Individual theophylline dosing based on bioelectrical impedance analysis

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The role of bioelectrical impedance (BI) analysis in determining slow-release theophylline dosage was evaluated in fifteen healthy subjects given a standard 200 mg dose. Reactance and $1/\text{resistance}$ were identified as the most significant predictors of pre-dose, steady-state theophylline concentrations ($C_{ss,pre}$). Compared with doses based on body weight ($8.8 \text{ mg kg}^{-1} \text{ day}^{-1}$), theophylline doses determined by BI analysis ($9.6 \pm 2.4 \text{ mg kg}^{-1} \text{ day}^{-1}$) resulted in less biased (mean prediction error = 0.6 vs 1.4) though slightly less precise (mean squared error = 7.1 vs 6.3) $C_{ss,pre}$ values. These differences were statistically insignificant ($P > 0.05$).

Keywords theophylline bioelectrical impedance non-invasive predictive models

Introduction

Bioelectrical impedance (BI) analysis is a safe, simple and non-invasive technique that has been established for assessing body composition (Lukaski, 1990; Malina, 1987). Total body impedance (Z), measured as resistance (R), reactance (X_c) and phase angle (ϕ), to the flow of a low voltage, alternating current is a function of the amount of aqueous, electrolyte-containing tissue in the body. BI analysis has been proposed as a means of predicting the pharmacokinetic parameters and, therefore, the dosage regimens of various hydrophilic drugs without reliance on serum drug concentration data (Zarowitz & Pilla, 1989). We have recently reported a strong predictive relationship between BI and theophylline pharmacokinetics in premature neonates (Sidhu *et al.*, 1992). While BI has a unique ability to assess the extent of drug distribution, its role in predicting drug clearance is less well defined.

In this study we assessed the relationships between pre-dose, steady-state serum theophylline concentration ($C_{ss,pre}$), dose and BI, and $C_{ss,pre}$, dose and body weight in a group of young, healthy adults given repeated doses of a slow-release preparation of theophylline.

Methods

Non-smoking, healthy volunteers aged between 18 and 30 years (Table 1) participated in the study. Subjects

were tertiary students who were judged to be responsible in understanding the importance of strict dosage compliance. None was taking any other prescribed or over-the-counter medications. The exercise and sporting activity of each subject was also recorded. The protocol was approved by the Human Research Ethics Committee of The University of Queensland and informed, written consent was obtained from all volunteers prior to the study.

Subjects took 12 hourly doses of theophylline (TheoDur®) for five consecutive days. Alcohol was not permitted from 24 h before and during the study and subjects refrained from food and beverages containing caffeine during the last 2 days. Exact dosage times and dietary intake over the 5 days were recorded by each subject. The average of serum theophylline concentrations measured just prior to the morning dose on day 5 and at the same time the following day was taken as the mean $C_{ss,pre}$ value. BI was measured in each subject (BIA-101, RJL Systems, Detroit, USA) as described previously (Lukaski *et al.*, 1986). The average of left- and right-sided ipsi-lateral impedances was recorded. Theophylline was measured in serum by h.p.l.c. using the method of Miksic & Hodes (1979). Within and between day imprecision, respectively, were 5.4% and 4.7% at $0.2 \mu\text{g ml}^{-1}$ and 1.9% and 3.9% at $20 \mu\text{g ml}^{-1}$.

In phase I of the study 15 subjects took doses of 200 mg theophylline. R and X_c were measured 2 h after lunch on the fifth day, during which exercise was disallowed. $C_{ss,pre}$ values were modelled as a function of

various expressions of BI and dose (D , $\text{mg kg}^{-1} \text{ day}^{-1}$) as independent predictor variables by multiple regression analysis (SAS, Cary, NC, USA). The model selection criteria encompassed a minimum number of variables significant at the $P < 0.05$ level, collinearity diagnostics, adjusted R^2 ($\text{Adj } R^2$), model CV%, and the prediction sum of squares (PRESS) statistic (Hocking, 1976).

