A Markov approach to characterizing the PK-PD relationship of anti-migraine drugs

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A model-based approach to treatment comparison in acute migraine.

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Currently, direct comparisons are used in the clinical development of 5-HT$_{1B/1D}$-receptor agonists to assess differences and similarities in treatment response. Such comparisons depend on the time-point under consideration and therefore do not allow evaluation of complete response profiles. Therefore, any comparison of efficacy and 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).

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 in terms of potency ($EC50$) and maximum effect ($Emax$). Parameters were estimated using headache measurements from clinical efficacy studies of sumatriptan and naratriptan. Based on these estimates the efficacies of the two drugs were compared in a non-time dependent way.

Efficacy parameters could be derived for the two drugs allowing for comparison between them. The potency ratio ($EC50_{suma}/EC50_{nara}$) for providing headache relief was 3.3 (0.9-12). The ratio of maximum effects ($Emax_{suma}/Emax_{nara}$) for this endpoint was 0.74 (0.55-0.97). To demonstrate the applicability of the model-based efficacy measures, estimated potencies were evaluated against reported in vitro at 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors.

In conclusion, comparison of the anti-migraine effects of two or more drugs solely based on preset sampling times does not allow proper assessment of differences in pharmacological properties in vivo. Dependence on time must be considered to adequately evaluate treatment response and optimise dosing regimen in migraine.

4.1 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. Pharmacological anti-migraine 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 of 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, 3, 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 anti-migraine effects for two well-known drugs, namely, sumatriptan and naratriptan.

Sumatriptan and naratriptan are 5-$HT_{1B/1D}$-receptor agonists commonly prescribed for migraine headache. These drugs cause 5-HT_{1B} receptor-mediated constriction of intra-cranial blood vessels [5, 6], inhibition of neurogenic dural inflammation [7] and 5-HT_{1D} receptor-mediated inhibition of pain signal transmission to and from within central trigeminal neurons [8, 9, 10, 11]. Sumatriptan and naratriptan distinctly differ in their pharmacokinetic properties. Sumatriptan has a shorter elimination half-life and lower oral bioavailability, and is absorbed faster after oral administration than naratriptan [12]. From clinical experience it is known that both drugs have different efficacy profiles.

As it 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 is 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 pre-clinical experiments. Hopefully, such parameters confirm the differences observed clinically between the drugs.

4.2 Methods

4.2.1 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 [13]. 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 (Figure 4.1). The characteristic property of a Markov chain is that only the current state determines what the next state in the process will be. 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 jumping to the next state 'y' is exponentially distributed with rate parameter '$r_(x, y)$'. Markov chains are best described by diagrams such as Figure 4.1, showing the allowed transitions between states.

In the 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-blown migraine attack (state 1) [1]. Trigeminal pathophysiology may well be a biological substrate for this differentiation [11]. 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 anti-migraine drugs the observed variable is not the clinical state (full-blown, pain relief, pain free) but rather the headache intensity score which is defined on a four-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 of the states (Figure 4.1). 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 form the hidden Markov model.

The expected probability distributions of the scores over 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-blown 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 be occupied by score 0.

4.2.2 Covariates

As shown in Figure 4.1, 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.

$$r(t)_{x,y} = r(0)_{x,y} \cdot exp\left(\frac{Emax_{x,y} \cdot C(t)}{EC50_{x,y} + C(t)}\right) \tag{4.1}$$

Equation 4.1 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. $Emax_{x,y}$ represents the maximum drug effect on the transition rate from state x to state y. $EC50_{x,y}$ is defined as drug concentration corresponding to the effect reached at half of the value of $Emax_{x,y}$.

