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MODELLING THEOPHYLLINE RESPONSE IN INDIVIDUAL PATIENTS WITH CHRONIC BRONCHITIS

BRIAN WHITING, ANDREW W. KELMAN, JOYCE BARCLAY & GEORGE J. ADDIS

Department of Materia Medica, University of Glasgow, Stobhill General Hospital, Glasgow G21 3UW
and
Department of Clinical Physics and Bio-Engineering, West of Scotland Health Boards, 11 West Graham Street, Glasgow G4 9LF

1 In six patients with chronic bronchitis, serial changes in both ventilatory function and plasma theophylline concentrations were measured simultaneously for 8 h following 500 mg aminophylline intravenously.

2 Using empirical mathematical models which can integrate this data, parameters were estimated which can express response as a linear function of steady state plasma theophylline levels.

3 Taking Forced Vital Capacity (FVC) as the target response, the mean (± s.d.) increase in FVC was 0.06 ± 0.02 l/μg ml^{-1}, starting with pretreatment values in the range 1–2 l.

4 This analytical approach could be used to determine whether or not a patient with chronic bronchitis would obtain a satisfactory response to theophylline at plasma levels normally encountered in clinical practice.

Introduction

Patients with chronic bronchitis present a spectrum of airways narrowing which may respond in varying degree to theophylline. The extent of any bronchodilator response is usually determined by trial and error over relatively long periods of time and no attempt has yet been made to assess this response quantitatively in terms of plasma concentrations of theophylline.

Empirical mathematical techniques have been developed which enable the whole time course of response to a number of drugs to be modelled in terms of simultaneously observed plasma concentrations (Sheiner *et al.*, 1979; Whiting, Holford & Sheiner, 1980; Whiting & Kelman, 1980a, b; Kelman & Whiting, 1980). These techniques have been applied to data obtained following continuous intravenous infusions or single intravenous or oral doses of drugs. Results have been expressed in terms of a number of parameters which clearly define the concentration-response relationship in individual subjects.

As theophylline clearance varies from subject to subject and the degree of reversibility of airways narrowing in chronic bronchitis depends on a number of factors, there is every reason to try to identify the magnitude of the response which can be obtained from a range of plasma concentrations in individual patients. Response, of course, is limited either by the severity of the disease or by the attainment of plasma levels which would incur the risk of toxicity.

In this paper, we use two mathematical models to describe the time course of bronchodilation following a single intravenous dose of theophylline.

Methods

Six patients with chronic bronchitis (MRC criteria, 1965) were studied. There were five males, aged 54 to 71 years and one female aged 42 years. Any theophylline preparation was withheld for 48 h before a study, as were any other xanthine containing compounds, such as tea, coffee and cocoa. Other bronchodilators, such as salbutamol, were withheld for 12 h but no restriction was imposed on steroids. To minimise the influence of any diurnal variation in bronchomotor tone, all observations were made over the period 12.00 h to 20.00 h (with a final blood sample at approximately 24 h).

The study had two essential elements (a) the determination of an individual patient's pharmacokinetic parameters following a single intravenous dose of aminophylline and (b) the simultaneous measurement of changes in ventilatory response. For descriptive purposes, the kinetic and dynamic aspects of the study will be described separately.

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(a) *Single dose pharmacokinetics*

One hour before theopylline administration, a 'Venflon' indwelling intravenous cannula was inserted into a forearm vein and a sample was withdrawn to check that the theopylline plasma concentration at that time was zero. Theophylline concentrations throughout the study were measured by high pressure liquid chromatography (Gere & Bente, 1977) and at this point, rapid feedback was available. At 12.00 h, 500 mg aminophylline (equivalent to 450 mg theophylline) were administered intravenously over a period of 10 min into a contralateral forearm vein by hand held syringe. Blood samples (5 ml in lithium heparin) were then withdrawn from the 'Venflon' at the following times after the end of the 10 min infusion: 2, 4, 8, 12, 20, 30, 40, 50, 60, 90 and 120 min and 3, 4, 6, 8 and 24 h.