In phase II, the predictive performance of $C_{\text{ss,pre}}$ models was compared in two groups of 10 subjects, none of whom had participated in phase I. Using relationships developed in phase I, doses of theophylline required to achieve a $C_{\text{ss,pre}}$ of $10 \mu\text{g ml}^{-1}$ were determined based either on BI (group A) or on total body weight (group B). Theophylline doses in phase II were rounded to the nearest 50 mg and the predicted $C_{\text{ss,pre}}$ adjusted accordingly. Predictive performance was assessed statistically ($P < 0.05$ level) in terms of mean predicted error (MPE; bias) and mean squared prediction error (MSE; precision) (Sheiner & Beal, 1981).

Results

Demographic data, measures of BI, dosages and $C_{\text{ss,pre}}$ values are shown in Table 1. Average $C_{\text{ss,pre}}$ values in phase I subjects were inversely correlated with $\emptyset$ ($r = -0.71$) and positively correlated with R ($r = 0.58$). Variability between $C_{\text{ss,pre}}$ values for subjects in both

phases ranged from 0.9 to 10.8% ($5.5 \pm 3.3\%$). The following equations express the optimal models for the estimation of $C_{\text{ss,pre}}$:

$$C_{\text{ss,pre}} = 37.14 + 1.04(D) - 7739.36(1/R) - 0.43(Xc) \quad \text{Model 1}$$

$$[\text{CV} = 21.33\% \quad \text{Adj } R^2 = 0.62 \quad P < 0.005 \quad \text{PRESS} = 49.67]$$

$$C_{\text{ss,pre}} = -0.83 + 1.23(D) \quad \text{Model 2}$$

$$[\text{CV} = 28.57\% \quad \text{Adj } R^2 = 0.31 \quad P < 0.01 \quad \text{PRESS} = 76.69]$$

The expansion of the relationship between $C_{\text{ss,pre}}$ and body weight (Model 2) to include BI parameters resulted in significantly improved model statistics. Xc and inverse R in Model 1 express $\emptyset$, which was the most significant descriptor of $C_{\text{ss,pre}}$.

Theophylline doses, calculated to achieve a $C_{\text{ss,pre}}$ of $10 \mu\text{g ml}^{-1}$ (phase II), ranged from 5.4 to 13 $\text{mg kg}^{-1} \text{ day}^{-1}$ in group A (Model 1) compared with 8.8 $\text{mg kg}^{-1} \text{ day}^{-1}$ in group B (Model 2). Average observed values of $C_{\text{ss,pre}}$ in group A and group B were not significantly different. Furthermore, neither value was significantly different from the respective predicted $C_{\text{ss,pre}}$ (Table 2). Model 1 appeared less biased while Model 2 was slightly more precise, although these differences were statistically insignificant ($P > 0.05$); the 95% confidence intervals (CI) for differences in MSE ($\Delta\text{MSE} = -11.9$ to 10.1) and MPE ($\Delta\text{MPE} = -1.5$ to 3.1) encompassed zero.

Table 1 Demographic and bioelectrical impedance characteristics, dose (D) and pre-dose, steady-state serum theophylline concentrations ($C_{\text{ss,pre}}$) for phase I and II subjects*. All values are expressed as mean $\pm$ s.d.

	Phase I (n = 15)	Phase II Group A (n = 10)	Group B (n = 10)
Sex (M/F)	7M/8F	5M/5F	6M/4F
Age (years)	22 $\pm$ 3	19 $\pm$ 1	21 $\pm$ 3
Weight (kg)	63.4 $\pm$ 12.1	60.7 $\pm$ 11.0	66.9 $\pm$ 9.9
Height (cm)	170.6 $\pm$ 8.5	174 $\pm$ 10.5	171 $\pm$ 6.1
Resistance (ohms)	556 $\pm$ 75	591 $\pm$ 70	550 $\pm$ 39
Reactance (ohms)	53 $\pm$ 5	56 $\pm$ 7	56 $\pm$ 5
Phase angle (degree)	5.5 $\pm$ 0.5	5.5 $\pm$ 0.7	5.8 $\pm$ 0.7
D ($\text{mg kg}^{-1} \text{ day}^{-1}$)	6.6 $\pm$ 1.2	9.6 $\pm$ 2.4	8.8
$C_{\text{ss,pre}}$ ($\mu\text{g ml}^{-1}$)	7.2 $\pm$ 2.5	9.1 $\pm$ 2.6	9.0 $\pm$ 2.2

* No statistical difference ($P > 0.05$) for demographic and bioelectrical impedance variables between phases I and II and between groups A and B as determined by one-way ANOVA.