Backward transition rates represent the activity of a migraine generator [14], which may differ between states of response and is not affected by drug treatment. These rates

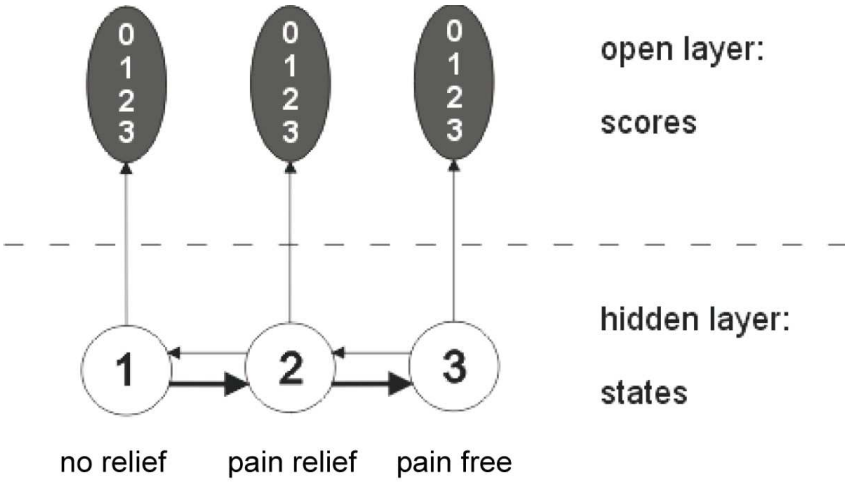

Figure 4.1: *Structure of the migraine model. Migraine attack dynamics is assumed to occur within three clinical states represented by a Markov chain. Patients enter the study in the first state and, in the course of an attack progress to the second and third states representing pain relief and pain-free status, respectively. Headache scores corresponding to the clinical states are ascribed to a second layer of the model.*

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 2 forward and 2 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 that in adults [15]. As the current analysis does not include data from paediatric trials, the effect of age was not considered.

The sex of the patient was also considered a potential covariate. There is evidence that the duration of untreated migraine attacks is somewhat shorter in male patients [16]. However, given the small percentage of male patients in trials of anti-migraine drugs (typically $\sim 10\%$ in studies with adult patients), any difference between the sexes will likely not be detected. Furthermore, the number of male patients in this analysis is too small to obtain confident parameter estimates using a Markov modelling approach.

4.2.3 Data

Sumatriptan and naratriptan pharmacokinetic and efficacy data were obtained from the SNAP database [17]. Details about the data source have been described elsewhere [13]. 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 as well. 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. 25 mg, 50 mg and 100 mg oral sumatriptan tablets were administered to treat 46, 44 and 698 attacks, respectively. All patients included in the analysis were adults, age 39 $\pm$ 10 years (mean $\pm$ standard deviation). Pharmacokinetic data from 513 subjects, across a range of oral, intranasal and subcutaneous doses ranging from 2.5 – 100 mg, were derived from different clinical trials than 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 were treated with 0.1 mg, 0.25 mg, 1 mg, 2.5 mg, 5mg, 7.5 mg and 10 mg naratriptan, respectively. Patients included in the analysis were aged 38 $\pm$ 10 years (mean $\pm$ standard deviation). 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.

4.2.4 Pharmacokinetic analysis

The studies from which the headache scores were derived did not contain pharmacokinetic data. In order to provide all headache observations with sumatriptan or naratriptan concentration values, population-based concentration profiles were generated using data from pharmacokinetic studies. First, these data were fit to pharmacokinetic models.

Sumatriptan concentration data were fit to a model proposed by Cosson and Fuseau [18]. This model consists of two compartments with a combined first-order and zero-order absorption rate, describing the irregular absorption characteristics of sumatriptan. For naratriptan a two-compartment pharmacokinetic model with first-order absorption was used [19]. Model precision was assessed by inspection of residual plots and plots of observed *vs* predicted concentrations (Figure 4.2). Based on the pharmacokinetic parameter estimates, concentration profiles were simulated matching the doses and time points in the headache score data (Figure 4.3). A data set was constructed containing both the observed headache scores and the simulated concentration data. This data set was then applied to estimate the parameters in the hidden Markov model.

