JPP Journal of Pharmacy and Pharmacology

JPP 2005, 57: 183–189

Received August 27, 2004
Accepted November 12, 2004
DOI 10.1211/0022357055452
ISSN 0022-3573

A pharmacokinetic/pharmacodynamic model for a platelet activating factor antagonist based on data arising from Phase I studies

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Abstract

A nonlinear mixed-effects modelling approach was used to analyse pharmacokinetic and pharmacodynamic data from two Phase I studies of a platelet activating factor (PAF) antagonist under development for the treatment of seasonal allergic rhinitis. Data for single-dose (8 subjects) and multiple-dose (9 subjects) administration were available for analysis with a program based on an EM algorithm. Pharmacokinetic analyses of plasma drug concentrations were performed using a bi-exponential model with first-order absorption. PAF response data were modelled with a hyperbolic E_{max} model. The drug showed nonlinear pharmacokinetics, with the clearance decreasing from 46.0 to 27.1 L h^{-1} over a dose range of 160–480 mg. There was an apparent dose dependency within the C50 (concentration producing 50% of the maximum effect) but at higher doses most of the data was above the estimated C50 and when the data was analysed simultaneously a value of 17.57 ng mL^{-1} was obtained for C50, with considerable intersubject variability (103%). Consistent results were obtained from the two studies and the population and individual pharmacodynamic parameter estimates from the analyses provided predicted responses that were in good agreement with the observed data. The results were used to simulate a 320-mg twice-daily dosing regimen.

Introduction

The relationship between the pharmacological response of a drug and its pharmacokinetics is important as it can provide valuable insight into the time course of the drug response (Holford & Sheiner 1982). The use of nonlinear mixed effects modelling in this type of analysis has proved effective and is now widely used (Rowland & Aarons 1992). It has also highlighted the need for drug-concentration data to be available when analysing the pharmacodynamic response (Aarons et al 1991; Hashimoto & Sheiner 1991). While population pharmacokinetics was originally developed for sparse data analysis (Sheiner 1984), it is an equally viable method for rich data sets that are traditionally analysed using two-stage methods. A drawback of the two-stage method is that intersubject variability can be overestimated, whereas in a nonlinear mixed-effects one-stage approach, inter- and intrasubject variability are treated separately. The most widely used software package for population analyses is NONMEM (Beal & Sheiner 1979), although there are other programs (Bruno et al 1992; Davidian & Gallant 1992; Racine-Poon 1992).

Since the introduction of antihistamines over 50 years ago (Halpern 1942), treatments for allergic disorders have improved and now allergic symptoms can be well controlled. Although pharmacokinetic/pharmacodynamic (PK/PD) modelling is extensively used (Mandema & Danhof 1990; Holford & Peace 1992a, b; Wald et al 1992), there has been relatively little interest in drugs for allergic disorders (Heykants et al 1992). Data from Phase I trials of a drug (UK-112,214 (Pfizer 1994)) that was under development for the treatment of seasonal allergic rhinitis (hay fever) were obtained for population pharmacodynamic analysis. It should be noted that development of this drug has now been terminated. The drug is a dual platelet activating factor (PAF) and histamine H_1 antagonist. Clinical studies indicate that, while H_1 antagonists control the acute symptoms of hay fever mediated by histamine activation of sensory nerve reflexes, congestion due to dilatation of and extravasation from nasal

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Acknowledgment and funding: All data were provided by Pfizer Central Research, Sandwich, UK. L. Evans gratefully acknowledges financial support from Pfizer Central Research, Sandwich, UK.

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blood vessels and ocular symptoms are little affected. There is evidence that PAF may be responsible for these effects and blockade of both PAF and histamine receptors should allow more comprehensive symptomatic relief than can be achieved by H_1 antagonists.

The purpose of this report was to analyse response data arising from the Phase I studies of UK-112,214 (4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-[4-(2-methyl-1*H*-imidazo[4,5-c]pyridin-1-yl) benzoyl]-piperidine). The histamine response data from the studies (wheal and flare measurements) were highly variable and did not show any overall pattern in the shape of the response curve. In addition, in the multiple dosing study the plasma drug concentrations dropped below the limit of quantification before any reduction in the response was seen, even though flare measurements were taken up to 60 h post dose. Consequently information was only available on the maximum response and we therefore only modelled the PAF response.

