A Pharmacokinetic Model for Tenidap in Normal Volunteers and Rheumatoid Arthritis Patients

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Purpose. To develop a pharmacokinetic model for tenidap and to identify important relationships between the pharmacokinetic parameters and available covariates.

Methods. Plasma concentration data from several phase I and phase II studies were used to develop a pharmacokinetic model for tenidap, a novel anti-rheumatic drug. An appropriate pharmacokinetic model was selected on the basis of individual nonlinear regression analyses and an EM algorithm was used to perform a nonlinear mixed-effects analysis. Scatter plots of posterior individual pharmacokinetic parameters were used to identify possible covariate effects.

Results. Predicted responses were in good agreement with the observed data. A bi-exponential model with zero order absorption was subsequently used to develop the mixed-effects model. Covariate relationships selected on the basis of differences in the objective function, although statistically significant, were not particularly strong.

Conclusions. The pharmacokinetics of tenidap can be described by a bi-exponential model with zero order absorption. Based on differences in the log-likelihood, significant covariate-parameter relationships were identified between smoking and CL, and between gender and Vss and CL_d. Simulated sparse data analyses indicated that the model would be robust for the analysis of sparse data generated in observational studies.

KEY WORDS: tenidap; pharmacokinetics; EM algorithm; nonlinear mixed-effects modelling; covariates.

INTRODUCTION

In the course of a drug's development, pharmacokinetic studies are initially performed on small, well controlled, homogeneous groups of volunteers. Experimental data from these studies can be used to define the pharmacokinetic and pharmacodynamic models by modelling each individual separately. However, there are problems extrapolating these results to later studies which are carried out on large, heterogeneous groups of patients who are likely to be prescribed the drug therapeutically, as the pharmacokinetics and pharmacodynamics could be very different. Furthermore, as these later studies are generally observational with only a few samples per individual, classical pharmacokinetic analysis techniques of modelling each individual separately cannot be applied to such sparse data. Instead, the population approach can be used to analyse data from these patient groups. The general aim of this type of data analysis is to assess the central tendency of drug response in a population, and also to quantify the variability around it. Sub-groups within the population can be identified and factors affecting drug response, such as age and weight, can be used to account for some of the variability.

Tenidap is a novel anti-rheumatic drug which combines some of the properties of non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti-rheumatic drugs (DMARDs) (1). It has been shown to be as effective as NSAID/DMARD combination therapies such as hydroxychloroquine and piroxicam (2) without exhibiting typical DMARD side-effects, which can be severe (3).

The purpose of the present report was to describe the development of a pharmacokinetic model for tenidap from rich data which could then be applied to sparse data. Individual nonlinear regression and nonlinear mixed-effects analyses of rich phase I and II data were used to develop the structural and variance models of a population model. Individual nonlinear regression was performed on the phase I data to define the basic pharmacokinetic model. The nonlinear mixed-effects analyses of the phase I and phase II data was used to develop the pharmacostatistical model. The phase II studies were carried out on a more heterogeneous patient population, with covariates, such as age and albumin levels, varying across the population. Plots of individual pharmacokinetic parameter estimates against each covariate were examined for noticeable trends and covariate-parameter relationships were also tested in the population model. The robustness of the developed model was investigated by analysing sparse data sets generated from the phase II data.

METHODS

Data

The plasma data from four tenidap studies were used—two from phase I (4) and two from phase II (5) of the drug's development. Descriptions of these studies are given below. In all cases approval was obtained from local ethics committees and subjects gave their informed, written consent to participate in the studies. Details of the assay used are given in (6). The limit of quantification of the assay was 0.5 mg/L and the precision of the assay over the linear dynamic range was better than 17%.

Study 1 (Phase I)

This study was performed on ten healthy male volunteers who received single and multiple oral doses of tenidap (120 mg). Doses were administered on day 1 (single dose) and then on days 7 (dose 1) through 20 (dose 14). Blood samples were taken pre-dose and frequently post-dose (up to 144 hours after dosing) on days 1 and 20. Measurable drug concentrations in the plasma were found up to 96 hours post dose. There were a total of 110 data points for the single dose data set and 120 data points in the multiple dose data set. Classical pharmacokinetic analyses indicated that the accumulation of the drug after multiple dosing was less than predicted from single dose (AUC decreased by an average of 28%).