4.2.5 Disease Modelling

The observed headache scores (the modelling variable) and triptan plasma concentrations (the time-varying covariate) were fit to the hidden Markov model. Data derived from the sumatriptan and naratriptan studies were analysed separately. In both analyses, 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 of the Markov chain.

4.2.6 Model evaluation and prediction

Parameter estimates of the hidden Markov model were used to construct predicted pain relief and pain free response profiles. By comparing the predicted profiles with those obtained from the observed headache scores the goodness of fit in both analyses was assessed. Model estimates were subsequently compared with literature values obtained from *in vitro* and *ex vivo* experiments. To enable comparisons between effects with different units, $Emax$ estimates for sumatriptan are expressed relative to naratriptan.

Statistical comparisons involving the estimated maximum effects ($Emax$) and potencies ($EC50$) were based on the 95% confidence intervals of these parameters. Further pharmacodynamic comparison of sumatriptan and naratriptan was performed based on predicted concentration *vs* effect relations for the two drugs. These relations were obtained by first simulating headache scores using the estimates of the hidden Markov model and repeating the simulation for different doses. Headache responses were then plotted against concentration. Concentration effect relations were generated at 1 h and 2 h post-dose, as these are important regulatory cut-off times for evaluating responses.

4.2.7 Software

Pharmacokinetic modelling was performed using the non-linear mixed effects software package NONMEM (version V, Globomax LLC, Maryland, US). Models were written in subroutine ADVAN4 and the first order estimation algorithm was adopted. The migraine