(b) *Single dose pharmacodynamics*

Assessment of ventilatory response following the single intravenous dose of aminophylline was performed in a manner similar to that previously reported (Barclay *et al.*, 1981). Pretreatment, baseline values were established by recording one maximal forced expiratory flow-volume (MEFV) curve every minute for 7 min and obtaining a second set of such recordings after 30 min. A Lilly pneumotachograph provided the signal for an electronic spirometer (Mercury Electronics, Glasgow) which gave a digital display of PFR, FEV_1 and FVC, the FVC values being subsequently used to analyse ventilatory response.

Following intravenous aminophylline, this response was assessed at 4–8 min intervals by repeated single maximum expiratory efforts for 2 h, then at hourly intervals, seven consecutive minute observations were made for the next 6–8 h. Response profiles were constructed using the mean of the 14 baseline FVC values, the single 4–8 min observations made over the first 2 h and the mean values at each hourly interval for the subsequent 6–8 h. A minimum of 20 and a maximum of 31 response data points were therefore available for analysis.

Data analysis

Following intravenous aminophylline, post infusion curves were analysed by nonlinear least squares regression on a Varian V70 series digital computer to yield the four parameters, A, α, B and β of the biexponential expression

$$Cp(t) = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

associated with a two compartment pharmacokinetic model (Gibaldi & Perrier, 1975). Standard techniques were then used to calculate other relevant pharmacokinetic parameters, viz. V_C, the volume of the central compartment and the inter-compartmental transfer rate constants, k_{12} and k_{21}.

Pharmacodynamic data was then analysed by two alternative strategies:

(a) multiple linear regression (Whiting & Kelman, 1980a, b; Kelman & Whiting, 1980) and
(b) an integrated effect model approach (Sheiner *et al.*, 1979; Whiting *et al.*, 1980).

Using *multiple linear regression*, the observed effect, FVC, at any time, t, was modelled according to the following equation:

$$FVC(t) = \theta_0 + \theta_1 f_1 (Q_C(t)) + \theta_2 f_2 (Q_P(t)) \quad (2)$$

where $f_1 (Q_C(t))$ and $f_2 (Q_P(t))$ are functions of the calculated amounts of drug in the central and peripheral compartments of a two compartment model at time t. θ_0 is the intercept and θ_1 and θ_2 are the partial regression coefficients of the multiple linear regression model. The f_i in equation (2) can be linear or a more complex, nonlinear, function such as is described by the Hill or Langmuir equations. In the present study, it was considered adequate to approximate the f_i by linear functions. Thus FVC(t) was described by the following equation:

$$FVC(t) = \theta_0 + \theta_1 Q_C(t) + \theta_2 Q_P(t) \quad (3)$$

$Q_C(t)$ and $Q_P(t)$ are calculated by standard formulae, (Gibaldi & Perrier, 1975) thus:

$$Q_C(t) = \frac{X_0(\alpha - k_{21})}{\alpha - \beta} e^{-\alpha t} + \frac{X_0(k_{21} - \beta)}{\alpha - \beta} e^{-\beta t} \quad (4)$$

and

$$Q_P(t) = \frac{k_{12} X_0}{\alpha - \beta}(e^{-\beta t} - e^{-\alpha t}) \quad (5)$$

where X_0 is the intravenous dose.

Using the *effect model,* the classical pharmacokinetic model is extended by an explicitly defined 'effect' compartment which does not influence the kinetic parameters of the original model. The amount of drug, X_e, in the effect compartment is described by an equation of the form:

$$\frac{dX_e}{dt} = k_{1e} X_1 - k_{eq} X_e \quad (6)$$

where X_1 is the amount of drug in the central compartment and k_{1e}, k_{eq} are first order rate constants associated with the effect compartment. Response is then described as a function of drug concentration C_e, in the effect compartment, thus:

$$FVC(t) = f(C_e(t)) \quad (7)$$

where again, f can be linear or a more complex function (as above) and C_e is as has been defined previously (Sheiner *et al.*, 1979; Whiting *et al.*, 1980). With the data available in the present study, f was

approximated by a linear function. Thus FVC(t) was described by the following equation:

$$FVC(t) = mC_e(t) + i \quad (8)$$

and the values of the model parameters m, i and k_{eq} were obtained by nonlinear least squares regression.