Study 2 (Phase I)

Thirteen healthy male volunteers received single and multiple doses to study the absorption, protein binding, clearance

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and absolute bioavailability of tenidap. Subjects received a single 120 mg oral dose and a 20 mg iv infusion of deuterated tenidap on day 1. This was followed by a six day wash-out period and then further daily doses (120 mg) for 21 days with an additional 20 mg *iv* infusion of deuterated tenidap on the last day. Data from twelve subjects were available for pharmacokinetic analysis. Blood samples were taken pre-dose and frequently post-dose on the first and last days (25 samples taken per subject on the two days) for the determination of plasma concentrations of deuterated and non-deuterated tenidap. Steady-state was achieved by the eleventh day of dosing. The systemic clearance of deuterated tenidap was 29% greater on day 28 than on day 1, indicating a significant increase in intrinsic clearance (CL_{int}), since protein binding of tenidap in plasma did not change. Consistent with this increase, the ratio of AUC_{0-24} (day 28)/AUC_{0-inf} (day 1) was less than one (0.72). The increase in CL_{int} suggests that tenidap may induce its own metabolism since it is subject to extensive hepatic metabolism. Absolute bioavailability (single and multiple dose) was calculated as 85%. Individual nonlinear regression was performed on the data and also individual absorption rates were calculated using deconvolution techniques.

Study 3 (Phase II)

The purpose of this study was to assess the effects of age and gender on the pharmacokinetics of tenidap after a single dose (120 mg) to eighty patients with rheumatoid arthritis. The patients were grouped according to age and gender so that sixteen (eight male, eight female) patients were included in each of the following groups: <45, 46–55, 56–65, 66–75 and >75 years of age. Blood samples were collected at pre-dose and frequently post-dose (up to 120 hr). There were a total of 880 data points in the final data file. Standard pharmacokinetic analyses showed that neither age nor gender significantly influenced AUC, C_{max} or elimination half-life.

Study 4 (Phase II)

The purpose of this study was to assess the effects of age and gender on the pharmacokinetics of tenidap after a single dose (120 mg) to sixty-five patients with osteoarthritis. The patients were again grouped according to age and gender so that approximately eight patients of each sex were included in each of the following groups: 45–55, 56–65, 66–75 and >75 years of age. The same blood sampling schedule as study 3 was employed. There were a total of 713 data points in the final data file. Classical pharmacokinetic analyses showed that there were no significant changes due to age or gender in the drug's disposition or absorption, although a significantly lower C_{max} was associated with larger body weight.

Tenidap was found to be highly bound to albumin in plasma (approximately 99%) and the fraction unbound was not influenced by plasma concentration, gender or age. For the two phase II studies (3 and 4) the following covariates were provided for each patient: age, weight, height, gender, serum creatinine concentration, albumin levels in plasma, race, alcohol consumption (number of drinks per week) and whether or not the patients smoked (supplied as a categorical variable, 0-nonsmokers, 1-smokers). The race covariate data were discarded as inadequate for covariate analysis because only 4 patients (in total from both the studies) were non-white. Albumin levels or serum creatinine concentrations were missing for some patients: for these the mean value was assumed.

Data Analysis

Individual nonlinear regression was performed on the data using weighted nonlinear least squares (7). Nonlinear mixed-effects modelling was performed with an implementation of the nonlinear EM-algorithm (8). The Loo-Riegelman two-compartmental method (9) was applied to the iv and oral data from study 2 in order to estimate the absorption profile. Based on results from the individual data fitting, a bi-exponential model with zero-order absorption was used for the mixed-effects analyses. The bioavailability of tenidap is high, and so it was assumed that all the drug is absorbed (F = 1). Zero order absorption assumes a constant rate of input of drug, R_0, as the input function over time, T_{inf} (R_0 = dose/T_{inf}). The model was parameterized in terms of clearance (CL), initial volume (V_1), distributional clearance (CL_d), volume of distribution at steady state (Vss) and T_{inf}. The parameters of the mixed-effects model arise from a distribution characterised by a population mean and interindividual variance. Preliminary analyses suggested that the pharmacokinetic parameters were best described by a lognormal distribution, for example:

$$CL_j = \overline{CL} \cdot \exp(\eta_{CLj}) \quad (1)$$

where $\overline{CL}$ is the population mean clearance and η_{CL} is the difference between the population (log) mean and the individual (log) parameter. It was found that the residual departure of the pharmacokinetic model from the observations was best described by a log-normal error model, so that the plasma concentration - time profile for the j^{th} subject could be described by the following relationship:

$$\ln(C_{ij}(t)) = \ln(f(\ln(p_j), t_{ij})) + \varepsilon_{ij} \quad (2)$$

where p_j are the pharmacokinetic parameters of the j^{th} subject, t_{ij} is the time of the i^{th} measurement, f represents the predicted plasma concentration and ε_{ij} is the residual error which is assumed to follow a normal distribution with mean of zero and variance of σ^2_ε.

