A model-based approach to treatment comparison in acute migraine

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Keywords

sumatriptan, naratriptan, PK/PD
modelling

Received

2 October 2005

Accepted

1 February 2006

Published OnlineEarly

26 May 2006

Aims

Currently, direct comparisons between 5-HT_{1B/D} receptor agonists are used to assess differences and similarities in antimigraine response. Such comparisons depend on the selected sampling time and do not allow evaluation of entire response profiles. A thorough evaluation of drug properties requires that the time course of the response be taken into account. In this investigation we show the advantages of a model-based approach to compare the efficacy of two triptans (sumatriptan vs. naratriptan).

Methods

A Markov model was used to describe the course of a migraine attack over three clinically identified stages. Drug effects were modelled as concentration-dependent increases in transition rates and were parameterised as potency (EC₅₀) and maximum effect ($E_{\max}$). Parameters were estimated using headache measurements from efficacy studies. Model estimates were then used to compare the pharmacodynamics of the two drugs in a time-independent manner.

Results

Efficacy parameters could be derived, allowing for comparison between compounds. The potency ratio (EC50_{suma}/EC50_{nara}) for headache relief was 3.3 (0.9, 12). The ratio of maximum effects ($E_{\max\text{suma}}/E_{\max\text{nara}}$) for this endpoint was 0.74 (0.55, 0.97). To interpret these efficacy measures and explore their value for the development of antimigraine drugs, results were evaluated against the reported *in vitro* potency at 5-HT_{1B} and 5-HT_{1D} receptors.

Conclusions

Comparison of the effects of two or more drugs based on preset sampling times does not allow proper assessment of the antimigraine properties *in vivo*. Disease dynamics must be considered to evaluate treatment response adequately and optimise the dosing regimen in migraine.

Introduction

Ideally, in clinical pharmacology research one requires distinct parameters that are independent of each other to compare different drugs. In migraine, the clinical effect on headache perception is the result of an interaction between drug pharmacokinetics, pharmacodynamics and disease dynamics. Treatment efficacy in the patient

population is commonly expressed as the cumulative response (e.g. headache relief) at a specific time and these measures are then used to compare efficacy across drugs [1]. However, these measures are somewhat arbitrary, ignoring the time course of disease. Furthermore, their cumulative nature complicates comparison of effects at different time points, as the response at any

time is rendered dependent on all previous responses. Most importantly, these are hybrid measures that encompass the pharmacodynamics of a drug but also depend on pharmacokinetic parameters such as elimination half-life and constants such as dose and route of administration. For example, absorption rate influences the initial rate of pain relief and half-life affects the rate of recurrence [2–4]. Whilst comparison of pharmacokinetic properties of different drugs is an accepted approach to infer efficacy, the approach is not appropriate in the presence of time dependence as is the case in migraine attacks. Thus, whereas pharmacokinetic parameters can be compared across drugs, the use of time-dependent efficacy measures is not appropriate to compare the pharmacodynamic properties of drugs in a clinical population of interest. In the current investigation, we show the relevance of disease dynamics in the evaluation of the antimigraine effects for two well-known drugs, namely, sumatriptan and naratriptan.

As is the case with clinical pharmacokinetics, the availability of unambiguous parameters in the evaluation of clinical efficacy is a valuable asset. A model-based approach enables the identification of such parameters and provides accurate evaluation of drug properties when comparing treatments. The aim of this study was to obtain pharmacodynamic parameters of sumatriptan and naratriptan in a population of migraineurs using a statistical model that takes into account disease dynamics and can be related to those obtained *in vitro* and in preclinical experiments. Hopefully, such parameters confirm the differences observed clinically between the drugs.

Methods

Migraine attack model

A statistical model of a migraine attack taking into account disease dynamics and pharmacokinetics has been recently developed. The model considers the time course of migraine as transitions between disease states [5]. This so-called hidden Markov model has been conceived to predict concentration–effect relationships in migraine.

