1979), the predicted daily maintenance dose, $D_{\text{M,PRED}}$, was determined using values for the plasma theophylline concentration at 6 h obtained following both intravenous and oral test doses ($C(6)$ i.v. and $C(6)$ o. respectively). Each patient was then commenced on a sustained-release oral theophylline preparation (Nuelin SA, Riker Laboratories) given in equal 12 hourly doses with food. The dose was increased at 3-day intervals until, using both 175 mg and 250 mg tablets, the total dose given as whole tablets was the best approximation to $D_{\text{M,PRED}}$. Where the administered dose exceeded 1000 mg/day, trough plasma theophylline concentrations at 'steady-state' were determined at each incremental point before further increases in the dose were made: if therapeutic levels had been established ($10\text{--}20\text{ }\mu\text{g/ml}$), no further dose adjustment was made. Where values for $C(6)$ following both oral and intravenous test doses resulted in significantly different values for $D_{\text{M,PRED}}$, trough theophylline concentrations were, where possible, determined for each of the predicted doses. All blood samples were obtained 12 h after the last theophylline dose.

The results are presented as the mean $\pm$ s.e. mean.

Results

Twenty-four outpatients (20 male, four female) volunteered for the study. Their mean age was 61.3 years (range 41–84), six had bronchial asthma and 18 had chronic obstructive airways disease. Eight were smokers at the time of the study.

The mean value for $C(6)$ o. was $5.6 \pm 0.4\text{ }\mu\text{g/ml}$ resulting in nomogram predictions for theophylline dosage of $4.5\text{--}25.1\text{ mg kg}^{-1}\text{ day}^{-1}$ (mean $13.6 \pm 1.4\text{ mg kg}^{-1}\text{ day}^{-1}$, $n = 24$). The mean value for $C(6)$ i.v. was $5.7 \pm 0.4\text{ }\mu\text{g/ml}$ resulting in oral dose predictions from the nomogram of $2.2\text{--}25.1\text{ mg kg}^{-1}\text{ day}^{-1}$ (mean $12.8 \pm 1.1\text{ mg kg}^{-1}\text{ day}^{-1}$, $n = 24$). There was no significant difference between values for $C(6)$ o. and $C(6)$ i.v., using Student's paired *t*-test. The mean of the differences between $D_{\text{M,PRED}}$ based on $C(6)$ o. and $D_{\text{M,PRED}}$ based on $C(6)$ i.v., a measure of accuracy, was $0.76\text{ mg kg}^{-1}\text{ day}^{-1}$ and the standard deviation, a measure of precision, was $\pm 3.56\text{ mg kg}^{-1}\text{ day}^{-1}$. In 11 patients $D_{\text{M,PRED}}$ based on $C(6)$ o. lay outside the 95% confidence limits for $D_{\text{M,PRED}}$ based on $C(6)$ i.v. The prediction error for the oral model compared to the intravenous model was $3.59 \pm 2.38\text{ mg kg}^{-1}\text{ day}^{-1}$, although there was no means of comparing either of these to an absolute standard (Sheiner & Beal, 1981).

Two patients were intolerant of oral theophylline when given on a chronic basis and had to be withdrawn from further study. One further patient failed to attend satisfactorily during the period of oral dose titration and was excluded. In two further patients (20 and 21), the dose predicted using $C(6)$ o. was not given because satisfactory plasma concentrations had been achieved on the dose predicted by $C(6)$ i.v. and further increase was considered undesirable. In two patients the dose predicted by $C(6)$ i.v. was not administered: one refused further increase in his medication (patient 18) and one other died at home with a myocardial infarction (patient 19). Thus in 17 patients, both oral and intravenous models were tested in predicting dose requirements. In 14, the dose predictions based on each model were identical: in the other three, therapeutic plasma concentrations were achieved by both oral and intravenous predicted doses in one (patient 16), by oral prediction only in one (patient 1) and by neither in the other (patient 5).