Materials and Methods

Data

The data that were analysed were taken from two Phase I studies. In both studies approval was obtained from local ethics committees and subjects gave their informed, written consent to participate in the studies.

Study PH1
This was a single-blind, placebo-controlled study in three groups of 8 healthy male subjects with single escalating oral doses of the drug. Although the doses ranged from 5 to 480 mg, only data from the three highest doses (160, 320, 480 mg) were used in the analyses because these were the doses considered for subsequent studies. These doses were confined to the last group in the study and hence only data from 8 individuals were used. Each subject received all doses and placebo. Plasma samples were taken pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18 and 24 h post dose. Dermal response to intradermal histamine injections and inhibition of ex-vivo platelet aggregation to PAF were measured at 1 h pre-dose and at 2, 4, 8, 12 and 24 h post dose.

Study PH2
This was a double-blind, placebo-controlled, 14-day multiple-dose study with oral administration of 160-mg doses of the drug to healthy male subjects. There were 18 subjects, of which half took active drug twice daily and half took matched placebo twice daily. Subjects received one dose on the morning of day 15. Plasma samples were taken pre-dose and then up to 12 h post dose after the first dose. After the final dose on day 15, samples were taken up to 48 h post dose. PAF was measured at 1 h pre-dose and at 2, 4, 8 and 12 h post dose after the first dose. After the last dose, measurements were taken at the same time as the first dose with additional measurements beyond 12 h up to 48 h post dose at 12 h intervals.

Drug assay and PAF measurement

Drug concentrations were measured by reverse-phase high-performance liquid chromatography, after liquid–liquid extraction of plasma samples, using ultraviolet absorption detection. The assay was linear over the concentration range 5–2000 ng mL^{-1} and the limit of quantification was 5 ng mL^{-1}. The coefficient of variation for replicate samples was less than 9% over the working range of the assay. The accuracy, determined from control samples, was consistently less than $\pm$ 5% of the nominal value.

The measurement of platelet aggregation ex-vivo was carried out as follows. Blood samples were taken before (pre-dose) and at various times post dose and platelet rich plasma (PRP) was prepared from these samples. Platelet aggregation was measured in these samples by adding various concentrations of PAF (0.01, 0.10 and 1.00 μM) to induce aggregation, which was then measured by an aggregometer. The responses were normalized using the aggregation to a supramaximal concentration of ADP (20 μM), whose action is unaffected by PAF antagonists. The inhibition of platelet aggregation was calculated as follows:

$$\text{Inhibition}(\%) = 100 \times [(\text{agg.count}_{\text{predose}} - \text{agg.count}_{\text{current}})/\text{agg.count}_{\text{predose}}] \quad (1)$$

Data analysis

The population analyses were performed with a program developed for population analysis based on an EM algorithm (Dempster et al 1977; Laird 1982; Laird & Ware 1982; Lindstrom & Bates 1990), which has been successfully used previously for population analyses (Aarons 1993).

Based on the results of individual data fittings (weighted nonlinear least squares), a bi-exponential model with first-order absorption was used for the pharmacokinetic analyses. After suitable transformation, the model provided estimates of clearance (CL), initial volume (V_1), distributional clearance (CL_d) and volume of distribution at steady state (Vss).

Preliminary analysis revealed that the PAF inhibition response data were best fitted by an E_{max} model (equation 2).

$$E(C) = (E_{max} \times C)/(C50 + C) \quad (2)$$

where E_{max} is the maximum response, E is the predicted effect, C the drug concentration and C50 is the concentration producing 50% of the maximum effect. Observed response (% inhibition) was plotted against observed response and also predicted plasma concentrations for each individual to check for hysteresis. No hysteresis was apparent, which was not surprising given that the drug acts at the platelet PAF receptor. An inhibitory model (equation 3) was also used to model the aggregation count data.

$$E(C) = (E_0 \times C50)/(C50 + C) \quad (3)$$

where E_0 is the baseline drug effect. The individual parameters in these models were assumed to arise from a distribution,

either normal or lognormal, characterized by a population mean and inter-individual variance (e.g. equation 4).

$$C50 = \overline{C}\ 50 + \eta_{C50} \quad (4)$$

Where $\overline{C}$ 50 is the population mean and η_{C50} is the difference between the population mean and the individual value for the jth subject, C50. The interindividual error, η_{C50}, was assumed to follow a normal distribution with mean zero and variance σ^2_{C50}. The pharmacodynamic parameters were modelled as independently normally distributed parameters (as shown in equation 4), whereas the pharmacokinetic parameters were modelled as independently distributed parameters with a lognormal distribution (equation 5).