The full statistical model is shown below (Eq. 3):

$$\ln(C_{ij}(t)) = \ln(f(\ln(\overline{p_j}), t_{ij})) + \sum_k \left[\frac{\partial \ln f}{\partial p_k}\right] \cdot \eta_{kj} + \varepsilon_{ij} \quad (3)$$

where there is a separate term for each of the pharmacokinetic parameters CL, V_1, Vss and CL_d (k = 1..4), indicating that each parameter contributes to the interindividual error.

Comparisons between the different models and weighting schemes were drawn 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

Individual Nonlinear Regression

Phase I Data—Study 1

Analyses showed that a weighting scheme of $1/y^2_{calc}$ gave the best fit to the data. The elimination of the drug was biphasic,

Table I. Mean Parameter Estimates from Individual Nonlinear Regression on Phase I Data (Study 1)

Parameter	CL(L/hr)	V_1(L)	Vss(L)	CL_d(L/hr)	T_{inf}(hr)	T_{lag}
Single dose						
mean	0.42	4.34	7.18	0.70	2.39	0.38
sd	0.11	1.02	1.67	0.47	1.33	0.15
Multiple dose						
mean	0.67	6.47	8.91	0.53	1.88	0.55
sd	0.18	1.49	1.27	0.72	0.92	0.11

thus requiring a bi-exponential pharmacokinetic model. However, the absorption model was less obvious and there was a small time lag present which was more evident after multiple dosing. Absorption models for zero order, first order and Weibull distribution functions were implemented. The Weibull function is an exponential-type model which has been used previously to describe absorption kinetics (10). It can be viewed as a more general form of first-order kinetics with greater flexibility due to the inclusion of a 'shape' parameter.

Generally, the first-order model failed to fit the peak of the individual profiles. Although a few individuals were fitted very accurately using the Weibull distribution model, it was no better overall than the first order model when considering all the individual data sets. Furthermore, even with more parameters, it gave inferior fits to the zero order model. Mean parameter estimates from the zero-order model for both the single and multiple dose data are given in Table I. Figure 1 shows an example of an individual fit.

The estimated clearance values increased from single to multiple dosing for each individual, leading to more rapid elimination because of the associated decrease in the elimination half-life. This is consistent with the decreased AUC after multiple dosing (study 2). It can be seen from Table I that the mean values of CL, Vss and V_1 increased following multiple dosing. There was wide variability in the CL_d estimates, especially following multiple dosing. A time lag was not present for all individuals.

Phase I Data—Study 2

Analysis of the iv data with a bi-exponential model gave low individual estimates of V_1 (mean 3.90 L), confirming the low estimates seen already in the individual analyses from study 1. For half the subjects, the absorption was clearly a zero-order process (plot of percentage of drug unabsorbed against time was linear—see Fig. 2). For the other subjects, the absorption profiles appeared more complicated. One interpretation is that there was an initial (zero order) fast absorption phase, followed by a slower, undefined phase. In half of these subjects, this second phase only appeared after >75% of the drug had been absorbed. These results confirmed that the zero-order input model was more representative of the absorption of the drug. A model combining two phases of absorption, for example zero order and first order input, might provide a more accurate description of the data. However, this would increase the complexity of the model and the number of parameters to be estimated. The zero-order rates which were calculated from the percent unabsorbed plots were in good agreement with the population estimate (see next section). There was no apparent link between individually calculated bioavailabilities (mean value 91% from single dose data) and the parameters of the absorption profiles.

