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Time and Theophylline Concentration Help Explain the Recovery of Peak Flow Following Acute Airways Obstruction

Population Analysis of a Randomised Concentration Controlled Trial

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Summary Peak expiratory flow rate, adverse effects and serum theophylline concentration were measured during treatment of episodes of severe airways obstruction. 174 patients were randomised to target theophylline concentrations of 10 mg/L or 20 mg/L. The recovery of peak flow rate towards normal values was explicable in terms of time and theophylline concentration using semiparametric and parametric nonlinear regression models. In the absence of theophylline, recovery takes place with a half-time of 16 hours. Theophylline is less effective in achieving recovery than the passage of time but achieves 50% of possible recovery at a concentration of 11 mg/L. The action of theophylline is most marked at the start of treatment. It may no longer have important beneficial effects after 72 hours. The incidence of adverse effects increased at theophylline concentrations >20 mg/L.

In recent years the place of theophylline in the management of acute airways obstruction has come into question, but the drug continues to be recommended especially when dosage is guided by suitable interpretation of serum theophylline concentrations. One of us has recently reported the outcome of episodes of acute airways obstruction in 174 patients participating in a randomised, concentration-controlled trial (Holford et al. 1993). No important difference was detectable in potential beneficial effects of theophylline when patients were treated with the intention of obtaining target theophylline concentrations of 10 or 20 mg/L. There was a significant excess of adverse effects at higher concentrations, which suggested that 10 mg/L was an appropriate target concentration.

These conclusions were derived from an intention-to-treat analysis of the 2 target concentration groups. While this is appropriate for testing hypotheses about treatment strategies, it does not provide explanatory insight about the concentration-effect relationship in individuals. We report here a population-based pharmacodynamic analysis based on serial timed observations of peak ex-

piratory flow rate (PEFR), adverse effects and theophylline concentrations during hospital treatment of episodes of acute airways obstruction.

Methods

Concentration-Controlled Trial

Patient details and experimental design are reported elsewhere (Holford et al. 1993). In brief, all patients with acute airways obstruction who were thought to require intravenous theophylline treatment, administered as the ethylenediamine salt, aminophylline, were randomised to a double-blind trial of target concentrations of either 10 or 20 mg/L. Initial doses and subsequent adjustment were determined by each patient's physician using scaled reports of actual theophylline concentrations to maintain blinding yet mimic actual clinical practice. PEFR, theophylline concentration and an assessment of theophylline adverse effects were obtained several times during the first 24 hours and at least daily until discharge. All patients received similar intensive treatment with nebulised then inhaled salbutamol and intravenous hydrocortisone followed by oral prednisone.

There were 591 simultaneous records of theophylline concentration and effect measures (PEFR, presence of nausea, tremor, palpitations or headache). The characteristics of the patient group are shown in table I.

Table I. Demographic characteristics of the 174 patients enrolled in the study. Unknown values are those that were not recorded on patient records before discharge

Covariate	Value	Unknown value
Bodyweight (kg)	66.7	2 patients
Age (years)	38.5	7 patients
Females (%)	59.8	1.2%
Caucasian (%)	57.5	
Maori/Polynesian (%)	25.3	
Other race (%)	17.2	
Smoker (%)	20.7	20.7%
Asthma (%)	77.6	
COPD (%)	14.3	
Asthma + COPD (%)	2.3	
Unknown diagnosis (%)	5.8	

Abbreviations: COPD = chronic obstructive pulmonary disease.

Peak Expiratory Flow Rate

Patients were admitted to a hospital ward for an average of 110 hours (4.6 days). Timed recordings of PEFR and matching theophylline concentrations during the first 100 hours of patient follow-up are shown in figure 1.

It should be noted that the time course reflects not only the changes associated with the passage of time and differences in theophylline concentration, but also alterations in the composition of the patient population. The dip in PEFR starting at about 12 hours is due to discharge of patients whose PEFR had improved, leaving those with lower PEFRs.

The rise in PEFR seen in both groups after 20 hours, while theophylline concentrations are stable or slowly falling, suggests an effect on PEFR, independent of theophylline, that is associated with the passage of time.