The constants X_0, V_C, k_{21}, α and β were used to generate $C_e(t)$ thus:

$$C_e(t) = \frac{k_{eq}X_0}{V_C}\left[\frac{k_{21}-\alpha}{(\beta-\alpha)(k_{eq}-\alpha)}e^{-\alpha t} + \frac{k_{21}-\beta}{(k_{eq}-\beta)(\alpha-\beta)}e^{-\beta t} + \frac{k_{21}-k_{eq}}{(\alpha-k_{eq})(\beta-k_{eq})}e^{-k_{eq}t}\right] \quad (9)$$

Using equation (3), unrealistic values for θ_1 were obtained from two data sets (patients 3 and 6) suggesting that a simple linear regression model of the form

$$FVC(t) = \theta_0 + \theta_2 Q_P(t) \quad (10)$$

might be more appropriate. As equation (3) contains terms which account for the amounts of drug in each compartment, it is called the *full* model. Equation (10), however, has one parameter set to zero (θ_1) and is a *reduced* version of the full model, having one less parameter. Whether or not a reduced model fits a set data as well as the corresponding full model can be tested with the General Linear Test (Neter & Wasserman, 1974). This involves calculating the ratio of the model variances, F, thus:

$$F = \frac{SSQ(R) - SSQ(F)}{df(R)-df(F)} \div \frac{SSQ(F)}{df(F)} \quad (11)$$

where SSQ(R) and SSQ(F) are the residual sums of squares for the reduced and full models respectively, and df(R) and df(F) are the corresponding degrees of freedom. If the F value does not achieve significance at the 5% level, the variation explained by the full model is not significantly greater than that explained by the reduced model, and this provides a justification for rejecting the full model in favour of the reduced model.

While the General Linear Test can be applied to models which belong to the same hierarchy, a different approach is required when different types of models are to be compared. Thus the appropriate linear regression model was compared to the corresponding effect model using the Akaike information criterion (AIC), calculated as follows:

$$AIC = N.\ln(SSQ) + 2p \quad (12)$$

where N is the number of observations, p is the number of parameters and SSQ is the total residual sum of squares (Akaike, 1973; Akaike, 1976; Yamaoka, Nakagawa & Uno, 1978). The model providing the better fit is considered to be the one corresponding to the lower AIC value.

The strength of the relationship between FVC and relevant independent variables (Q_C, Q_P and C_e) was assessed by calculating the coefficient of determination (r^2) for each fit.

Results

Unless otherwise specified, all results are presented as mean ± s.d.

An example of the plasma concentration and ventilatory response data collected in this study is shown in Figures 1 and 2 respectively (Subject 2). Pharmacokinetic parameters estimated for each patient are shown in Table 1. These values were used to calculate $Q_C(t)$ and $Q_P(t)$ (equations (4) and (5)) and to determine $C_e(t)$ (equation (9)). Parameter estimates for both the full multiple linear regression model and

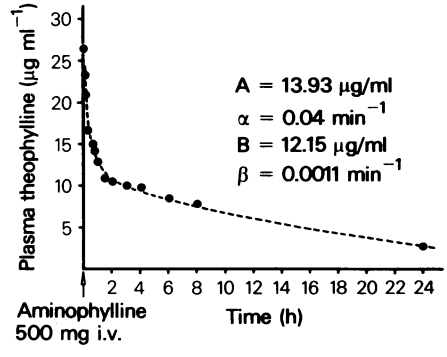

Figure 1 Theophylline plasma concentrations in the 24 h following 10 min intravenous infusion of 500 mg aminophylline (equivalent to 450 mg theophylline). The line of best fit (---) was derived from final parameter estimates produced by nonlinear least squares regression analysis (Patient 2).