Mixed-Effects Modeling

Phase I

Different error models were investigated with the combined single and multiple dose data from study 1. Additive residual errors were only investigated for the zero order model as the residual plots from this analysis quite clearly showed that the errors were multiplicative (as was seen in the individual fits). The best fit was achieved when the four pharmacokinetic

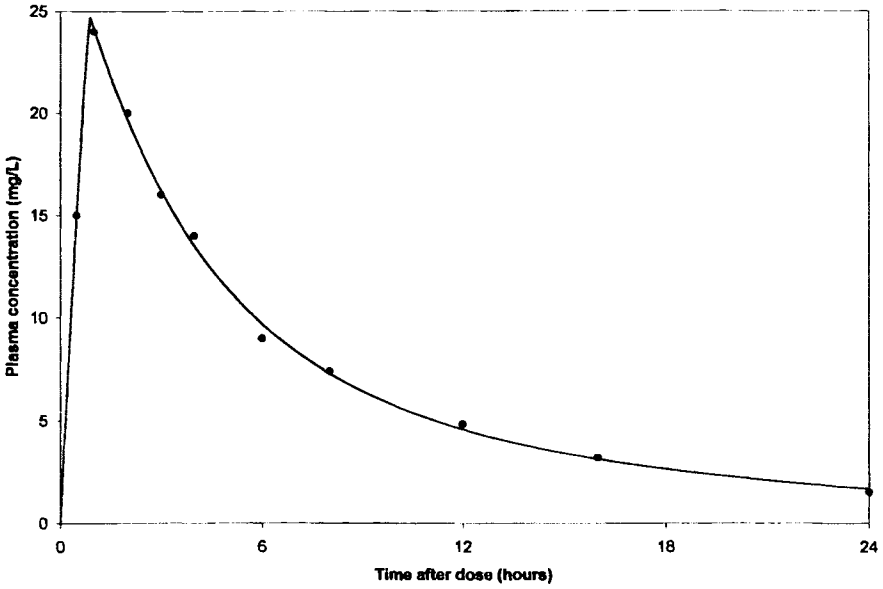

Fig. 1. Phase I (study 1) single dose plasma data: individual nonlinear regression (subject 6) using a bi-exponential model with zero order input.

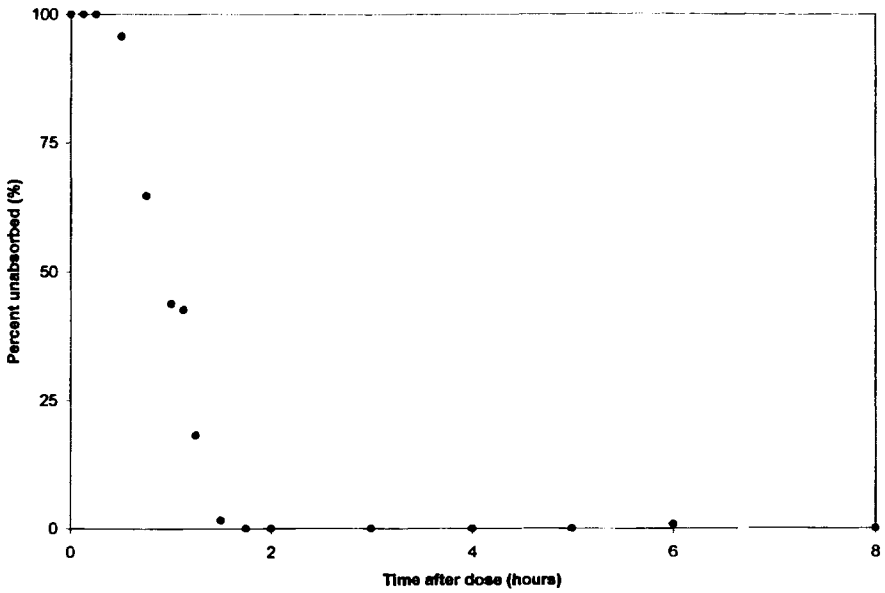

Fig. 2. Phase I (study 2) single dose data. Plot of percent unabsorbed drug after oral dosing (subject 3).

parameters CL, V_1, Vss and CL_d contributed to the interindividual error and the residual variability was multiplicative. Although a small time lag in absorption was seen in the individual fitting, including this delay in absorption into the model had no influence on the fit or the parameter estimates. Consequently a time lag was not included in the final model. The population parameter estimates from the zero order and first order input models were similar. However, the first order model did not adequately describe the peak data, as was previously seen with the individual fits. The population fit of the bi-exponential model with zero order input for the multiple dose data is shown in Fig. 3. Parameter estimates are given in Table II.