Theophylline Concentration

The target concentrations of 10 and 20 mg/L were maintained during supervised administration of theophylline in hospital. The fall in theophylline concentration at about 5 hours in the high target group may be either because there were changes in theophylline dosage after initial concentrations were above the target value, or because the response in this group was greater, leading to the discharge of patients with higher PEFRs.

Exploratory Analysis

Plots of potential independent explanatory variables versus PEFR were examined using a smoothing technique (Cleveland 1979) to distinguish the average behaviour associated with different subgroups.

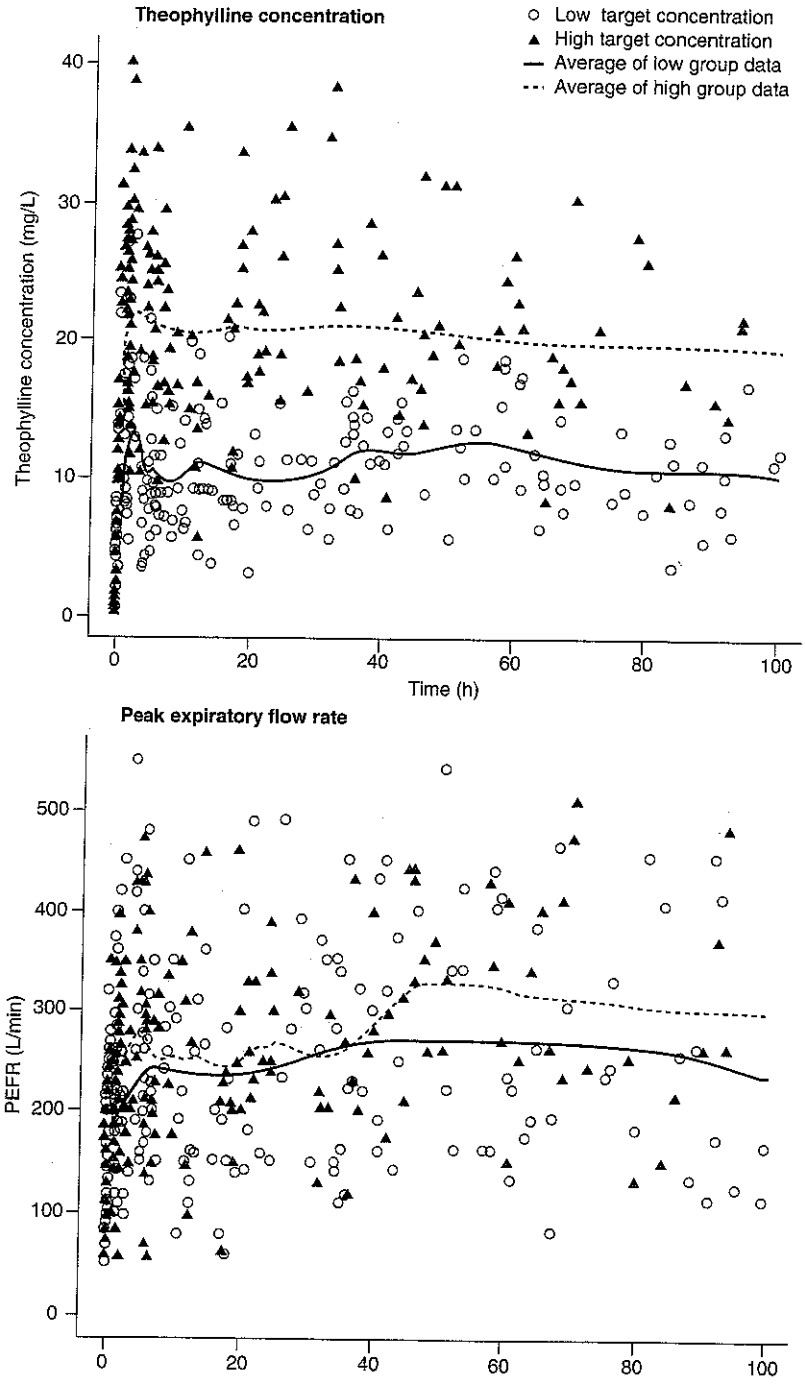

Fig. 1. Time course of theophylline concentration and peak expiratory flow rate (PEFR) in Low and High target concentration groups. Smoothed lines reflect a running average of the Low and High group data. Only values recorded during the first 100 hours of observation are shown.