The model consists of a three-state Markov chain expressing disease dynamics with specific transitions allowed between states (Figure 1). A unique property of a Markov chain is that only the current state determines the probability of transition to the next state in the process. Previous states do not influence the course of the process, making the Markov chain a powerful modelling tool. Furthermore, the transition time from one state to the next is a random variable. That is, the time spent in the current state ‘x’, before moving to the next state ‘y’,

Figure 1

Structure of the migraine model. Migraine attack dynamics is assumed to occur within three clinical states represented by a Markov chain. Patients enter the study in the first state and, in the course of an attack, progress to the second and third states representing pain relief and pain-free status, respectively. Headache scores corresponding to the clinical states are ascribed to a second layer of the model. Bold arrows indicate transitions that are affected by drug exposure

is exponentially distributed according to a rate parameter ‘ r_{xy} ’.

In the current migraine attack model, the choice of the states is based on the clinical differentiation between attaining pain relief (state 2) and attaining pain-free status (state 3), starting from a full migraine attack (state 1) [1]. Trigeminal pathophysiology may well be a biological substrate for this differentiation [6]. A major advantage of this approach is the ability to estimate transition rates from one state to another, which makes the evaluation of treatment effects independent of sampling time and observation windows. However, in trials of antimigraine drugs the observed variable is not the clinical state but rather the headache intensity score, which is defined on a 4-point scale. In this scale, scores 0, 1, 2 and 3 indicate ‘no pain’, ‘mild pain’, ‘moderate pain’ and ‘severe pain’, respectively. In order to relate the Markov states to the headache intensity scores, the states are coupled to a layer that gives the probability distributions of the headache scores for each state (Figure 1). The layer containing the probability distributions is referred to as the ‘open’ layer, as it contains the observed variable, which is the variable to be modelled. The Markov chain is referred to as the ‘hidden’ layer of the model, as it describes the unobserved clinical states. Together, the two layers constitute the hidden Markov model.

The expected probability distributions of the scores across the states can be deduced from clinical guidelines [1], which state that pain relief is defined as a decrease in headache score from 3 or 2 to 1 or 0, whereas pain free is defined as a decrease from a score 3 or 2 to 0.

Therefore, it is expected that the distribution of the first Markov state (representing a full attack) will be made up of scores 2 and 3, the second state (similar to pain relief) will contain score 1 and the last state (pain free) will consist of score 0.

Covariates

As shown in Figure 1, forward transitions towards states of decreasing pain as well as backward transitions towards states of increasing pain are allowed in the Markov chain. Forward transitions reflect resolution of the attack, following administration of either active or placebo treatment. By treating drug exposure as a time-varying covariate that increases the forward transition rates, the effect of active treatment can be modelled explicitly.

$$r(t)_{x,y} = r(0)_{x,y} \cdot \exp\left(\frac{E_{\max;x,y} \cdot C(t)}{EC_{50;x,y} + C(t)}\right) \quad 1$$

Equation 1 describes the rates $r(t)_{x,y}$ of the forward transitions from some state x to another state y during active treatment. Parameter $r(0)_{x,y}$ represents the rates in the absence of drug (placebo model). $C(t)$ is the plasma drug concentration at time t . $E_{\max;x,y}$ represents the maximum drug effect on the transition rate from state x to state y . $EC_{50;x,y}$ is defined as drug concentration corresponding to the effect reached at half of the value of $E_{\max;x,y}$.

Backward transition rates represent the activity of a migraine generator [7], which may differ between states of response and is not affected by drug treatment. These rates do not vary in time and are parameterised only by $r_{y,x}$ where y,x denotes any allowed backward transition. In total, the model contains two forward and two backward transition rates, the parameters of which are to be estimated.

Covariates other than drug concentration may also affect the dynamics of the migraine attack. Age is known to influence the response in placebo-treated migraine patients. More specifically, the placebo response observed in children is considerably higher than in adults [8]. As the current analysis does not include data from paediatric trials, the effect of age was not considered. Gender was also considered as a potential covariate. There is evidence that the duration of untreated migraine attacks is somewhat shorter in male patients [9]. However, given the small percentage of male patients in trials of antimigraine drugs (typically ~10% in studies with adult patients), gender differences are not likely to be detected. In fact, the number of male patients in this analysis was too small to obtain meaningful estimates.