In general all parameter estimates were higher following multiple dosing. Compared to the mean parameter values from the individual data fitting (Table I), the estimates of CL were very similar. However, the population V_1 estimates were lower, particularly following multiple dosing. The estimates of T_{inf} were also lower, in contrast to the Vss estimates which were slighter higher. The population estimate of CL_d following a single dose was close to the mean value from the individual analyses, whereas the estimate of CL_d following multiple dosing was higher. However, the mean value from the individual analyses had a high sd (135% CV).

Phase II Data

As with the phase I population analyses, including a time lag in the model had no effect on the fit or the parameter

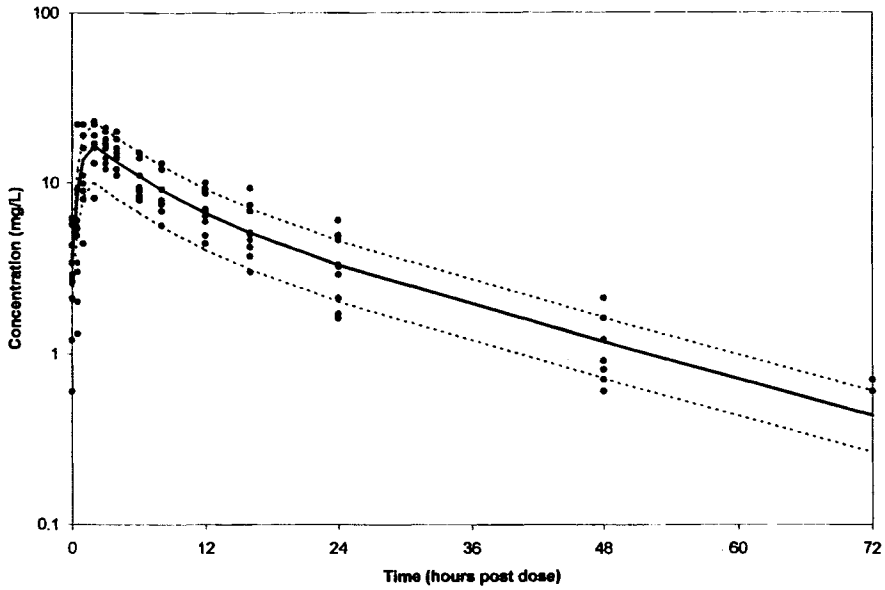

Fig. 3. Phase I (study 1). Population fit of bi-exponential model with zero order input to multiple dose data (--- indicates +/−1 sd).

Table II. Population Analyses of Phase I, Study 1 Data

Parameter	Single dose Estimate (SE)	Single dose Variance[a]	Multiple dose Estimate (SE)	Multiple dose Variance[a]
CL (L/hr)	0.43 (0.03)	0.05	0.63 (0.03)	0.05
V_1 (L)	2.87 (0.16)	0.72	3.17 (0.19)	0.49
Vss (L)	9.66 (0.62)	0.08	10.08 (0.41)	0.04
CL_d (L/hr)	0.82 (0.10)	0.05	0.94 (0.17)	0.04
T_{inf} (hr)	1.34 (0.05)		1.61 (0.36)	
Residual variance[a]	0.05		0.06	

[a] No estimate of SE is available for the variance terms.

estimates and was therefore not included in subsequent models. The best fit was again obtained when contributions from the parameters CL, V_1, Vss, and CL_d were included in the interindividual error model. As with the phase I population analyses, the zero order and first order fits gave similar population parameter estimates. It was obvious from all the population analyses that the absorption of tenidap is more complicated than can be represented by a simple first or zero order process. However, the aim of developing this model was to use it for sparse data analysis, and so keeping the model as simple as possible was important. With this view in mind and considering the results from individual nonlinear regression and deconvolution, the biexponential model with zero order input was considered to be the most appropriate model. Results from the zero order model are given in Table III. The population parameter estimates of CL, V_1 and Vss for the two data sets were in good agreement, whereas the CL_d and T_{inf} estimates were more disparate. Estimates of interindividual variability from the analysis of study 4 were generally higher than those from study 3. The variability estimates for the two data sets followed a similar pattern, with the highest variability estimated for V_1.

The data from the two studies were combined and the results of that analysis are also given in Table III. Comparing the results from this combined analysis with the results from the separate analyses, it was clear that the results were very similar to those from the study 3 analysis, with lower standard errors (SEs) of the population parameters. Estimates of interindividual variability followed the same pattern, with the highest variability again predicted for V_1. The low estimate for CL_d may indicate that the program was experiencing difficulties estimating this variance term. Residual variabilities of the phase I and II analyses were similar. Even though the phase II studies involved patients, they still were well controlled experimental studies.