Model Analysis

We used 2 types of model, semiparametric and parametric, to explore the relationship between PEFR and time, theophylline concentration, and other covariates such as gender and age. The 2 modelling approaches are complementary. The semiparametric model seeks to discover the presence and 'shape' of important influences on PEFR, while the parametric attempts to provide a more mechanistic framework in which to interpret these influences. As such, it is more speculative, but potentially more powerful.

The assumptions made for both kinds of model are (a) the concentration effect (improvement in PEFR is a non-decreasing function of theophylline venous concentration which reaches a maximum value); (b) the time effect (improvement in PEFR due to factors other than theophylline is a non-decreasing function of time, beginning at the time of starting theophylline treatment, and after sufficient time, recovery reaches a limiting value and proceeds no further); and (c) the combined effect [time and theophylline effects are non-competitive (i.e. at any time, an increase in theophylline concentration either increases PEFR or has no effect, and *vice versa*)].

Semiparametric Effect Model

Let f_T be a function describing the shape of the time effect, $f_T(0) = 0$ and $f_T(t_{max}) = 1$. Let f_C be a similar function describing the shape of the drug effect. The combined effect model is then:

$$PEFR(t,c) = Base + (Normal - Base) \cdot \{f_T(t) + \varepsilon_{theo} \cdot [1 - f_T(t)] \cdot f_c(c)\}$$

where Base is the baseline PEFR, Normal is the maximum attainable PEFR, t is time in hours, c is theophylline concentration and ε_{theo} is the fraction of Normal – Base that theophylline is capable of restoring.

Each of the functions f_T and f_C is approximated by a smooth monotonically non-decreasing function [natural cubic spline with 2 internal break points (De Boor 1978)] beginning at zero and asymptoting to unity. For each function, 2 free parameters for each internal break point (roughly corresponding to the location on the abscissa and the height on the ordinate) determine the shape, and a fifth free parameter determines the point at which the function attains its asymptotic value of unity.

Parametric Effect Model

In order to incorporate some explanatory insight for the marked association of increasing PEFR with time after start of treatment (independent of theophylline concentration) a hypothetical bronchoconstrictor factor (BCF) model was developed. For the purposes of this model it is proposed that hospitalisation is associated with the abrupt termination of production of a factor causing bronchoconstriction. If BCF is eliminated by a first-order process, then the time course of BCF can be defined by its half-life, $T50_{bcf}$:

$$BCF(t) = BCF_0 \cdot e^{-\ln(2) / T50_{bcf} \cdot t}$$

Bronchoconstriction may be then be related to BCF concentration according to an inhibitory pharmacodynamic model (Holford & Sheiner 1981):

$$PEFR(t) = Normal \cdot [1 - BCF(t)]/[BCF(t) + C50_{bcf}]$$

where Normal is the PEFR when BCF is zero and $C50_{bcf}$ is the concentration producing 50% reduction in PEFR from Normal. If Base is the PEFR at the start of treatment then the concentration of BCF at this time (BCF_0) is given by:

$$BCF_0 = C50_{bcf} \cdot (Normal/Base - 1)$$

Thus, PEFR(t) can be predicted in terms of the pretreatment PEFR (Base), the asymptotic fully recovered PEFR (Normal), the notional concentration of BCF producing a PEFR which is 50% of Normal (C50 • bcf) and the half-life of BCF elimination ($T50_{bcf}$)

Because it is generally accepted that theophylline has little bronchodilator effect in asthmatic patients with normal PEFR, the maximum effect theophylline may exert is that component of PEFR which remains to be achieved when PEFR is subnormal, i.e. Normal – PEFR(t). The effect of theo-

phylline may then be related to its concentration (c) by:

$$PEFR(c,t) = [Normal - PEFR(t)] \cdot \frac{C^n}{C^n + C50^n_{theo}}$$

where $C50^n_{theo}$ is the concentration of theophylline producing 50% of the potentially recoverable PEFR and n is a coefficient controlling the steepness of the curve. This is a model of theophylline acting as a bronchodilator agonist.