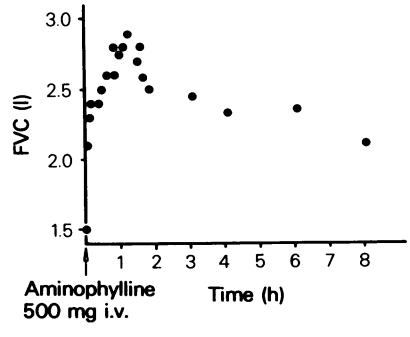

Figure 2 Forced vital capacity values in the 8 h following a 10 min intravenous infusion of 500 mg aminophylline (equivalent to 450 mg theophylline) (Patient 2).

Table 1 Pharmacokinetic constants used to calculate compartmental theophylline levels ($Q_C(t)$ and $Q_P(t)$ in equations (4) and (5) respectively and to predict changes in FVC according to equations (8) and (9)

Patient	Dose (mg)	V_C (l)	α ($min^{-1} \times 10^{-2}$)	β ($min^{-1} \times 10^{-2}$)	k_{12} ($min^{-1} \times 10^{-2}$)	k_{21} ($min^{-1} \times 10^{-2}$)
1	450	27.40	5.96	0.151	1.986	3.89
2	450	17.30	4.01	0.110	1.960	1.92
3	450	28.20	9.81	0.0827	6.490	3.15
4	450	23.20	15.00	0.0917	5.155	9.80
5	450	21.50	1.60	0.176	0.427	1.10
6	450	14.30	15.28	0.130	6.770	8.42
Mean		22.00	8.61	0.289	3.800	4.71
s.d.[a]		5.50	5.73	0.399	2.680	3.60

[a] s.d. estimated from individual values assuming each value has no error.

the corresponding reduced model are shown in Table 2 together with coefficients of determination and the results of the General Linear Test. The full model explained the data best in patients 1, 2, 4 and 5: the reduced model was equally good in patients 3 and 6, although it is obvious from the coefficients of determination that neither model fitted the data from patient 3 very well. Excluding the full model parameter values estimated for patient 3, mean values for the multiple linear regression model were as follows: θ_0, 1.35 ± 0.72 l; θ_1, 0.171 × 10^{-2} ± 0.107 × 10^{-2} l/mg and θ_2, 0.647 × 10^{-2} ± 0.265 × 10^{-2} l/mg.

Parameter estimates for the effect model are shown in Table 3 together with coefficients of determination. The intercept, i, had a man value of 1.84 ± 0.65 l. The slope, m, expressing sensitivity to theophylline in terms of steady state plasma concentrations, had a mean value of 0.056 ± 0.015 l/μg ml^{-1} and the first order rate constant, k_{eq}, had a mean value of 0.049 ± 0.017 min^{-1}.

Figure 3 shows the observed and predicted changes in FVC in patient 2. The predicted form of the response-time relationship was generated from the parameters estimated for the multiple-linear regression model (θ_0, 0.92 ± 0.18 l; θ_1, 0.208 × 10^{-2} ± 0.039 × 10^{-2} l/mg and θ_2, 0.694 × 10^{-2} ± 0.059 × 10^{-2} l/mg). Also shown in Figure 3 are the predicted time courses of the amounts of drug in the central ($Q_C(t)$) and peripheral ($Q_P(t)$) compartment.

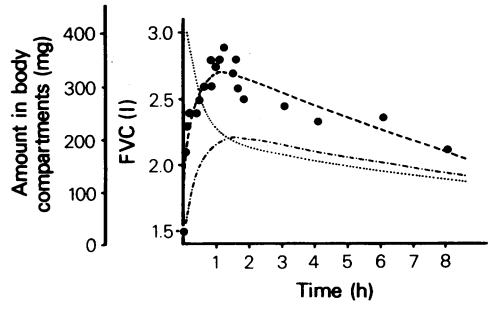

Figure 3 Response (FVC)-time profile fitted to the multiple linear regression model. Also shown are the calculated amounts of theophylline in the central (.....) and peripheral (_._._) compartments of a two compartment pharmacokinetic model (Patient 2). The line of best fit (---) was derived from final parameter estimates for θ_0, θ_1 and θ_2 (see text) by multiple linear regression analysis.