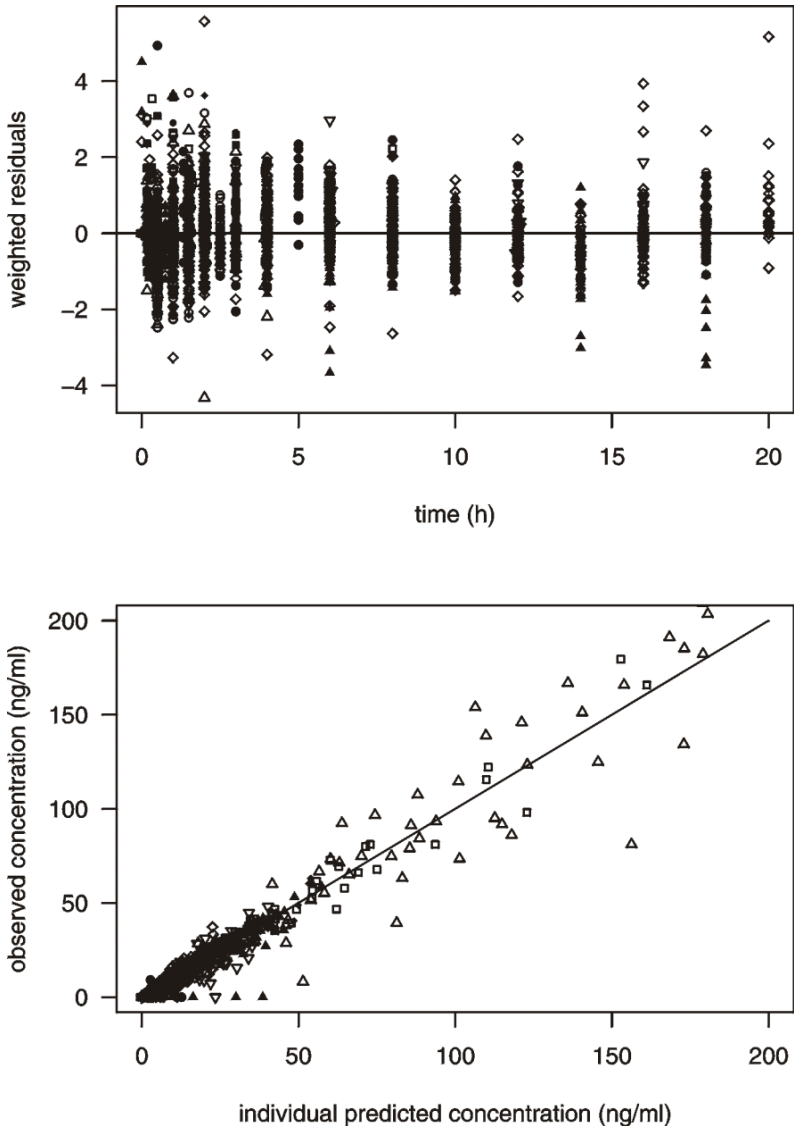

Figure 4.2: *Residual plots of the pharmacokinetic analysis of naratriptan data. In the upper panel, weighted residuals of the population model are plotted against time (0 to 20 h). In the lower panel, observed data are plotted against predicted individual concentrations (ng/ml). Symbols represent the different dose groups and administration routes of the PK studies.*

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 [20].

Confidence intervals for the parameters 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/).

4.3 Results

Estimates were obtained for the 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 4.1). The parameter estimates were used to predict the clinically derived response for 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. Com-

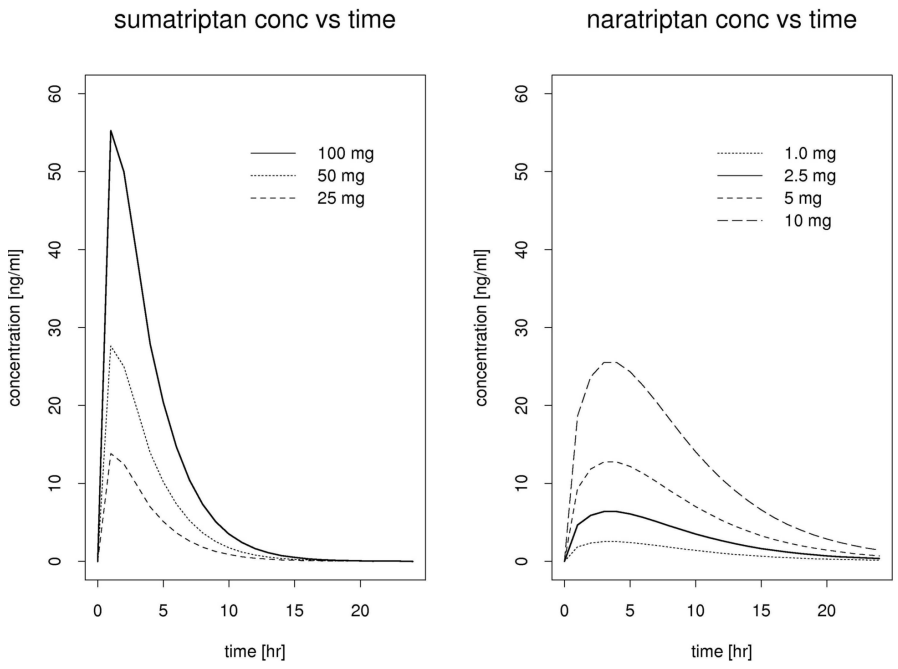

Figure 4.3: *Concentration vs time profiles following oral administration of different doses of sumatriptan (25, 50 and 100 mg) and naratriptan (1.0, 2.5, 5.0 and 10 mg). Standard doses of either drug are depicted in bold.*

Table 4.1: *Probability distributions of headache scores after treatment with sumatriptan (suma) or naratriptan (nara) over the clinically defined states in the migraine model. The probabilities in each column add up to 1.*

	state 1		state 2		state 3	
score	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

parison of observed and predicted responses at other dose levels is not 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 [21]. 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% confidence intervals are given in Table 4.2 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, respectively (mean and 95% confidence interval). 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 4.3 compares the predicted values of $EC50$ and $Emax$ on both transitions with results from *in vitro* experiments (stimulation of [35S]GTP γ S binding to recombinant human 5-HT$_{1B/1D}$ receptors in C6 glial cell lines [22]). Both the *in vitro* and modelled values of potency show that naratriptan is more potent than sumatriptan. It is further observed in this comparison that the potencies of sumatriptan measured at the 5-HT$_{1B}$ receptor and estimated at the second model transition are both significantly smaller than the other *in vitro* values and estimates of potency. According to the *in vitro* studies, the $Emax$ of sumatriptan is larger than that of naratriptan. This in contrast to the $Emax$ values estimated at the model transition from state 1 to state 2, which indicate that the maximum effect of naratriptan is largest.