The combined influences of BCF and theophylline on PEFR can then be predicted by a function of time and theophylline concentration:

$$PEFR(t,c) = PEFR(t) + \varepsilon_{theo} \cdot PEFR(c,t)$$

The efficacy of theophylline relative to effects predicted by PEFR(t) is described by ε_{theo}, as before.

Diagnosis, Age, Gender, Weight and Ethnic Origin

The influence of diagnosis, age, gender, weight and racial origin was examined as potential modifiers of the structural model parameters, Base and Normal. For example, the predicted Normal in the *i*th individual may be defined by:

$$Normal_i = Normal_{std} \cdot [(1 - S_{bw}) \cdot (BW - 70)] \cdot [(1 - S_{age}) \cdot (AGE - 40)] \cdot F_{org} \cdot F_{diag} \cdot F_{gen}$$

$Normal_i$ is thus determined by the typical value for a 40-year-old, 70kg bodyweight (BW), Caucasian male with asthma ($Normal_{std}$) modified by scale factors for bodyweight (S_{bw}) and age (S_{age}) and fractions of the typical value for racial origin (F_{org}), diagnostic category (F_{diag}) and gender (F_{gen}).

Statistical Model

Individuals are regarded as varying randomly with respect to Base, Normal, T50 and C50. The variability of these parameters, after adjustment when necessary for covariates, was modelled as a proportional error. PEFR also varies randomly and independently about its expected value using a proportional error model.

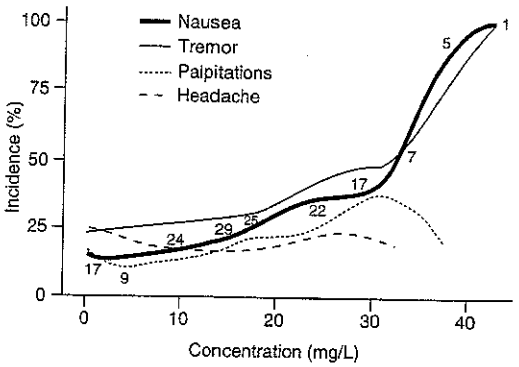

Fig. 2. The incidence of 4 symptoms is shown in relation to theophylline concentration. Each point was obtained by counting the number of patients with each symptom over a 5 mg/L band of concentration and a smooth line drawn between the points.

Model Fitting

The above models were fit to the data using the program NONMEM (Beal & Sheiner 1992). The program finds normal theory maximum likelihood estimates of a model linearised in the random effects using the first order conditional estimate method, a method similar to that presented by Lindstrom and Bates (1990). Hypothesis tests are performed by comparing the goodness of fit of the model with fixed parameter values to a model in which these values are estimated. The difference in goodness of fit is distributed asymptotically χ^2, with degrees of freedom (df) equal to the number of fixed parameters (Cox & Hinckley 1974).

Results

Adverse Effects

The incidence of nausea, tremor, palpitations and headache as a function of theophylline concentration is shown in figure 2. The number of patients with each symptom was noted in 5 mg/L concentration bands. Nausea and tremor began to increase at concentrations above 15 mg/L and approached 100% incidence above 35 mg/L. Palpitations became more frequent above 20 mg/L while headache did not appear to be related to concentration.

Semiparametric Model

Figure 3 compares the semiparametric model predictions, obtained with and without the use of covariates, with the observed time course of PEFR. Nonparametric smooths through the observations and predictions are used to facilitate visual comparison. The difference in goodness of fit (124) between the fits with and without covariates of age, gender and diagnosis (table II) was highly significant (χ^2, 0.95 with 6 df, = 12.59) and confirms the importance of including the covariate values.

The time at which maximum improvement in PEFR is achieved was estimated to be 190 hours. The concentration producing the maximum increase in PEFR was greater than 11 mg/L, but there were insufficient data to determine this value more precisely. Accordingly, this parameter was fixed at 25 mg/L, which did not significantly change the fit from other values greater than 11 mg/L.