Data

Sumatriptan and naratriptan pharmacokinetic and efficacy data were obtained from the SNAP database [10]. Details about the data source have been given elsewhere [5]. Headache score measurements performed at 0, 0.5, 1, 1.5, 2, 4 and 8 h post dose were included for all patients in the current analysis. Whenever available, scores at 0.17, 0.33, 3 and 6 h were included also. Measurements up to 24 h were used only for the prediction of headache recurrence, as required by the clinical definition of recurrence [1].

For sumatriptan, efficacy data included headache scores from 1180 migraine attacks; 392 attacks were treated with placebo. Oral sumatriptan tablets (25 mg, 50 mg and 100 mg) were administered to treat 46, 44 and 698 attacks, respectively. All patients included in the analysis were adults, age 39 ± 10 years (mean $\pm$ SD). Pharmacokinetic data from 513 subjects, across a range of oral, intranasal and subcutaneous doses ranging from 2.5 to 100 mg, were obtained from different clinical trials from the efficacy data, since both data types were not simultaneously available in the same trials.

For naratriptan, efficacy data were obtained from three clinical studies describing 1608 attacks, 258 of which were treated with placebo and 228, 232, 280, 328, 93, 93 and 96 attacks treated with 0.1 mg, 0.25 mg, 1 mg, 2.5 mg, 5 mg, 7.5 mg and 10 mg naratriptan, respectively. Patients included in the analysis were aged 38 ± 10 years (mean $\pm$ SD). The pharmacokinetics of naratriptan was derived from clinical studies including 174 healthy volunteers across a range of oral, intranasal and subcutaneous doses that varied between 0.5 mg and 10 mg.

Pharmacokinetic analysis

Blood sampling for pharmacokinetic analysis was not performed in the efficacy studies from which headache scores were assessed. In order to link headache observations to drug exposure, population concentration–time profiles were generated for sumatriptan or naratriptan by fitting data from pharmacokinetic studies to pharmacokinetic models. Sumatriptan concentration data were fit to a model proposed by Cosson and Fuseau [11]. This model consists of two compartments with a combined zero- and first-order absorption rate, describing the irregular absorption characteristics of sumatriptan. For naratriptan a two-compartment pharmacokinetic model with first-order absorption was used [12]. Model precision was assessed by inspection of residual plots and plots of observed *vs.* predicted concentrations (Figure 2). Concentration–time profiles were simulated matching doses and sampling times used for the assess-

Figure 2

Residual plots of the pharmacokinetic analysis of naratriptan data. In the upper panel, weighted residuals of the population model are plotted against time (0–20 h post dose). In the lower panel, observed data are plotted against predicted individual concentrations. Symbols represent the different dose groups and administration routes of the pharmacokinetic studies

ment of headache scores (Figure 3). To estimate the parameters in the hidden Markov model, a dataset was then constructed containing both the observed headache scores and the simulated concentration data.

Disease modelling

The observed headache scores (i.e. the modelling variable) and triptan plasma concentrations (i.e. the time-varying covariate) were fit to the hidden Markov model. Data from the sumatriptan and naratriptan studies were analysed separately. In both cases, placebo data and active treatment data were modelled simultaneously. Two sets of parameter estimates were thus obtained: one for the sumatriptan studies and one for the naratriptan studies. These sets included the parameters of the forward and backward transition rates of the Markov chain and the probability distributions of the headache scores in each of the states.

Figure 3

Concentration vs. time profiles following oral administration of different doses of sumatriptan (25, 50 and 100 mg) and naratriptan (1.0, 2.5, 5.0 and 10 mg)

Model evaluation and prediction

Parameter estimates of the hidden Markov model were used to construct predicted pain relief and pain-free response profiles. The goodness of fit in both analyses was assessed by comparing the predicted profiles with those obtained from the observed headache scores. Model estimates were subsequently compared with literature values obtained from *in vitro* and *ex vivo* experiments. To normalize for differences in units, $E_{\max}$ estimates for sumatriptan were expressed relative to naratriptan. Statistical comparisons involving the estimated maximum effect ($E_{\max}$) and potency (EC_{50}) were based on the 95% confidence intervals (CIs) of these parameters.