In the 19 patients whose theophylline concentration at 'steady-state' was determined while receiving the dose most approximate to $D_{\text{M,PRED}}$ based on $C(6)$ o. (Table 1), the administered dose following 'rounding up' or 'rounding down' ranged from $4.2\text{--}21.1\text{ mg kg}^{-1}\text{ day}^{-1}$ (mean $12.6 \pm 1.1\text{ mg kg}^{-1}\text{ day}^{-1}$). This did not differ significantly from $D_{\text{M,PRED}}$ for these patients (mean $12.7 \pm 1.3\text{ mg kg}^{-1}\text{ day}^{-1}$). No significant bias was introduced by adjusting the doses in this fashion (Sheiner & Beal, 1981). Trough concentrations at 'steady-state' in the range $10\text{--}20\text{ }\mu\text{g/ml}$ were established in nine of the 19 patients, while in the

Table 1 Results in 19 patients whose administered dose was based on C(6) o.

Patients		C(6) o. ($\mu\text{g}\cdot\text{ml}$)	$D_{M,PRED}$ ($\text{mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$)	$D_{M,PRED}$ ($\text{mg}\cdot\text{day}$)	Administered dose ($\text{mg}\cdot\text{day}$)	Administered dose ($\text{mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$)	Theophylline concentration at trough ($\mu\text{g}\cdot\text{ml}$)
C.B.	(1)	5.1	13.5	702	700	13.5	15.8
J.H.	(2)*	4.3	17.0	901	850	16.3	12.5
G.C.	(3)	6.1	10.2	612	700	11.7	8.2
D.C.	(4)	3.0	24.6	1402	1200	21.1	15.1
T.C.	(5)	8.5	5.2	411	500	6.3	7.0
D.G.	(6)	4.5	16.2	1053	1000	15.4	13.6
F.C.	(7)*	4.4	16.6	1029	1000	16.1	11.0
M.McM.	(8)	4.7	15.1	1057	850	12.1	11.2
S.McL.	(9)	6.5	9.1	692	700	9.2	9.6
S.S.	(10)	9.1	4.5	270	250	4.2	6.4
M.P.	(11)	3.6	20.4	1000	1000	20.4	13.0
J.D.	(12)*	8.3	5.5	418	500	6.6	6.2
E.McG.	(13)	5.6	11.8	938	1000	12.5	12.6
J.M.	(14)	4.8	14.8	873	1000	16.9	5.4
R.G.	(15)*	5.8	11.2	1075	1050	10.9	5.9
N.H.	(16)	6.5	9.1	500	500	9.1	11.4
J.B.	(17)*	5.5	12.0	708	700	11.9	5.9
S.H.	(18)*	3.8	19.5	1560	1500	18.8	6.8
J.R.	(19)	8.9	4.7	362	500	6.5	8.7
M.B.	(20)	2.9	25.1	1104	—	—	—
W.H.	(21)	3.5	21.4	1455	—	—	—
Mean ($n = 19$)			12.7	819.1	815.8	12.6	10.0
s.e. mean			1.3	80.0	68.7	1.1	0.7

* Denotes smoker

Table 2 Results in 19 patients whose administered dose was based on C(6) i.v.

Patients		C(6) i.v. ($\mu\text{g}\cdot\text{ml}$)	$D_{M,PRED}$ ($\text{mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$)	$D_{M,PRED}$ ($\text{mg}\cdot\text{day}$)	Administered dose ($\text{mg}\cdot\text{day}$)	Administered dose ($\text{mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$)	Theophylline concentration at trough ($\mu\text{g}\cdot\text{ml}$)
C.B.	(1)	6.6	8.9	463	500	9.6	8.4
J.H.	(2)*	4.4	16.6	880	850	16.3	12.5
G.C.	(3)	5.8	11.2	672	700	11.7	8.2
D.C.	(4)*	2.9	25.1	1431	1200	21.1	15.1
T.C.	(5)	6.1	10.2	806	850	10.8	22.0
D.G.	(6)	5.0	13.8	897	1000	15.4	13.6
F.C.	(7)*	4.8	14.8	918	1000	16.1	11.0
M.McM.	(8)	4.7	15.1	1057	850	12.1	11.2
S.McL.	(9)	6.9	8.1	616	700	9.2	9.6
S.S.	(10)	11.6	2.2	132	250	4.2	6.4
M.P.	(11)	3.5	21.4	1049	1000	20.4	13.0
J.D.	(12)*	8.5	5.2	396	500	6.6	6.2
E.McG.	(13)	5.3	12.9	1026	1000	12.5	12.6
J.M.	(14)	4.6	15.5	915	1000	16.9	5.4
R.G.	(15)*	6.3	9.8	941	1050	10.9	9.9
N.H.	(16)	5.6	11.8	650	700	12.7	11.3
J.B.	(17)*	6.6	8.9	525	700	11.9	5.9
S.H.	(18)*	3.4	21.9	1752	—	—	—
J.R.	(19)	6.8	8.5	880	—	—	—
M.B.	(20)	5.1	13.5	594	700	15.9	12.6
W.H.	(21)	4.5	16.2	1102	1000	14.7	13.3
Mean ($n = 19$)			12.7	793.2	818.4	13.1	11.0
s.e. mean			1.2	69.3	54.0	1.0	0.9