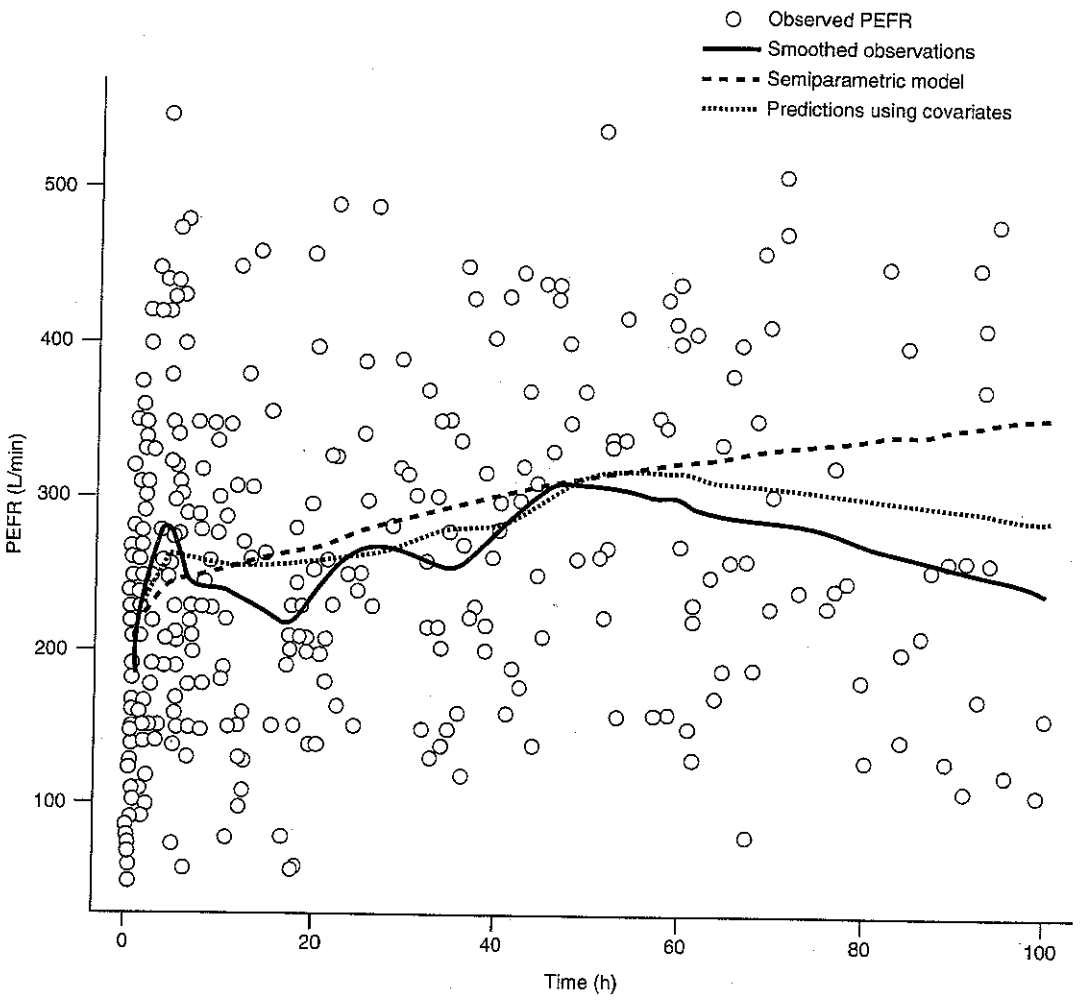

Fig. 3. Time course of observed peak expiratory flow rate (PEFR) over the first 100 hours of observation. The lines show the smoothed observations, the semiparametric model predictions based on time and theophylline alone and the predictions also using the covariates of diagnosis, age and gender.