Figure 4 shows the same response time data fitted to the effect model. The predicted form of the response-time relationship was generated from the following parameter estimates: i, 1.72 ± 0.074 l; m, 0.077 ± 0.0071 l/μg ml^{-1} and k_{eq}, 0.028 ± 0.0033 l/μg ml^{-1}.

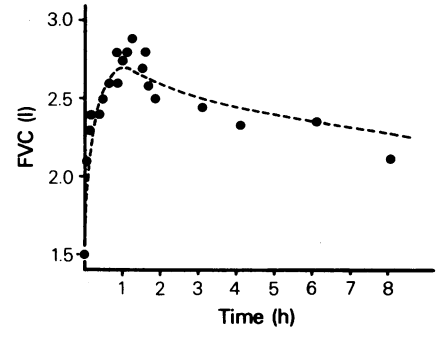

Figure 4 Response (FVC)—time profile fitted to the effect model (Patient 2). The line of best fit (---) was derived from final parameter estimates for m, i and k_{eq} (see text) by nonlinear least squares regression analysis.

The AIC values for the linear regression models and the effect model are given in Table 4. There was no consistent trend in the abilities of either type of model to fit the data more efficiently.

Discussion

We have previously defined a positive response to intravenously administered theophylline as the point

Table 2 Linear regression model parameters (mean ± s.d.) with coefficients of determination (r^2) and General Linear Test results

	Full model[a]					*Reduced model*[b]						
Patient	θ_0 *(l)*	θ_1 *(l/mg × 10^{-2})*	θ_2 *(l/mg × 10^{-2})*	*SSQ*[c]	r^2	θ_0 *(l)*	θ_2 *(l/mg × 10^{-2})*	*SSQ*[c]	r^2	*'F' relative to Full model*	*d.f.*	*P value*
1	0.72 (0.12)	0.140 (0.029)	0.490 (0.060)	0.264	0.724	1.22 (0.09)	0.381 (0.075)	0.498	0.476	24.04	1,27	< 0.005
2	0.92 (0.18)	0.208 (0.039)	0.694 (0.059)	0.327	0.867	1.81 (0.08)	0.438 (0.049)	0.664	0.740	28.87	1,28	< 0.005
3	2.73 (0.19)	−0.072 (0.044)	0.039 (0.052)	0.269	0.354	2.45 (0.08)	0.106 (0.031)	0.295	0.292	2.65	1,27	> 0.05 (NS)
4	1.32 (0.48)	0.323 (0.109)	0.805 (0.154)	0.706	0.518	2.69 (0.16)	0.471 (0.118)	0.934	0.360	8.72	1,27	< 0.01
5	1.33 (0.15)	0.153 (0.032)	0.961 (0.112)	0.274	0.774	2.01 (0.07)	0.589 (0.115)	0.566	0.533	23.50	1,22	< 0.005
6	1.07 (0.10)	0.031 (0.025)	0.285 (0.035)	0.126	0.764	1.17 (0.05)	0.265 (0.032)	0.135	0.740	1.57	1,22	> 0.05 (NS)
Mean	1.35[d]	0.171[d]	0.647[d]	—	—	1.89	0.375	—	—	—	—	—
s.d.[e]	0.72	0.107	0.265			0.62	0.169					

[a] Full model: $FVC(t) = \theta_0 + \theta_1 Q_C(t) + \theta_2 Q_P(t)$
[b] Reduced model: $FVC(t) = \theta_0 + \theta_2 Q_P(t)$
[c] SSQ is the total sum of squared deviations from the best fit associated with each model.
[d] Mean and s.d. exclude patient 3.
[e] s.d. estimated from individual mean values assuming no error in each value.