$$CL_j = \overline{CL}\ \exp(\eta_{CL_j}) \quad (5)$$

Preliminary analyses suggested that the residual departure of the pharmacodynamic model from the observations was best described by an additive error model, so that the effect–concentration profile in the jth subject could be described by equation 6.

$$E_{ij}(C) = f(p_j, t_{ij}) + \varepsilon_{ij} \quad (6)$$

where p_j are the pharmacodynamic parameters of the jth subject, t_{ij} is the time of the ith measurement, f represents the predicted effect (equation 2 or 3) and ε_{ij} is the residual error, which was assumed to follow a normal distribution with a mean of zero and variance of $\sigma^2\xi$. It was found that the residual variability in the pharmacokinetic analyses was better described by a lognormal distribution. The plasma concentration–time profile for the jth subject could thus be described by the following relationship:

$$\ln(C_{ij}(t)) = \ln(f(p_j, t_{ij})) + \varepsilon_{ij} \quad (7)$$

where the terms are similar to equation 6 but f now represents the predicted plasma concentration. The pharmacokinetic data were modelled separately from the PAF response data and the individual posterior pharmacokinetic parameters generated from the population analysis were used to define the concentration, C, in equations 2 and 3. Response data of 100% inhibition, which corresponded to measurements below the limit of determination, were omitted.

Comparisons between different models and weighting schemes were made by examining the predicted fits, residual plots (such as absolute standardized residuals versus model predicted values) and correlations between the parameters. In the case of mixed-effects modelling, model selection was also based on differences in the objective function.

Results and Discussion

Pharmacokinetic modelling

The pharmacokinetic model was initially developed using the data from study PH1 and was subsequently used with the data from the multiple dose study, PH2. As the bioavailability (F) is unknown, all parameters estimated were assumed to be scaled by F.

Plasma data from study PH1

Visually, the plasma profiles showed bi-exponential decay and a preliminary analysis showed that the data were best described by a two-compartment model with first-order absorption, including a time lag between the dose being given and drug appearing in the plasma. Plots of the data from each individual in study PH1 for the three doses (160, 320, 480 mg) indicated that there was a nonlinear increase in plasma levels as the dose administered increased (Figure 1). Analyses were performed on the 160, 320 and 480 mg doses separately and also together, with separate population estimates for clearance of the three dose groups in the combined analyses. Estimates of parameters from this last analysis are shown in Table 1.

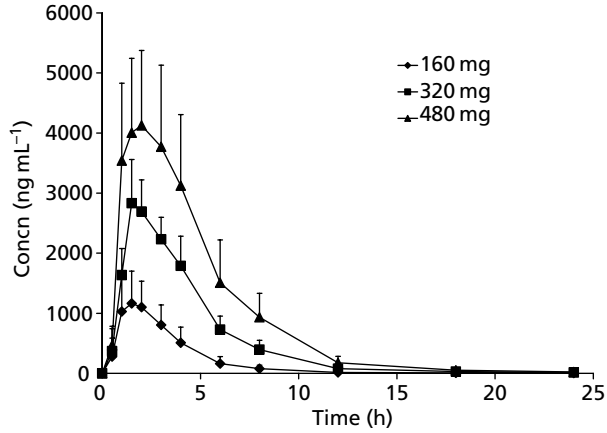

Figure 1 Mean concentration–time profiles from study PH1 for 160, 320 and 480 mg doses. Error bars are +1 s.d.

Table 1 Combined population analysis of plasma data from study PH1 (single doses of 160, 320 and 480 mg). Bi-exponential model with first-order absorption and time lag

Parameter	Population mean	Interindividual variability	
	Estimate (s.e.)	Estimate	%CV[a] in population
CL(L h^{-1}) 160 mg dose	46.0 (9.9)	0.203	45%
CL(L h^{-1}) 320 mg dose	30.8 (6.6)		
CL(L h^{-1}) 480 mg dose	27.1 (5.8)		
V_1 (L)	29.7 (6.1)	0.284	53%
V_{ss} (L)	57.3 (11.6)	0.177	42%
CL_d (L h^{-1})	1.88 (0.27)	0.131	36%
k_a (h^{-1})	0.519 (0.037)		
T_{lag} (h)	0.423 (0.011)		
Intra-individual variance	0.078		

[a]%CV calculated as square root of inter-individual variance term (multiplicative errors).