Most importantly, model predictions enabled the assessment of the concentration–effect relations of sumatriptan and naratriptan. These relations were obtained by calculating headache scores using the estimates of the hidden Markov model and replicating the simulation procedures for different doses. Headache responses were then plotted against concentration at 1 h and 2 h post dose, as these are important regulatory cut-off times for evaluating response in efficacy trials.

Software

Pharmacokinetic modelling was performed using the nonlinear mixed effects software package NONMEM (version V; Globomax LLC, Ellicott City, MD, USA). Models were written in subroutine ADVAN4 using the first order (FO) estimation method.

The migraine attack model (hidden Markov model) was implemented in S-Plus for Linux and run on SuSE Linux 7.2 Professional, kernel version 2.4.4-4GB-SMP [13].

CI for the parameter estimates of the hidden Markov model were based on the standard errors of the estimates and were calculated using the EPC software tool (D. Kelley, <http://epc.sourceforge.net/>).

Results

Estimates were obtained for all parameters in the migraine attack model. The distribution of headache scores over the clinically defined states was similar for sumatriptan and naratriptan, with all severe and moderate pain scores assigned to state 1, most mild pain scores assigned to state 2 and all no-pain scores assigned to state 3 (Table 1). The parameter estimates were used to predict the clinically derived response (pain relief) after administration of placebo and either triptan. Figure 4 shows the predicted response together with the observed values. Only the 100-mg sumatriptan dose is shown. Comparison of observed and predicted responses at other dose levels was not deemed informative due to the limited availability of data for those doses. For naratriptan, the 2.5-mg dose is shown as this is the standard prescribed dose and is often compared with the sumatriptan 100-mg dose [14]. However, the responses to other doses could be predicted equally well. Placebo data from the naratriptan studies were less well predicted than those from sumatriptan studies.

Estimates of mean transition times, drug effects and their 95% CI are given in Table 2 for both drugs. From these estimates, it was calculated that sumatriptan is 3.3 (0.89, 12) and 56 (10, 336) times less potent than naratriptan on the first and second transitions, respec-

tively (mean and 95% CI). The maximum effect of sumatriptan is 0.74 (0.55, 0.97) times that of naratriptan on the first transition and 6.8 (0.48, 15) times that of naratriptan on the second transition. Whereas all parameters could be precisely estimated for naratriptan, sumatriptan-related parameters on the transition from state 2 to state 3 were less well estimated.

In order to establish the predictive value of this model with regard to preclinical findings, *in vitro* and *ex vivo* data from literature were used. Table 3 compares the predicted values of EC_{50} and E_{max} on both transitions with results from *in vitro* experiments (stimulation of ^{35}S -GTP γ S binding to recombinant human 5-HT $_{1B/D}$ receptors in C6 glial cell lines [15]) and *ex vivo* experiments (vasoconstriction of isolated human cortical cerebral arteries and canine middle cerebral arteries [16, 17]). Both *in vitro* and model-predicted values of potency show that naratriptan is more potent than sumatriptan. It is further observed in this comparison that the potency of sumatriptan measured at the 5-HT $_{1B}$ receptor and estimated at the second model transition are both significantly lower than that at the first model transition. In contrast to the similarities between *in vitro* and model-predicted estimates, *ex vivo* data do not seem to discriminate between compounds in terms of affinity for either receptor subtype. All point estimates of the E_{max} ratios were close to unity, with the exception of that obtained for the second transition in the Markov model.

Table 1

Probability distributions of headache scores after treatment with sumatriptan (Suma) or naratriptan (Nara) over the clinically defined states in the migraine model

StateScore	1		2		3	
	Suma	Nara	Suma	Nara	Suma	Nara
No pain	0	0	0	0	1	1
Mild	0	0	0.96	0.95	0	0
Moderate	0.55	0.52	0.04	0.05	0	0
Severe	0.45	0.48	0	0	0	0

The probabilities in each column add up to 1.