Table 3 Effect model parameters (mean ± s.d.) with coefficients of determination (r^2)

Patient	*m* ($l/\mu g\ ml^{-1}$)	*i* (*l*)	k_{eq} (min^{-1})	r^2
1	0.058 (0.074×10^{-2})	1.14 (0.67×10^{-2})	0.066 (0.029×10^{-3})	0.590
2	0.077 (0.071×10^{-1})	1.72 (0.74×10^{-1})	0.028 (0.033×10^{-1})	0.813
3	0.061 (0.033×10^{-1})	2.44 (0.15×10^{-1})	0.042 (0.065×10^{-1})	0.312
4	0.056 (0.014)	2.73 (0.160)	0.066 (0.022)	0.392
5	0.050 (0.036×10^{-1})	1.83 (0.38×10^{-1})	0.033 (0.034×10^{-1})	0.904
6	0.032 (0.034×10^{-1})	1.18 (0.48×10^{-1})	0.057 (0.092×10^{-1})	0.794
Mean	0.056	1.84	0.049	
s.d.[a]	0.015	0.65	0.017	

[a] s.d. estimated from individual mean values assuming no error in each value.

Table 4 Comparison of different models using the Akaike Information Criterion

Patient	*Appropriate linear regression model*	*Effect model*
1	−34.0[a]	−22.1
2	−28.7[a]	−18.0
3	−32.6[b]	−31.5
4	−4.4[a]	2.5
5	−26.4[a]	−47.7
6	−46.0[b]	−49.2

[a] Full model
[b] Reduced model

at which the upper 95% confidence limit of pretreatment, baseline observations is exceeded (Barclay *et al.*, 1981). This assumes that a sufficient number of baseline observations are made to assess the variance in any set of readings. The detection of a positive response, then, will depend on the magnitude of this variance and will not necessarily represent a change which is of significant benefit to the patient. While the techniques presented in this paper are based on models which assume linear relationships between response and changes in the amount or concentration of drug in various body compartments, they permit a useful assessment of the magnitude of response which can be obtained from the range of theophylline concentrations normally encountered in individual patients. The utilization of nonlinear functions for the f_i in equation (2) or the f in equation (7) would allow a more realistic description of the true sigmoid relationship between FVC and Q_C, Q_P or C_e, but the limitations imposed by relatively narrow concentration and effect ranges preclude this more general analytical approach. It is clear, however, that the linear approximations adopted in the present study yield satisfactory estimates for responses which are associated with theopylline concentrations in the upper part of the therapeutic range.

We have shown previously that in chronic bronchitis, there is considerable variation in the degree of response to theophylline (Barclay *et al.*, 1980). Individual response patterns were determined by assessing ventilatory function at a number of steady state levels produced by 3–6 incremental infusions over a period of 4–6 h. The complexity of such an approach can now be reduced by observing the response after a *single* intravenous dose of theophylline. While the linear approximations may not allow precise estimates of the maximum response available, substituting a value of 15–20 μg/ml for C_e in the effect model (equation (8)) or equivalent amounts for Q_C and/or Q_P in the appropriate linear regression models (equations (3) and (10)) gives a good indication of the magnitude of response at these levels. Table 5 presents the calculated response at a target average steady state concentration of 17.5 μg/ml. Although the degree of response indicated by the two models is not always identical, the small difference in the $FVC_{17.5}$ figures is insignificant. The AIC values presented in Table 4 indicate that there is some variation in the efficiency with which each model describes the data, but the similarities in the $FVC_{17.5}$ values shows that there is little to choose between the models. The

Table 5 Comparison of pretreatment FVC values with those calculated for a theophylline steady state concentration of 17.5 μg/ml.

Patient	Pretreatment FVC (l)	Calculated $FVC_{17.5}$ (l) Appropriate linear regression model	Effect model
1	1.4	2.6	2.2
2	1.5	3.7	3.1
3	2.3	3.5	3.5
4	2.8	4.4	3.7
5	1.5	3.3	2.7
6	1.2	1.7	1.7

range of parameter values showed that there were clear interindividual differences in response and it would then be a matter of clinical judgement as to whether or not theophylline would provide a useful degree of bronchodilation in any individual patient. Further work is now in progress to test whether such single dose studies can yield predictive information which would be useful in the assessment of individual patients who are being considered for theophylline therapy.

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