The estimate of the elimination half-life calculated from population parameter estimates from the analyses of these studies was around 28 hours, in comparison to the phase I study where the estimate was lower at around 16 hours.

The individual pharmacokinetic parameter estimates generated from the combined data analysis were then used to investigate possible covariate effects.

Covariate Analysis

Individual posterior parameter estimates for CL, V_1, Vss and CL_d were generated from the population analysis. The individual estimates from the combined analysis were plotted against covariates to identify possible covariate models to be included in the population model. The covariates can be added into the model in any mathematical form (linear, exponential, hyperbolic, etc) but linear relationships were adequate for the current analyses.

The covariates from the phase II data which were tested in this way were age, weight, gender, disease state (rheumatoid arthritis (RA) or osteoarthritis (OA)), albumin levels in plasma, serum creatinine concentration and smoking status. The albumin and creatinine clearance values were provided at two different visits. A paired t-test was used to test for a change in either covariate between visits. As there was no statistically significant difference, the average of the two values was used in subsequent analyses. Plots of residuals against each covariate did not reveal any discernable trends.

Several possible linear relationships were identified from the covariate-individual pharmacokinetic parameter plots. The covariates identified in this way were then included in the population model and tested for significance by comparison with the results from the base model analysis (no covariates). Where possible, the number of parameters was increased to allow the difference in the log-likelihood to be tested for statistical significance (for example, $CL = \theta_1 + \theta_2 * \text{weight}$). The

Table III. Population Analysis of Phase II Data

Parameter	Study 3 Estimate (SE)	Study 3 Variance[a]	Study 4 Estimate (SE)	Study 4 Variance	Combined Estimate (SE)	Combined Variance
CL (L/hr)	0.27 (0.01)	0.06	0.23 (0.01)	0.11	0.25 (0.01)	0.08
V_1 (L)	3.45 (0.31)	0.57	2.64 (0.59)	3.01	3.33 (0.24)	0.67
Vss (L)	10.34 (0.42)	0.10	9.79 (0.36)	0.07	10.13 (0.28)	0.07
CL_d (L/hr)	0.28 (0.01)	0.03	0.93 (0.08)	0.32	0.32 (0.01)	0.001
T_{inf} (hr)	2.53 (0.07)		1.50 (0.07)		2.51 (0.06)	
Residual Variance[a]	0.07		0.07		0.09	

[a] No estimates of SE available for variance terms.

Table IV. Studies 3 and 4: Covariate-Parameter Relationships Selected From Covariate-Individual Pharmacokinetic Parameter Plots

Parameter model	Log-likelihood
Base model (no covariates)	−1321.4
CL = P(1) non-smokers, P(2) smokers	−1334.5*
V_1 = P(2) (study 3), P(3)*WT/70 (study 4)	−1325.7
Vss = P(3) male, Vss = P(4) female	−1329.4*
CL_d = P(4) male, CL_d = P(5) female	−1337.3*
CL_d = P(4) + P(5)*WT/70	−1337.9*
CL = P(1) non-smokers, P(2) smokers, Vss = P(4) male, Vss = P(5) female, CL_d = P(6) male, CL_d = P(7) female	−1403.8
CL = P(1) non-smokers, P(2) smokers, Vss = P(4) male, Vss = P(5) female, CL_d = P(6)*WT/70 male, CL_d = P(7)*WT/70 female	−1406.5

* Significant difference in log-likelihood ($P < 0.005$).

significance level chosen for the acceptance or rejection of a covariate as significantly influencing the population fit was $P < 0.005$.

Results from the covariate analyses are shown in Table IV. All combinations of possible relationships were investigated (selected analyses are shown in the table). A representative plot of a visible trend is given in Fig. 4. This shows a categorical variable (gender) plotted against Vss: it can be seen that the Vss estimates for females tend to be lower than for males.

Significant relationships were found between CL and smoking, between Vss and gender, and between CL_d and weight and gender. Subsequent analyses with combinations of these selected covariates (see Table IV) showed that there was confounding between weight and gender for CL_d. None of the identified relationships were very strong and they did not exert much influence on the goodness of fit, as judged by the residual plots, changes in interindividual variabilities and residual variability. There was very little spread in the continuous covariate values, for example serum creatinine values were mostly within the range of 0.8–1.4 mg/dl and albumin levels generally between 36–42 g/L (a relationship with albumin might be suspected because tenidap is highly bound, 99%, to albumin in plasma).