Figure 4

Pain relief profiles vs. time. Left panel: sumatriptan 100 mg. Right panel: naratriptan 2.5 mg. Pain relief is attained when a patient's headache score equals 1 ('mild pain') or less, starting from score 2 ('moderate pain') or 3 ('severe pain'). Predictions are represented by lines, observations are indicated by markers (circles). The diameter of the circles is proportional to the number of observations available at the respective time point

Table 2

Parameter estimates of the migraine model for sumatriptan and naratriptan

Transition	Parameter	Sumatriptan		Naratriptan	
		Estimate	95% CI	Estimate	95% CI
State 1–2	$r(0)$ (h^{-1})	0.16	0.15, 0.18	0.12	0.10, 0.13
	EC_{50} (nM)	32	10, 105	9.6	5.7, 16
	E_{max}	1.3	0.9, 1.6	1.7	1.4, 2.0
	$T(0)$ (h)	6.3	5.6, 6.7	8.3	7.7, 10
	T_{min} (h)	1.8	1.3, 2.6	1.6	1.1, 2.1
State 2–1	r (h^{-1})	0.08	0.06, 0.10	0.07	0.05, 0.09
	T (h)	13	10, 17	14	11, 20
State 2–3	$r(0)$ (h^{-1})	0.24	0.22, 0.30	0.26	0.21, 0.31
	EC_{50} (nM)	600	180, 2000	11	2.9, 39
	E_{max}	6.0	0.79, 11.5	0.9	0.6, 1.2
	$T(0)$ (h)	4.2	3.3, 4.5	3.8	3.2, 4.8
	T_{min} (h)	0.45	0.01, 4.0	1.6	1.0, 2.2
State 3–2	r (h^{-1})	0.04	0.03, 0.05	0.03	0.02, 0.04
	T (h)	25	20, 33	33	25, 50

Parameters were derived from Equation 1. Mean transition times (denoted T) were calculated from the rates r . On drug-dependent transitions, $T(0)$ is the placebo mean transition time and T_{min} is the minimum transition time obtained after drug treatment. Modelling details are explained in the text (see Methods).

Table 3Comparison of potency and maximum effect ratios for sumatriptan (suma) and naratriptan (nara) as obtained *in vitro*, *ex vivo* and by the migraine model

Study type	EC_{50} suma (nM)	EC_{50} nara (nM)	E_{max} suma/ E_{max} nara
<i>In vitro</i> 5-HT _{1D} [13]	18 (12, 26)	4.4 (2.9, 6.6)	1.3 (1.1, 1.4)
<i>In vitro</i> 5-HT _{1B} [13]	230 (180, 310)	23 (12, 43)	1.2 (1.1, 1.4)
<i>Ex vivo</i> CCA(h) [14]	160 (63, 400)	100 (63, 160)	1.0 (0.56, 1.4)
<i>Ex vivo</i> MCA(c) [15]	210 (120, 360)	70 (50, 100)	0.85 (0.62, 1.08)
Migraine model transition state 1–2	32 (10, 105)	9.6 (5.7, 16)	0.74 (0.55, 0.97)
Migraine model transition state 2–3	600 (180, 2000)	11 (2.9, 39)	6.8 (0.48, 15)

CCA(h), Human cortical cerebral artery; MCA(c), canine middle cerebral artery. 95% confidence intervals are shown in parentheses.

In addition to data fitting, the model was also used to predict headache recurrence. This endpoint is defined as the fraction of patients that return to a moderate or severe headache score within 24 h post dose, after having experienced pain relief at 4 h. Figure 5 compares the simulated recurrence profiles after treatment with placebo, 100 mg sumatriptan and 2.5 mg naratriptan. Simulations could not be directly compared with observed data. This is because in clinical practice

recurrence cannot be derived from the sequence of scheduled pain observations. Quantifying recurrence based on a few observations would result in underestimation of the true rate, particularly at late time points when pain scores are recorded infrequently. Rather, recurrence is assessed separately on a 24-h basis. With the currently developed model, it is possible, however, to obtain predicted recurrence rates. Using the disease model to simulate pain scores short time intervals apart,