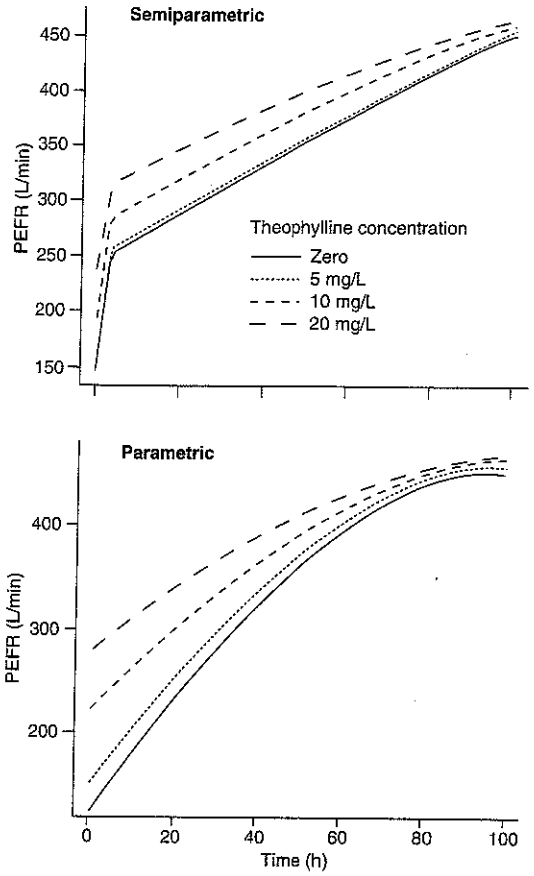

Fig. 4. Predictions of semiparametric model and parametric model of pure time effect in a 40-year-old asthmatic man, at various theophylline concentrations.

Figures 4 and 5 show the time and theophylline effects predicted by the semiparametric model. Of particular note is the difference between the shape functions describing the time and drug effects. Both are particular instances of the very flexible class of spline functions used in semiparametric analysis. Thus, the unique features of the shape of f_T and f_C are entirely a function of the data, not of the opinions or assumptions of the modellers. The time effect function, after a very sharp initial rise in the first few hours after beginning therapy, resembles an asymptotic exponential, while that for theophylline effect resembles the sigmoid E_{max}

Table II. Goodness of fit of the model with fixed parameter values to a model in which these values are estimated

Model		Number of parameters	Objective function
Semiparametric	No covariates	13	5351
	With gender, age, diagnosis	16	5227
Parametric	No covariates	6	5401
	With gender, age, diagnosis	9	5297

pharmacodynamic model (see e.g. Holford & Sheiner 1981).

In pharmacological terms, the estimated shape functions predict that the time to half-maximal recovery is 22 hours, while the theophylline concentration yielding half-maximal effect is 9.5 mg/L. Theophylline definitely has a bronchodilator effect because the fit is significantly worse when ε_{theo} is fixed at 0 (change in goodness of fit is 31, χ^2, 0.95 with 1 df, = 3.86).

The initial PEFR, Base, was estimated to be 145 L/min (table III). None of the covariates had a significant effect on Base. The maximum PEFR, Normal, was estimated to be 497 L/min in a 40-year-

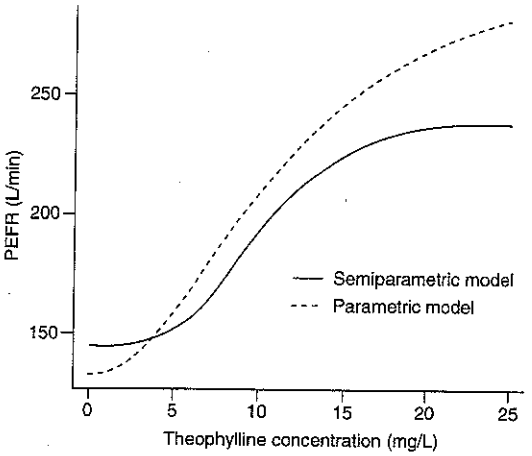

Fig. 5. Predictions of semiparametric and parametric models of pure theophylline effect in a 40-year-old asthmatic man, at zero time.