Results from the population pharmacokinetic analysis using the final covariate model are shown in Table V. The analysis indicated that smokers had a higher CL than nonsmokers and that females had a lower Vss and CL_d than males. If these results are compared to the associated base model analysis (see Table III), it can be seen that the addition of the covariates has had very little effect on the inter- and intraindividual variabilities. The interindividual variabilities for CL (29% to 27%) and Vss (27% to 22%) were reduced slightly, whereas for V_1 (82% to 89%) and CL_d (3.2% to 15%) the variability increased. The residual variability remained virtually unchanged. Examination of the weighted residuals from the covariate model did not reveal any noticeable differences from the weighted residuals of the base model fit. Although the covariates included in the analyses had a significant effect on the fit as judged by the difference in the log-likelihood, the goodness of fit was largely unaffected. This is an indication that the proposed covariate-parameter relationships are weak.

Table V. Population Analysis of Combined Phase II Data (Studies 3 and 4) Using Covariate Model

		Population estimate (se)	Inter-individual variance	CV (%)
CL	P(1)	0.24 (0.01)	0.08	27%
	P(2)	0.29 (0.02)		
V_1	P(3)	3.18 (0.30)	0.79	89%
Vss	P(4)	10.07 (0.45)	0.05	22%
	P(5)	8.95 (0.39)		
CL_d	P(6)	0.93 (0.06)	0.02	15%
	P(7)	0.33 (0.02)		
T_{inf}	P(8)	2.50 (0.06)		
Intraindividual variance = 0.08				

Note: Covariate relationships included in model: CL = P(1) nonsmokers, CL = P(2) smokers; Vss = P(4) male, Vss = P(5) female; CL_d = P(6) male, CL_d = P(7) female.

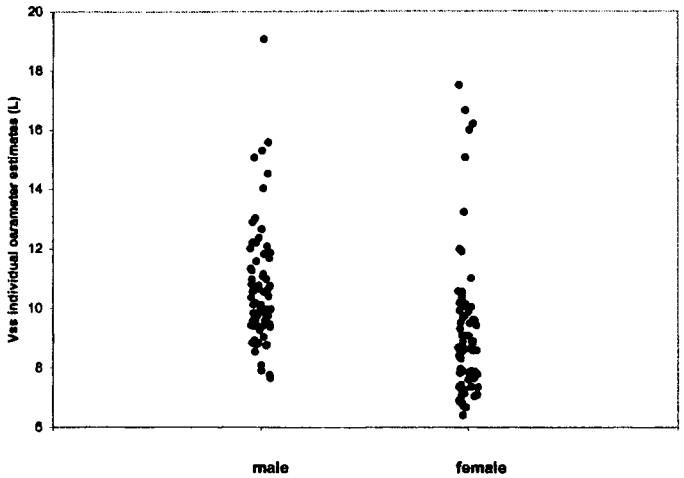

Fig. 4. Covariate-individual pharmacokinetic parameter plot (Vss and gender) generated from combined phase II (studies 3 and 4) analysis.

It is unlikely that there is a specific gender difference in the pharmacokinetics of tenidap, but that the selection of gender as a relevant covariate is probably indicative that there are more complicated relationships between the parameters and covariates that were not investigated.

The covariate model developed (Table V) was subsequently used to analyse reduced data sets generated from the combined phase II data.

Reduced Data Sets (Simulated Sparse Data)

Reduced data sets were created from the data-rich phase II studies data set (3 and 4 combined) to test the robustness of the model to sparse data. A program incorporating a random number generator was used to select between one and four samples per subject from the combined data set (original data had eleven samples per subject). Firstly the number of data points to be selected from a certain individual (1..4) was randomly chosen. Subsequently this number of data points were retrieved from the original data, without repetition (each data point had an equal probability of being selected). An unequal number of data points per individual was used as this was seen to reflect the structure of sparse data from observational phase II and III studies. Ten different sparse data sets were produced. The means of the results from the population analyses of these data sets are shown in Table VI.