Figure 5

Predicted recurrence rates for sumatriptan, naratriptan and placebo arms in the available clinical studies. Estimation is based on analysis of data up to 24 h after dosing

Figure 6

Concentration vs. pain relief responses after oral administration of sumatriptan and naratriptan. The role of disease dynamics on drug effect is described by the differences in the pharmacokinetic/pharmacodynamic relation at 1 h and 2 h after dosing

a realistic prediction of recurrence can be obtained. Whilst treatment with 2.5 mg naratriptan is predicted to result in less recurrence than treatment with 100 mg sumatriptan, it should be noted that the recurrence rate predicted for placebo is also less in the clinical studies with naratriptan.

The use of disease modelling also provided an estimate of the concentration–effect relationship at 1 h and 2 h after administration of sumatriptan and naratriptan, allowing both drugs to be compared in terms of efficacy

and overall clinical response (pain relief, Figure 6). For comparison of potency, drug concentrations are expressed in molar units (nM). Sumatriptan is approximately three times less potent than naratriptan, whereas $E_{\max}$ estimates were found to be similar for both drugs. One should note that $E_{\max}$ increases over time because pain relief is determined cumulatively after dosing.

Discussion

The analysis of ordered categorical data such as headache severity scores is not straightforward when the underlying measure (i.e. pain) is continuous. Two approaches can be used to deal with this incongruence. The data are either treated as continuous and discretised after analysis or treated as truly categorical and analysed in a model describing transition probabilities between the categories. The first approach enables the use of classical regression models and permits operations on the data that are not allowed for categories. On the other hand, the second approach is assumption-free as it does not try to characterise the intervals between categories.

We have presented a model-based approach to account for and identify the time course of headache during treatment of acute migraine. In our model, the course of disease is conceptualised as a sequence of transitions between three states. Based on the suppression of pain (i.e. pain-free status) in two transitions and the ability of triptans to shorten these transitions, pharmacodynamic parameters were obtained for naratriptan and sumatriptan. Naratriptan was three times more potent than sumatriptan in shortening the first transition leading to pain relief (10 nM vs. 32 nM, respectively). The potency of naratriptan associated with the second transition (11 nM) was similar to the estimates obtained for the first transition. The corresponding estimate for sumatriptan lacked precision and a comparison between the drugs on this transition level is probably not meaningful. This less precise estimate may have several causes. Whereas seven dose strengths were used to characterise the concentration–effect relation of naratriptan, data available for sumatriptan were mostly from the 100-mg dose. While this was sufficient to identify sumatriptan action on the first transition, identification of drug effect on the second transition may have been prevented by the rapidly decreasing sumatriptan concentrations (elimination half-life is approximately 1.5 h) or the intrinsically short duration of this transition.

The quality of the Markov model was verified in two ways. Using model parameter estimates, the course of pain relief (mean and 95% CI) was calculated for a large population of migraineurs and then predicted responses were compared with those observed. As shown in

Figure 4, most observations fell within the predicted 95% CI. The observed placebo response in the naratriptan analysis, however, deviated somewhat from the predicted response. This was the result of the relatively small proportion of placebo data used for this analysis (16% compared with 50% for sumatriptan). As a consequence, more importance was attached to the accurate estimation of the maximum effect and potency than to the estimation of baseline transition rates. Although balancing the dataset with respect to the proportion of placebo data improved the prediction of baseline transition rates, it came at the expense of precision in the other parameters (data not shown).

The quality of fitting was further assessed by comparison of estimated maximum effects and potencies with experimentally obtained values. Model-estimated potencies corresponded well with potencies reported in an *in vitro* assay. Particularly in the case of sumatriptan, these values seem to suggest that the transition from state 1 to state 2 in the model (i.e. pain relief) was predictive of activity at the 5HT_{1D} receptor, whereas the transition from state 2 to state 3 (i.e. pain free) was more indicative of 5HT_{1B} activity. It should be noted that insufficient sumatriptan doses were available to identify sumatriptan potency reliably on the second transition; hence the deviating maximum effect ratio on the second transition. Nevertheless, sumatriptan has been argued to be less effective at providing pain resolution in patients with central sensitization [6]. This limitation may be correlated to the lipophilicity of the compound. In fact, drugs showing higher lipophilicity, such as naratriptan, seem to overcome this problem [18]. Thus, the potency of sumatriptan on the second transition may not have been identifiable even if more data had been available.