Clearance decreased as the dose increased: 46.0, 30.8 and 27.1 L h^{-1} for the 160, 320 and 480 mg doses, respectively. As the primary aim of the analyses was to model the pharmacodynamic data, more sophisticated nonlinear pharmacokinetic models (e.g. involving Michaelis–Menten elimination) were not tested as the model that was used for the plasma concentration modelling was adequate for the purpose of predicting the concentrations for the pharmacodynamic model. There was a small time lag between the time the dose was administered and appearance of drug in the blood.

Plasma data from study PH2

Single-dose (first dose on day 1) and multiple-dose (last dose on day 15) data from study PH2 were analysed with the pharmacokinetic model described above, which provided good population and individual fits to the data. Figure 2 shows the population fit from the last dose data. Results from the population analysis with the bi-exponential model with first-order absorption and time lag are given in Table 2. Of the two estimates of clearance from study PH2, the last dose estimate (48 L h^{-1}) was closer to the estimate from the 160 mg single dose in study PH1 (46 L h^{-1}). The differences between the estimates from the single-dose and multiple-dose analyses of study PH2 (and between the single dose in study PH2 and the 160 mg dose in study PH1) may be due to incomplete characterization of the two-compartmental model with the single-dose data from study PH2, since the samples were only taken up to 12 h post dose. Also the s.e. values for the parameters from the first-dose data are higher than those from day 15, indicating that it was more difficult to characterize the parameters of the bi-exponential model with the first-dose data.

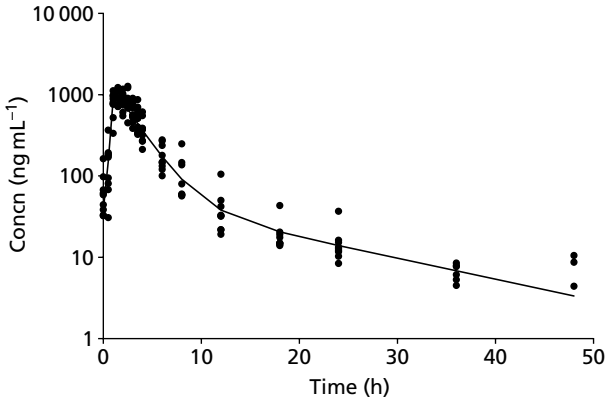

Figure 2 Study PH2 plasma data. Population fit of last dose (day 15) using a biexponential model with first-order absorption.

Pharmacodynamic modelling

As before, the model was developed with the data from study PH1 and subsequently used for analysis of the data from study PH2.

PAF response data from PH1

An E_{max} model (equation 2) was fitted to the data using the individual predicted plasma concentrations from the pharmacokinetic modelling. E_{max} was not significantly different to 100% and was subsequently fixed to this value. Also, a sigmoid E_{max} model did not significantly improve the fit. The complete response data set for all three doses and PAF concentrations was fitted in a combined analysis. The data were also fitted grouped into separate PAF concentrations for the three doses (referred to as separate PAF analyses) and with the data grouped into separate doses for the three PAF concentrations (referred to as separate dose analyses). Results from the combined population analysis are given in Table 3.

Investigation of the individual C50 parameter estimates generated from the combined analysis showed that there was a decrease in C50 values with increasing dose. Individual estimates from the 480-mg-dose data were

Table 2 Population analysis of plasma data from 160 mg dose study PH2 – single dose (day 1) and multiple dose (day 15). Bi-exponential model with first-order absorption and time lag

Parameters	First dose (day 1)			Last dose (day 15)		
	Population mean	Interindividual variability		Population mean	Interindividual variability	
	Estimate (s.e.)	Estimate	%CV[a] in population	Estimate (s.e.)	Estimate	%CV[a] in population
CL(L h^{-1})	70.6 (17.9)	0.117	34%	48.1 (5.0)	0.054	23%
V_1 (L)	28.4 (26.6)	2.372	154%	20.2 (9.1)	0.739	86%
V_{ss} (L)	114.2 (424.7)	0.010	10%	116.6 (20.9)	0.118	34%
CL_d (L h^{-1})	6.13 (7.51)	0.003	5.5%	6.52 (1.59)	0.162	40%
k_a (h^{-1})	0.618 (0.103)			0.436 (0.03)		
T_{lag} (h)	0.435 (0.021)			0.465 (0.01)		
	Intra-individual variance	0.035		Intra-individual variance	0.035	

[a]%CV calculated as square root of inter-individual variance term (multiplicative errors).