Table III. Semiparametric model parameter estimates

Parameter	Typical value	SE	Population CV (%)
Base (L/min)	145	5.7	30
Normal (L/min)	497	29	25
ε_{theo}	26	3.8	94
Residual error CV (%)	18	5.8	

Abbreviations: Base = baseline peak expiratory flow rate; Normal = maximum attainable peak expiratory flow rate; ε_{theo} = the fraction of Normal – Base that theophylline is capable of restoring; CV = coefficient of variation; SE = standard error.

old male with asthma. The efficacy of theophylline compared with that of time (ε_{theo}) was 26%. Normal was reduced to 57% in patients with COPD, 74% in females and declined linearly at a rate of 0.92% per year (table IV).

Parametric Model

Figures 4 and 5 show the predictions of the parametric model. The parameter estimates for the parametric model are shown in table V. The estimated PEFR on admission to the study (Base) was 133 L/min with a predicted fully recovered value of 477 L/min in a 40-year-old male asthmatic patient. The half-life of the bronchoconstrictor factor was 16 hours. The maximum effect of theophylline is to produce 51.8% (ε_{theo}) of the maximum effect associated with time alone. A concentration of 11 mg/L achieved 50% of the potential theophylline effect. The steepness of the curve was described by a coefficient of 2.13.

The model predictions were clearly improved by modification of the Normal parameter with respect to diagnosis, age and gender and were similar to the semi-parametric model estimates (table VI). There was no detectable influence of racial origin or weight on any population model parameter.

Discussion

Is Theophylline a Bronchodilator?

The results of this analysis demonstrate quite clearly a concentration-dependent response of PEFR to theophylline in patients with an acute exacerbation of airway obstruction requiring hospital treatment with intravenous theophylline. While this observation is entirely consistent with established clinical practice and intensive study of small groups of patients (Mitenko & Ogilvie 1973; Vožeh et al. 1982), it has subsequently been questioned (Murciano et al. 1989; Siegel et al. 1985). An accompanying description of an intention-to-treat trial comparing different target theophylline concentrations provided no clear evidence for a bronchodilator effect of theophylline (Holford et al. 1992). A model-independent statistical analysis of the pooled effects could not detect a significant difference between treatment groups even though the trial was large enough to detect a 25% benefit of the higher concentration.

We suggest that the failure to find a bronchodilator action of theophylline arises from a methodological defect. The wide degree of variation in achieved theophylline concentrations is concealed by the intention-to-treat analysis. Presentation of group responses based on actual theophylline concentrations reveals a consistent bronchodilator trend associated with higher concentrations (fig. 1). Application of simple pharmacological models in conjunction with a technique able to dissect the components of variance allows the effect of theophylline to be resolved and quantified.

Models of the Time Course of Recovery of PEFR

We have examined models to quantify the time course of recovery of PEFR following initiation of treatment with theophylline, β-agonists and steroids. Both the semiparametric and parametric

Table IV. Semiparametric estimates of covariate effects on the Normal parameter

Covariate	Typical value	SE
F_{diag}	0.57	0.06
F_{gen}	0.74	0.04
S_{age} (%/year)	–0.92	0.2

Abbreviation: SE = standard error; F_{diag} = fraction of the typical peak expiratory flow rate for diagnostic category; F_{gen} = fraction of the typical value for gender; S_{age} = scale factor for age.

Table V. Parametric model parameter estimates

Parameter	Typical value[a]	Population CV%
Base (L/min)	133	38
Normal (L/min)	477	22
$T50_{bcf}$ (h)	16	81
$C50_{bcf}$ (mg/L)	11	78
ε_{theo}	51.8	
n	2.13	
Residual error CV %	20.0	

a Standard errors could not be computed due to numerical difficulties.

Abbreviations: $T50_{bcf}$ = half-life for bronchoconstrictor factor; $C50_{bcf}$ = concentration producing 50% reduction in peak expiratory flow rate from Normal; n = coefficient controlling the steepness of the curve; for other abbreviations, see table III.

models share the same qualitative features, namely, time alone is associated with an increase in PEFR, theophylline definitely augments recovery towards Normal but does not go beyond it, and recovery of absolute PEFR is less in older persons, those with chronic obstructive pulmonary disease, and in females. Quantitatively, as can be seen from figures 4 and 5, there is also little difference between the models. We surmise that the inability of the parametric model to permit as sharp an initial rise in PEFR may cause it to ascribe greater efficacy (ε_{theo} 52 *vs* 26%) to theophylline. Nonetheless, as is evident in figure 3, the predictions of the 2 models differ little.