The vasoconstrictor activity of 5HT_{1B/D} agonists is mediated via activation of 5HT_{1B} receptors [19]. Recent investigations suggest that the main antiheadache effect of triptans arises from activation of presynaptic 5HT_{1D} receptors located at central terminals of trigeminal neurons [6, 20]. This may explain why the potencies reported in *ex vivo* studies are lower than most model-estimated potencies. Moreover, the EC₅₀ values from *ex vivo* studies are well above therapeutically relevant concentrations of sumatriptan and naratriptan and therefore may not reflect the clinical efficacy of these drugs. EC₅₀ values obtained from animal models of trigeminal activation are likely to show better correlation with clinical data. To date, however, no such values have been reported.

Recurrence of headache represents a secondary treatment failure [1] and is a common problem in the treatment of migraine. Clinical studies investigating recurrence are characterised by highly variable out-

comes [14, 21]. Despite the use of identical definitions of recurrence in the comparisons between studies, differences in outcome may arise from varying recording methods, such as the use of patient diaries, retrospective assessment, or questionnaires at fixed intervals during the study. In addition, recurrence rates reported for the placebo arm range from 13% to 65% [22–29]. Considering such a wide variability between studies, we endorse the requirement to present recurrence after active treatment relative to recurrence observed in the placebo arm of the study.

Whilst it has been shown that the incidence of recurrence in the active treatment arm is smaller for drugs with longer half-life and higher potency for the 5HT_{1B} receptor [4], the mechanisms causing recurrence after placebo treatment remain unknown and do not correlate with 5HT_{1B} receptor activity or headache severity. In the Markov model, recurrence is treated as a random event (i.e. the backward transition from state 2 to state 1), the probability of which is smaller with increasing drug exposure. Using the Markov model described with data up to 24 h, recurrence between 4 h and 24 h post dose has been predicted for treatment with placebo, sumatriptan 100 mg and naratriptan 2.5 mg. Although in our analysis a lower recurrence was found for naratriptan (36%) relative to sumatriptan (45%), recurrence in the placebo arm of naratriptan studies was also lower (55%) than that of sumatriptan studies (64%). Particularly after 8.0 h post dose, initially small differences in recurrence rate between the two placebo studies increase.

In addition to estimating intrinsic differences in pharmacodynamics, concentration–pain relief relations (Figure 6) were established for both drugs at different times after oral dosing. To our knowledge, no other approach seems accurately to quantify drug effect under nonstationary conditions, as in the case of a migraine attack. Since headache relief rates are expressed cumulatively over time, the response curves increase with assessment time. The midpoints of the relations however, are time-invariant. It should be noted that these midpoints are not equal to the potency estimated on the first transition in the model. While the potency characterises a single transition, the midpoints on the concentration–pain relief curves are the resultant of many different trajectories along all states and transitions. The information in Figure 6 can be used to determine the dose that gives the maximum clinical response. It also provides a means to compare the efficacies of different drugs or formulations.

In conclusion, we have characterised and compared the pharmacodynamic properties of sumatriptan and naratriptan in a population of migraineurs. Migraine

attack dynamics is assumed to occur within three clinical states represented by a Markov chain. The approach separates the various determinants of clinical headache response into pharmacokinetic, pharmacodynamic and disease-related components, thereby allowing direct comparison of different antimigraine treatments. Interestingly, model parameter estimates for both compounds also showed agreement with data from *in vitro* and *ex vivo* studies in migraine research. Apart from potential relevance to dose selection and comparison between drugs, the approach could be used to predict clinical response to new investigational drugs based on estimates of potency and maximum effect obtained from relevant preclinical studies.

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