Table 3 Analysis of PAF % inhibition data. E_{max} model with combined data

Parameter (s.e.)	C50 (ng mL^{-1})	17.6 (2.74)
Inter-individual variability (%CV[a])	C50	328.7 (103%)
Intra-individual variability		388.1

[a]The coefficient of variation (%CV) for a population parameter is calculated as square root of the interindividual variance term for that parameter divided by the parameter estimate.

consistently lower than those from the lower doses, and similarly for the estimates from the 320 mg dose data compared with the 160 mg dose data. Also the individual parameter estimates from the 0.01 μM PAF concentration data were higher than for both the 0.1 μM and 1.0 μM PAF concentrations, for all doses. These trends were also evident in the separate PAF and dose analyses.

The results from the separate dose analyses showed a decrease in the C50 estimates as the dose increased with values of 41.5, 21.1 and 11.6 ng mL^{-1} for the 160, 320 and 480 mg doses, respectively. The lower individual C50 estimates from the 480 mg dose data, and to a lesser extent the 320 mg dose data, are likely to be an artefact of the data analysis since there are very few, if any, concentrations below C50 for these doses. The estimated inter-individual variability on the population estimate of C50 in the 480 mg dose data analysis was relatively low in comparison with the other estimates. Again, this may be a reflection of the lack of data points in this data set at or below 50% inhibition.

For the separate PAF analyses, the population predicted C50 values for the 0.1 μM and 1.00 μM PAF data were similar (10.6 and 11.9 ng mL^{-1}, respectively) whereas for 0.01 μM PAF the estimate was considerably higher at 36.6 ng mL^{-1}. The lower population estimates of C50 for the 0.10 and 1.00 μM PAF data were probably influenced to some extent by the 480 mg (and possibly 320 mg) data. This was verified in the PH2 analyses (see below). The individual estimates of C50 from the combined analysis for the 0.01 μM PAF data were higher than for the other PAF concentrations. However, it seems unlikely that this is a real difference since there is no known pharmacological basis for it and there were no such differences apparent when the aggregation count data (see below) were modelled with an inhibitory E_{max} model (equation 3). One possible reason for this is that there was noticeably more variation in the inhibition values with this particular data set, with a higher proportion of negative inhibitions (relative to baseline) than the others. Results from similar analyses for response data from study PH2 (see below) also corroborate this as all three PAF concentrations gave very similar estimates for C50.

Results from the 320 mg separate dose analysis are shown in Figures 3 and 4. Figure 3 shows the mean observed and predicted response time profiles and the corresponding population fit of the concentration–response data is shown in Figure 4. Individual fits generated from the individual parameter estimates were generally in good agreement with the observed data.

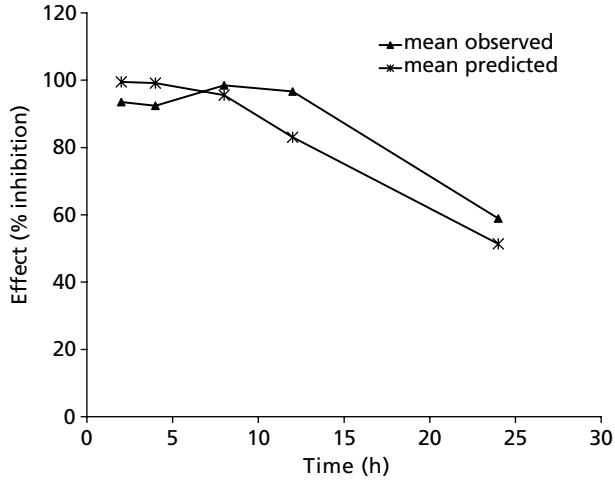

Figure 3 Study PH1. PAF % inhibition response data. Mean response with time from population fit with E_{max} model to 320 mg data.