* Denotes smoker

remainder, values lay between 5.4 and 9.6 $\mu\text{g/ml}$. The mean trough theophylline concentration was $10.0 \pm 0.7 \mu\text{g/ml}$ (range 5.4–15.8 $\mu\text{g/ml}$).

In the 19 patients whose theophylline concentration was determined while receiving the dose most approximate to $D_{M,PRED}$ based on $C(6)$ i.v. (Table 2), the administered doses ranged from 4.2–21.1 $\text{mg kg}^{-1} \text{day}^{-1}$ (mean $13.1 \pm 1.0 \text{ mg kg}^{-1} \text{day}^{-1}$). This did not differ significantly from the mean for $D_{M,PRED}$. Again, the bias introduced did not differ significantly from zero. Trough concentrations fell within the range 10–20 $\mu\text{g/ml}$ in 10 patients. In one patient the trough plasma concentration was 22.0 $\mu\text{g/ml}$, and in the remainder lay between 5.4 and 9.9 $\mu\text{g/ml}$. The mean trough theophylline concentration for this group was $11.0 \pm 0.9 \mu\text{g/ml}$ (range 5.4–22.0 $\mu\text{g/ml}$). A comparison of the numbers of patients in each of the plasma concentration ranges <10 $\mu\text{g/ml}$, 10–20 $\mu\text{g/ml}$, and >20 $\mu\text{g/ml}$ (Table 3) at steady state following oral and intravenous dose predictions showed no significant difference in the relative distribution between the two groups.

Side effects were reported only during chronic dosing. In two patients, anorexia and nausea necessitated withdrawal of theophylline. In three further patients, milder gastro-intestinal upset occurred, requiring a later reduction in dose. Trough concentrations in these latter patients were 8.2, 10.6 and 11.4 $\mu\text{g/ml}$.

Discussion

The results of this present study demonstrate that maintenance oral theophylline dose requirements may be predicted in patients with obstructive airways disease using the Koup nomogram after single oral theophylline test doses as well as intravenous ones. In the 17 patients who completed both parts of the study, 14 had the same dose predicted by oral and intravenous test doses. In the remaining three patients, oral test doses predicted adequately in two and low in one: in contrast, intravenous test doses predicted adequately in one, high in one and low in one. In two other patients (20 and 21) in whom the dose predicted by the intravenous test dose achieved

plasma concentrations of 12.6 and 13.3 $\mu\text{g/ml}$ respectively, the dose predicted by the oral test dose would also have produced plasma levels within the therapeutic range assuming a linear relationship between dose and plasma concentration existed.

Following administration of the test doses, there was no significant difference between the mean values or the ranges for $C(6)$ o. and $C(6)$ i.v. in our 24 patients. However, the differences between $C(6)$ o. and $C(6)$ i.v. ranged from 0–2.4 $\mu\text{g/ml}$ in any one patient, and such individual differences would be compounded when referring to the nomogram, since it is based on a logarithmic rather than a linear relationship. This was found to be the case. Although the mean values for the two methods of assessing $D_{M,PRED}$ did not differ significantly and the mean of the differences between them was small, the precision appeared to be less impressive and the predictive errors were large. In 11 of the 24 patients, $D_{M,PRED}$ based on $C(6)$ o. lay outside the 95% confidence limits for $D_{M,PRED}$ based on $C(6)$ i.v.