For the covariate model, the estimates (and SEs) of CL for both smokers and non-smokers compared well with the full data set estimates (Table V). V_1 had a modest increase with a loss in confidence (higher SE), and Vss estimates decreased slightly but Vss(female) was still lower than Vss(male), compared to the full data set analysis. T_{inf} increased slightly, but was well estimated. CL_d was again poorly estimated. The inter-individual variance terms followed the same pattern as the full data set.

Overall, the sparse data analyses compared favourably with the full data analyses. The SEs were generally larger, but this was not surprising since there was only approximately 20% of the original data in the sparse data sets.

Table VI. Analysis of Simulated Sparse Data Sets

Model estimates (full)	Estimates from full data set (Table VI)	Mean (10 runs)	SE (of mean)
CL (L/hr) (non-smokers)	0.24	0.24	0.01
CL (L/hr) (smokers)	0.29	0.28	0.02
V_1 (L)	3.18	4.23	1.07
Vss (L) (male)	10.07	9.23	0.54
Vss (L) (female)	8.95	8.26	1.10
CL_d (L/hr) (male)	0.93	1.24	1.35
CL_d (L/hr) (female)	0.33	1.31	1.67
T_{inf} (hr)	2.50	3.07	0.44
Estimates of se's for population parameters			
CL (non-smokers)	0.01	0.01	6×10^{-4}
CL (smokers)	0.02	0.02	3×10^{-3}
V_1	0.30	1.02	0.92
Vss (male)	0.45	0.47	0.07
Vss (female)	0.39	0.51	0.24
CL_d (male)	0.06	0.85	1.17
CL_d (female)	0.02	1.31	1.74
T_{inf}	0.06	0.27	0.10
Inter-individual variance terms for population parameters			
CL	0.08	0.04	0.01
V_1	0.79	1.53	2.31
Vss	0.05	0.03	0.05
CL_d	0.02	5×10^{-4}	2×10^{-4}
Intra-individual variance	0.08	0.10	0.02

SUMMARY

The absorption of tenidap was difficult to model. However, both the individual analyses and the simultaneous iv/oral dosing data analyses showed that a zero order model was more prevalent amongst normal volunteers. Although a small lag in absorption was identifiable from the individual analyses, it was not possible to estimate it with mixed-effects modelling. The disposition of tenidap was clearly bi-exponential. The best variance model was obtained with interindividual variability split between the pharmacokinetic parameters of the model-CL, V_1, Vss and Cl_d - and when the residual error was log-normal.

The pharmacokinetic parameter estimates were quite consistent throughout the individual and population data analyses. The estimate of V_1 was very low (around 3L), even with the iv data, which indicated that initially the drug is restricted to plasma. Vss was also low, varying between 7L and 18L. Clearance estimates varied between 0.2 and 0.69 L/hr. Elimination half-lives calculated from these values confirmed that the half-life was shorter (population estimate 16 hrs) in the phase I data from study I than the phase II data from studies 3 and 4 (population estimate 28 hrs). The difference in parameter estimates between the phase I and II studies could not be explained by available covariates and may reflect the influence of the disease on the pharmacokinetics. CL_d estimates varied quite widely from 0.21 to 1.11 L/hr. Differences in parameter estimates between single and multiple dosing remain unexplained. Intravenous data is required to differentiate possible time-dependent changes in absorption and disposition.

Investigation of covariate effects identified significant relationships between smoking and CL (higher values of CL for smokers) and between gender and Vss and CL_d (lower Vss and CL_d for females). Inclusion of these covariates into the population model caused a significant difference in the log-likelihood, but did not noticeably influence the goodness of fit as judged by residual plot and changes in the inter- and intraindividual variabilities. No relationship between albumin level and any of the parameters was found, despite the strong binding of the drug to albumin. The failure to detect any relationship between albumin level and the pharmacokinetics of the drug was probably due to the narrow range of albumin levels observed in the studies.

The reduced data set analyses reflected the results seen with the full data sets. There were specific problems estimating CL_d resulting in a loss of confidence in the parameter estimates (higher SEs), but this was not unexpected as the sparse data sets contained approximately only 20% of the original data. With 'real' sparse data this loss in confidence may be reduced by having a greater number of patients in the study.

In summary, the pharmacokinetics of tenidap can be described by a bi-exponential model with zero order absorption. Based on differences in the log-likelihood, significant covariate-parameter relationships were identified between smoking and CL, and

between gender and Vss and CL_d. Simulated sparse data analyses indicated that the population model would be robust for the analysis of sparse data generated in observational studies.

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