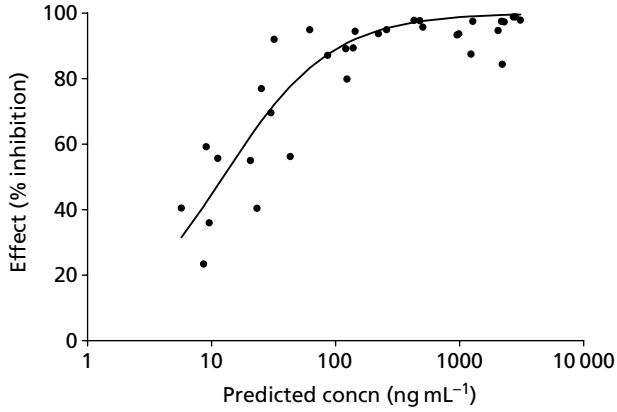

Figure 4 Study PH1. PAF % inhibition response data. Predicted population fit with E_{max} model to 320 mg dose data.

The weighted residuals for all the above analyses showed higher variability at lower inhibition (when the aggregation count is higher) and also a trend for the model to over-predict the inhibition at higher plasma concentrations. To try and overcome this difficulty, the aggregation count data were analysed with an inhibitory model (equation 3). The data were analysed as before, with a combined analysis of all the data as well as separate dose and separate PAF concentration analyses. Additive errors were used for the inter- and intra-individual variabilities. Zero data (no aggregation count) were excluded.

The results from the combined analysis with the inhibitory model are given in Table 4. The population estimate of C50 (16.4 ng mL^{-1}) was close to that from the comparable E_{max} model analysis (17.6 ng mL^{-1}) and the individual C50 parameter estimates were again lower at the higher dose. In contrast to the previous E_{max} model analyses, the individual C50 estimates showed no real

Table 4 Study PH1. Analysis of aggregation count data. Inhibitory model with combined data

Parameter (s.e.)	C50 (ng mL^{-1})	16.4 (3.1)
	E_0 (agg. count)	46.3 (2.7)
Inter-individual variability (%CV)	C50	331.9 (111%)
	E_0	378.6 (42%)
Intra-individual variability		133.2

Table 5 Study PH2. Combined analyses (all PAF concentrations) of PAF % inhibition data for 160 mg dose. E_{max} model

		First dose	Last dose
Parameter (s.e.)	C50 (ng mL^{-1})	31.43 (4.98)	24.90 (4.48)
Inter-individual variability (%CV)	C50	672.9 (83%)	381.5 (78%)
Intra-individual variability		328.5	339.8

difference between the different PAF concentrations: the population estimates of C50 from the separate PAF analyses were similar for the 0.10 and 1.00 μM data sets (12.2 and 14.4 ng mL^{-1}, respectively) to those estimated by the E_{max} model; the 0.01 μM data set estimate (17.3 ng mL^{-1}) was lower than that estimated by the E_{max} model and closer to the other PAF analyses. The population C50 estimates from the separate dose analyses followed the same pattern as the E_{max} model, with estimates becoming lower as the dose increased (23.1, 14.4 and 5.4 ng mL^{-1} for 160, 320, 480 mg doses, respectively). The differences between the estimates were less marked with this model.

The weighted residuals of these analyses with the inhibitory model showed the same distribution as before, with wide variability at the higher predicted effect (aggregation count) and a trend to under-predict at the lower values. There were no obvious solutions to the choice of error model that would help explain these weighted residuals – a multiplicative error model would reduce the wide variability seen at the higher values but would not affect the trend in the residuals at the lower values. As the E_{max} model fitting with an additive error model produced good population and individual fits, this was considered an adequate model to continue to use with the PH2 data.

PAF response data from study PH2

Inhibition data from the first and last doses given in study PH2 were modelled with the E_{max} model with additive errors that was used for the PH1 data. Initially the three PAF concentration data sets were modelled separately, but as the population estimates of C50 were very similar for each of the PAF concentrations, the data sets were combined for subsequent analyses. These results confirm that the higher doses (especially 480 mg) were influencing the population estimates of C50 in the 0.1 μM and 1.0 μM separate PAF analyses for study PH1. Results from the combined analyses are shown in Table 5. The weighted residuals from the population fits exhibited the same pattern as was seen for the PH1 data set.

There was very little difference in the individual estimates of C50 between the different PAF concentrations for both the single- and multiple-dose conditions. This confirms, together with the results from the corresponding inhibition model analysis, that the individual C50 estimates from the combined analysis of the PH1 data with the E_{max} model were unusually high. It can be seen from Table 5 that the population estimates of C50 for the single- and multiple-dose analyses were fairly close – 31.4 and 24.9 ng mL^{-1}, respectively. Figure 5 shows the population fit from the last-dose data.