Further error might be attributed to the 'rounding up' or 'rounding down' of the administered doses. This did not result in any significant bias, nor did the mean administered doses differ significantly from the predicted. The maximum adjustment required in any individual was 231 mg/day , and 28 out of 38 adjustments were less than 100 mg/day . It was, therefore, felt that the adjustment of dose by the limitations of tablet size available did not affect the overall result.

The range of trough concentrations achieved in those 19 patients receiving the dose predicted using values for $C(6)$ o. was 5.4–15.8 $\mu\text{g/ml}$. This might further suggest that lack of precision casts doubt on the usefulness of this predictive model and its modifications. However, in an analysis of a more definitive predictive technique similarly designed to achieve a 'mean' plasma concentration of 10 $\mu\text{g/ml}$, it has been shown that the 95% confidence limits for resultant 'steady-state' theophylline concentrations extended from 6.6–15 $\mu\text{g/ml}$ (Shapiro *et al.*, 1982).

The prediction of theophylline dose requirements based on any pharmacokinetic model is thus subject to considerable error. We have previously shown that the predictive errors contained in this nomogram, although considerable, are similar to those en-

Table 3 Steady-state plasma theophylline concentrations following maintenance oral theophylline doses predicted by single oral and intravenous test doses in 19 patients

Trough plasma theophylline concentration	< 10 $\mu\text{g/ml}$	10–20 $\mu\text{g/ml}$	> 20 $\mu\text{g/ml}$
Following oral test dose	10	9	0
Following intravenous test dose	8	10	1

χ -squared = 1.7: NS

countered using more detailed pharmacokinetic data (Taylor *et al.*, 1983). In his original hypothesis, Koup pointed out that typical errors in the magnitude of the test dose, sampling time, and assay technique, ought not to affect the nomogram dose predictions in any substantial way (Koup *et al.*, 1979). It may be that intra-patient variability in theophylline elimination, reported to be as much as 30% and occurring over periods of as little as 3–4 days (Upton *et al.*, 1982), offers an explanation as to why such errors are found using any predictive model.

Given that dose predictions based on oral and intravenous test doses were identical or similar in most patients, the question of their adequacy arises. In terms of individual patients, all had trough plasma concentrations greater than 5 $\mu\text{g/ml}$ and approximately 50% had levels greater than 10 $\mu\text{g/ml}$. This might be considered less than optimum but, in fact, the nomogram is designed to predict the dose required to achieve a 'mean' concentration of 10 $\mu\text{g/ml}$. In the present study, the trough concentration in patients receiving doses predicted using $C(6)$ o. was 10.0 ± 0.7 $\mu\text{g/ml}$, and the 'mean' concentration would be assumed to be even higher. Thus the nomogram dose based on predictions from $C(6)$ o. does appear to produce the expected result: in terms of a therapeutic concentration range of 10–20 $\mu\text{g/ml}$ it may tend to underprescribe but this may not be undesirable in view of the fact that some patients appear to get considerable bronchodilatation at concentrations less than 10 $\mu\text{g/ml}$ (Maselli *et al.*, 1970) and others demonstrate adverse effects to theophylline between 13–20 $\mu\text{g/ml}$ (Jacobs *et al.*, 1976).

Reasons why the 'mean' concentration probably lay above 10 $\mu\text{g/ml}$ were considered. With oral test

doses, the most likely problem would be less than 100% bioavailability, resulting in a low $C(6)$ o. and a high predicted dose. However, it can be seen that $C(6)$ o. and $C(6)$ i.v. were not significantly different and that the doses predicted by both methods were also either identical or similar. Another possibility could be the occurrence of a non-linear relationship between plasma concentrations and theophylline dosage. Using criteria suggested by Marlin *et al.* (1980), four of 11 patients in whom plasma theophylline concentrations were determined for each of several doses, showed some evidence of non-linearity—the most notable was a patient who achieved a trough concentration of 7 $\mu\text{g/ml}$ on a dose of 500 mg/day and 22 $\mu\text{g/ml}$ on 850 mg/day. Thus, although the problem of dose dependency was not considered important in the overall assessment of this predictive model, it may have had some influence on higher than expected 'mean' concentrations.