There was an apparent absence of influence of diagnosis, gender or age on the baseline PEFR. This may be more apparent than real, as initial PEFR is probably correlated with being enrolled in the study (i.e. only those with significant acute airways obstruction were studied) and the estimate of Base is close to the lower limit of the peak flow meter.

Chandler et al. (1990) have reported an age-related decrease in the slope of the theophylline concentration/FEV_1 relationship. This apparent decrease in sensitivity can be explained by an age-associated decrease in fully recovered forced expiratory volume in 1 second (FEV_1) which would be compatible with our lack of relationship of $C50^{n}_{theo}$ to age.

Mechanistic Interpretation

What pathophysiological mechanisms might underlie the rapid initial recovery of airway flow rates, which the parametric model attributes to the apparent disappearance of a 'bronchoconstrictor factor'? We suggest that improvement in peak flow begins at the time of hospitalisation because of the removal of influences such as allergens, suppression of the allergic response by steroids (and possibly theophylline), stabilisation of atmospheric temperature and humidity and by bedrest. The most readily identifiable of these mechanisms is the action of corticosteroids. Patients were initially treated with hydrocortisone 400mg followed by 200mg every 6 hours until intravenous theophylline was stopped. Oral theophylline and prednisone (40 mg/day reducing by 5 mg/day on alternate days) was then commenced. These dosages achieve concentrations which may completely suppress components of the immune system (Frey et al. 1982). The final result of relief of bronchoconstriction may be separated by several steps from the immunosuppressant action of steroids, e.g. requiring resolution of mucosal oedema and repair of structural damage to the epithelium. It is the component in this chain of events with the slowest time constant that will determine our estimate of the half-life of BCF.

Is Theophylline Therapeutically Effective?

We believe we have demonstrated unequivocally that theophylline provides additional bron-

Table VI. Parametric estimates of covariate effects on the Normal parameter

Covariate	Typical value[a]
F_{diag}	0.61
F_{gen}	0.76
S_{age} (%/year)	–0.82

a Standard errors could not be computed due to numerical difficulties.

Abbreviations: see table IV.

chodilation in patients receiving standard treatment for severe airways obstruction. It is most effective during the first few days of recovery (figs. 3 and 4).

The failure of Siegel et al. (1985) to demonstrate a bronchodilator effect of theophylline during the first 3 hours of treatment may be in part due to a substantial number of patients in the placebo group having theophylline present in their plasma arising from treatment prior to presentation. The inability to detect an effect could also indicate that the bronchodilator action of theophylline we have identified is very slow with respect to a 3-hour observation period but is indistinguishable from an immediate action when observations are extended for over 600 hours.

Simulations of the association between the passage of time and recovery of PEFR are shown in figure 4. This shows the expected time course of PEFR in a young male with asthma using the semi-parametric model and the parametric model. The greatest benefit is expected immediately after starting treatment. Both models predict that as time passes, the benefit attributable to theophylline diminishes. This suggests that theophylline should be started as soon as possible and consideration given to termination of theophylline treatment between 48 and 72 hours later. However, the existence of a benefit from theophylline which develops over a period longer than that examined in this study cannot be excluded.

Theophylline provides bronchodilator benefits to patients at a time when they are most severely affected. The duration of intravenous therapy is shortened by higher concentrations (Holford et al. 1993), but there is no advantage in terms of days in hospital. The benefit to patients must therefore be regarded as symptomatic by relieving dyspnoea. It would seem to be important therefore not to negate this benefit with unpleasant adverse effects. We observed that adverse effects were reported more frequently when concentrations exceeded 10 mg/L. This, coupled with the prediction (fig. 5) that most of the bronchodilator benefit from theophylline is provided by a concentration at or below 10 to 15 mg/L, reinforces the earlier conclusion (Holford et al. 1993) that the optimal intensity of treatment with theophylline is likely to be achieved at a concentration of 10 mg/L. Higher concentrations may produce worthwhile symptomatic benefit but this may be offset by the increasing probability of adverse effects.

Acknowledgements

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