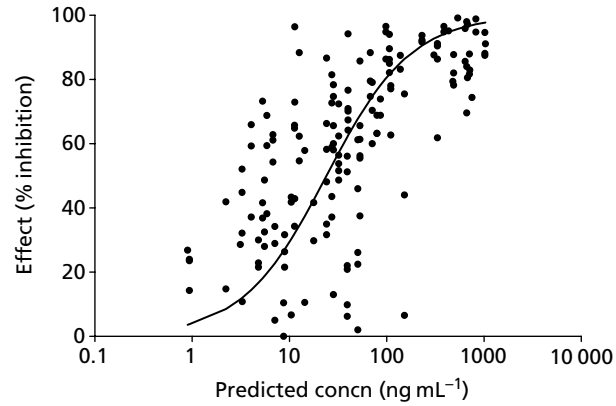

Figure 5 Study PH2. PAF % inhibition response data. Population predicted fit from last dose data with E_{max} model.

Overall, although the weighted residuals indicated a problem with the error model, the E_{max} model provided a good fit to all the data. The population C50 estimate from the inhibition model analysis of the 160 mg dose data of study PH1 (23.1 ng mL^{-1}) was in agreement with those from the single- and multiple-dose data (160 mg) of study PH2. The corresponding population C50 estimate from study PH1 with the E_{max} model was higher (41.5 ng mL^{-1}), but this result was probably influenced by the 0.01 μM inhibition data.

Predicted response to 320 mg (multiple dosing)

Of the three PAF concentrations used in the studies (0.01, 0.10 and 1.00 μM) the 0.10 μM was considered to be the closest to the actual concentration found in the nasal mucosa (Pfizer 1994). Of the three doses investigated in study PH1, 320 mg is considered to be the most likely to be used in subsequent studies as the therapeutic dose.

As the 320 mg dose is of the most interest for subsequent studies, the response to multiple dosing with 320 mg twice daily was predicted with the E_{max} model. The pharmacokinetic parameters and their corresponding inter-individual variances required to predict the plasma drug concentrations were taken from the results of the pharmacokinetic analysis of the 320 mg single-dose data in study PH1 (Table 1). These were then used with a multiple-dose pharmacokinetic model (bi-exponential model with

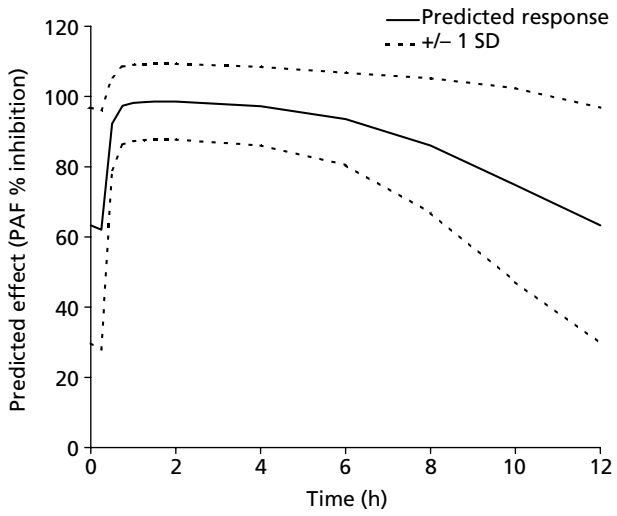

Figure 6 Population predicted response (over one dosing interval) to multiple doses of 320 mg (twice daily) with E_{max} model.

first-order absorption and time lag) previously used with data from study PH2. The values used for C50 and its inter-individual variance were taken from the results of modelling the 320 mg single dose PAF response data from study PH1 with the E_{max} model (Table 4).

The predicted population response for one dosing interval of 12 h is depicted in Figure 6. It can be seen that there is a high percentage inhibition over a large proportion of the dosing interval. The upper prediction is over 100%, which is not possible (see equation 2). This is due to using an additive error model in the analysis, which was suitable for fitting the observed data but is inappropriate for predicting such intervals.

Conclusion

In conclusion, the pharmacokinetics and pharmacodynamics of Phase I studies of a new drug for hay fever have been successfully modelled using a population approach. Good population and individual parameter estimates were generated from the analyses and the model has the potential for use in sparse data analyses in later studies. The use of a mixed-effects modelling approach was invaluable in combining studies and rationalizing apparent differences in parameters when studies were analysed separately.