The problem of variability in the satisfactory use of theophylline may best be compensated for by dose adjustments based on plasma theophylline concentration measurements in the individual patient: this will optimize effect and minimize adverse reactions (Hendeles *et al.*, 1978). Unfortunately, this is impracticable in many of the clinical circumstances in which theophylline is commonly prescribed. This present study would suggest that the plasma theophylline concentration 6 h following a single oral dose may allow satisfactory dose prediction in a majority of patients. It appears to offer no disadvantages of intravenous test doses and is clearly easier to administer.

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References

- HENDELES, L., WEINBERGER, M.M. & JOHNSON, G. (1978). Monitoring serum theophylline levels. *Clin. Pharmacokin.*, **3**, 294–312.
- JACOBS, M.H., SENIOR, R.M. & KESSLER, G. (1976). Clinical experience with theophylline: relationships between dosage serum concentrations and toxicity. *J. Am. med. Ass.*, **235**, 1983–1986.
- JENNE, J.W., WYZE, E., ROOD, F.S. & McDONALD, F.M. (1972). Pharmacokinetics of theophylline: Application to the adjustment of the clinical dose of aminophylline. *Clin. Pharmac. Ther.*, **13**, 349–360.
- KELLY, J.G. & LEAHEY, W.J. (1976). Measurement of theophylline in plasma by high performance liquid chromatography. *Br. J. clin. Pharmac.*, **3**, 947.
- KOUP, J.R., SACK, C.M., SMITH, A.L. & GIBALDI, M. (1979). Hypothesis for the individualisation of drug dosage. *Clin. Pharmacokin.*, **4**, 460–469.
- McDEVITT, D.G., ELWOOD, R.K. & RUSSELL, C.J. (1979). Why measure plasma theophylline concentrations? *Curr. Med. Res. Opin.*, Suppl. **6**, 26–34.
- MARLIN, G.E., BUTCHER, M.A., KLUMPP, J.A. & THOMPSON, P.J. (1980). Serum level monitoring of a new slow release theophylline formulation in patients with chronic lung disease. *Br. J. clin. Pharmac.*, **10**, 265–271.
- MASELLI, R., CASAL, G.L. & ELLIS, E.F. (1970). Pharmacological effects of intravenously administered aminophylline in asthmatic children. *J. Pediatr.*, **76**, 777.
- MITENKO, P.A. & OGILVIE, R.I. (1973). Rational intravenous doses of theophylline. *New Engl. J. Med.*, **289**, 600.
- OGILVIE, R.I. (1978). Clinical pharmacokinetics of theophylline. *Clin. Pharmacokin.*, **3**, 267–293.
- RAMSAY, L.E., MACKAY, A., EPEL, M.L. & OLIVER, J.S. (1980). Oral sustained release aminophylline in medical inpatients: factors related to toxicity and plasma theophylline concentrations. *Br. J. clin. Pharmac.*, **10**, 101–107.
- RIEGELMAN, S. & JENNE, J.W. (1980). Controlled release theophylline. *Chest*, **78**, 250–257.

- SHAPIRO, G., KOUF, J.R., FURUKAWA, C., PIERSON, W.E., GIBALDI, M., FUQUAY, D. & BIERMAN, C.W. (1982). Individualisation of theophylline dosage using a single serum sample following a test dose. *Pediatrics*, **69**, 70.
- SHEINER, L.B. & BEAL, S.L. (1981). Some suggestions for measuring predictive performance. *J. Pharmacokin. Biopharm.*, **9**, 503–512.
- TAYLOR, D.R., KINNEY, C. & McDEVITT, D.G. (1983). Prediction of optimum oral theophylline dose in patients with obstructive airways disease. *Br. J. clin. Pharmac.*, **15**, 689–694.
- UPTON, R.A., THERCELIN, J.F., GUENTERT, T.W., WALLACE, S.M., POWELL, J.R., SANSOM, L. & RIEGELMAN, S. (1982). Intraindividual variability in theophylline pharmacokinetics: statistical verification in 39 of 60 healthy young adults. *J. Pharmacokin. Biopharmac.*, **10**, 123–133.

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