Table 2 Mean (95% CI) predicted and achieved pre-dose serum theophylline concentrations ($C_{\text{ss,pre}}$, $\mu\text{g ml}^{-1}$), mean prediction error (MPE) and mean squared prediction error (MSE) for BI and WT dosing models*

Model	n	$C_{\text{ss,pre}}$		MPE	MSE
		Predicted	Achieved		
BI (group A)	10	9.7 (9.3 – 10.1)	9.1 (7.3 – 11.0)	0.6 (–1.4 – 2.5)	7.1 (–2.2 – 16.3)
WT (group B)	10	10.4 (10.0 – 10.8)	9.0 (7.5 – 10.6)	1.4 (–0.2 – 2.9)	6.3 (1.0 – 11.5)

* Both groups statistically comparable ($P > 0.05$) in all parameters.

Discussion

BI analysis involves minimal subject discomfort and is highly reliable. The reproducibility (CV%) of repeated impedance measurements has been reported to range from 0.3% to 1.9% (Kushner & Scholler, 1986) and from 0.9% to 3.6% (Kushner & Scholler, 1986; Lukaski *et al.*, 1985) for intraday and interday variability, respectively.

Phase angle ($\emptyset$), expressed as I/R and X_c in the BI model (1), was the best descriptor of $C_{ss,pre}$ in this study. Similarly, theophylline distribution volume and clearance, derived following the administration of intravenous aminophylline to healthy male volunteers, were also found by Zarowitz and colleagues (1989) to be described by a series of impedance and demographic variables including expressions of $\emptyset$ and lean body mass. $\emptyset$ is a measure of the reactive or capacitive component of the body and is proportional to cellular membrane integrity and body cell mass, and is inversely related to extracellular fluid content.

TheoDur® was chosen as the theophylline dosage form because of its widespread use and good oral bioavailability (Hendeles *et al.*, 1984). It is known that most of the clearance of theophylline is by hepatic metabolism and we assumed that clearance and bioavailability remained constant in each subject during the study period.

In estimating individual theophylline doses, BI and total body weight (WT) were equally predictive of individual differences in the clearance of theophylline. There were statistically insignificant differences between Models 1 (BI, Group A) and 2 (WT, Group B) in terms of precision and bias. However, the variability in Group A was largely due to one subject (18 year old female, $D = 8.2 \text{ mg kg}^{-1} \text{ day}^{-1}$) who had a very low

serum theophylline concentration ($C_{ss,pre} = 4.1 \mu\text{g ml}^{-1}$). There was no statistical justification ($P > 0.05$) for excluding her data from the BI predictive model as determined by Dixon's Test for Extreme Values (Dixon & Massey, 1969). Poor compliance was ruled out in this subject. Her $C_{ss,pre}$ variability (CV%) was 5.5%. Unfortunately, a follow up study to determine this subject's clearance was not possible. If this subject's low $C_{ss,pre}$ value was due to an abnormally high clearance then this data would support previous conclusions that BI has limited application in subjects with significantly perturbed hepatic function (Pilla *et al.*, 1990; Sidhu *et al.*, 1992). Rather, the development of predictive models for hepatic induction or inhibition may be more prudent.

Interestingly, significantly lower ($P < 0.05$) $C_{ss,pre}$ values ($5.4 \pm 0.6 \mu\text{g ml}^{-1}$) were also observed in phase I subjects who exercised for at least 1 h per day, compared with those who did not exercise ($8.4 \pm 2.5 \mu\text{g ml}^{-1}$). Although anecdotal, this may help explain the ability of BI to model hepatic clearance of theophylline since it is known that hepatic drug metabolism is enhanced in subjects with above average fitness, which, in turn, is related to the amount and activity of liver microsomal enzymes (Boel *et al.*, 1984; Gikalov & Bircher, 1977). This contention is supported by the strong correlation between $C_{ss,pre}$ and $\emptyset$ in our study.

Clearly, the predictive relationship between BI response and theophylline clearance requires further investigation and validation using larger numbers of patients who are suffering a variety of illnesses. Nonetheless, the results of this preliminary study are somewhat encouraging and suggest that BI analysis may be a potentially useful adjunct in the dosing of orally administered theophylline as opposed to empirically adjusted doses based on body weight.

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