References

Aarons, L. (1993) The estimation of population pharmacokinetic parameters using an EM algorithm. *Comp. Meth. Prog. Biomed.* **41**: 9–16

Aarons, L., Mandema, J. W., Danhof, M. (1991) A population analysis of the pharmacokinetics and pharmacodynamics of midazolam in the rat. *J. Pharmacokinet. Biopharm.* **19**: 485–496

Beal, S. L., Sheiner, L. B. (1979–1989) *NONMEM users guides, parts I–VI.* NONMEM Project Group, University of California, San Francisco

Bruno, R., Iliadis, M. C., Lacarelle, B., Cosson, V., Mandema, J. W., Le Roux, Y., Montay, G., Durand, A., Ballereau, M., Alasia, M. (1992) Evaluation of Bayesian estimation in comparison to NONMEM for population pharmacokinetic data analysis: application to pefloxacin in intensive care unit patients. *J. Pharmacokinet. Biopharm.* **20**: 653–669

Davidian, M., Gallant, A. R. (1992) Smooth nonparametric maximum likelihood estimation for population pharmacokinetics, with application to quinidine. *J. Pharmacokinet. Biopharm.* **20**: 529–556

Dempster, A. P., Laird, N. M., Rubin, D. B. (1977) Maximum likelihood from incomplete data via the EM algorithm. *J. R. Stat. Soc.* **39**: 1–38

Halpern, B. N. (1942) Les antihistaminiques de synthèse. Essai de chimiothérapie des états allergiques. *Arch. Int. Pharmacodyn. Ther.* **68**: 339–408

Hashimoto, Y., Sheiner, L. B. (1991) Designs for population pharmacodynamics: value of pharmacokinetic data and population analysis. *J. Pharmacokinet. Biopharm.* **19**: 333–353

Heykants, J. J. P., Snoeck, E., Awouters, F., Van Peer, A. (1992) Chapter 18: antihistamines. In: van Boxtel, C. J., Holford, N. H. G., Danhof, M. (eds) *The in vivo study of drug action.* Elsevier Science Publishers, BV

Holford, N. H. G., Peace, K. E. (1992a) Methodological aspects of a population pharmacodynamic model for cognitive effects in Alzheimer patients treated with tacrine. *Proc. Natl. Acad. Sci. USA* **89**: 11 466–11 470

Holford, N. H. G., Peace, K. E. (1992b) Results and validation of a population pharmacodynamic model for cognitive effects in Alzheimer patients treated with tacrine. *Proc. Natl. Acad. Sci. USA* **89**: 11 471–11 475

Holford, N. H. G., Sheiner, L. B. (1982) Kinetics of pharmacological response. *Pharmacol. Ther.* **16**: 143–166

Laird, N. M. (1982) Computation of variance components using the EM-algorithm. *J. Statist. Comput. Simulation* **14**: 295–303

Laird, N. M., Ware, J. H. (1982) Random-effects models for longitudinal data. *Biometrics* **38**: 963–974

Lindstrom, M. J., Bates, D. M. (1990) Nonlinear mixed effects models for repeated measures data. *Biometrics* **46**: 673–687

Mandema, J. W., Danhof, M. (1990) Pharmacokinetic-pharmacodynamic modelling of the central nervous system effects of heptabarbital using a periodic EEG analysis. *J. Pharmacokinet. Biopharm.* **18**: 459–481

Pfizer Central Research (1994) UK-112,214 *Investigator's brochure*, Sandwich

Racine-Poon, A. (1992) A Bayesian approach to the prediction of the plasma concentration range of carbamazepine in epileptic patients. In: Rowland, M., Aarons, L. (eds) *New strategies in drug development and clinical evaluation: the population approach.* CEC (Commission of the European Communities), Geneva

Rowland, M., Aarons, L. (eds) (1992) New strategies in drug development and clinical evaluation: the population approach. CEC (Commission of the European Communities), Geneva

Sheiner, L. B. (1984) The population approach to pharmacokinetic data analysis: rationale and standard data analysis methods. *Drug Metab. Rev.* **15**: 153–171

Wald, J. A., Law, R. M., Ludwig, E. A., Sloan, R. R., Middleton, E., Jusko, W. J. (1992) Evaluation of dose-related pharmacokinetics and pharmacodynamics of prednisolone in man. *J. Pharmacokinet. Biopharm.* **20**: 567–589