In Table 4.3 the predicted values of $EC50$ and $Emax$ are also compared with literature findings from *ex vivo* experiments (vasoconstriction of isolated human cortical cerebral arteries and canine middle cerebral arteries [23, 24]). Naratriptan is less potent in the vasoconstriction studies than in any of the comparators. The vasoconstrictive potency of sumatriptan is similar to that at the *in vitro* 5-HT$_{1B}$ receptor. All point estimates

of the $Emax$ ratios are close to unity, with the exception of that obtained for the second transition in the Markov model.

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 4.5 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 is not derived from the sequence of scheduled pain observations. Particularly at late time points, pain scores are recorded infrequently. Basing recurrence on a few observations would result in underestimation of the true recurrence rate. Rather, recurrence is separately assessed on a 24 h basis. Having available only the scheduled pain observations, the observed recurrence rate cannot be derived. Therefore, 24 h recurrence values were obtained from literature. With the currently developed model, however, obtaining predicted recurrence rates is

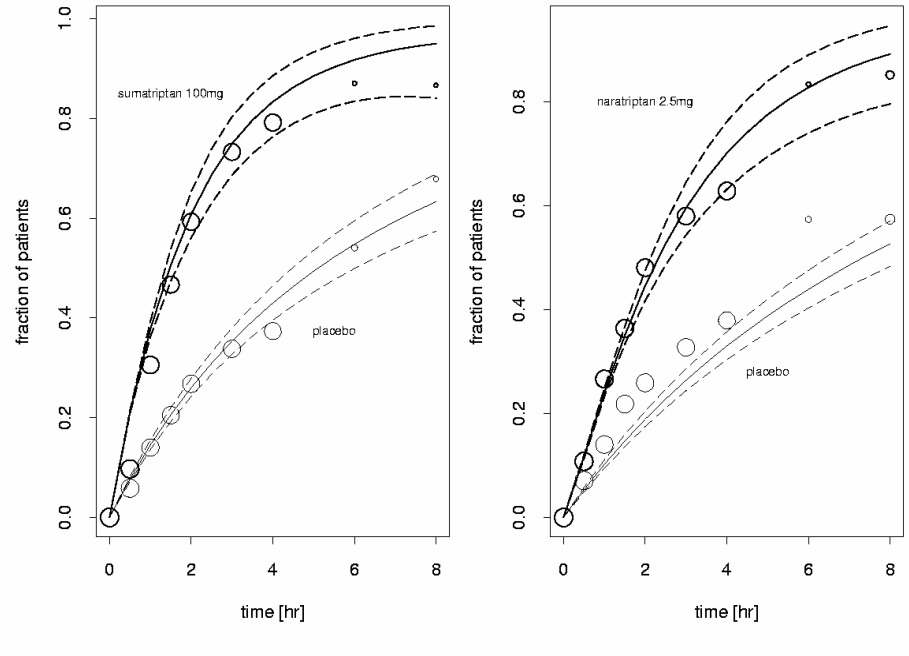

Figure 4.4: *Pain relief profiles vs time. Upper panel: sumatriptan 100 mg. Lower panel: naratriptan 2.5 mg. Pain relief is attained when a patient's headache intensity score equals 1 ("mild pain") or less, starting from score 2 ("moderate pain") or 3 ("severe pain"). Predictions are represented by lines, observations are indicated by markers (circles). The diameter of the markers is proportional to the number of migraine attacks available at the respective time points.*

Table 4.2: *Parameter estimates of the migraine model for sumatriptan and naratriptan. 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 $Tmin$ is the minimum transition time obtained after triptan treatment. Modelling details are explained in the text (see section 4.2.6).*

		sumatriptan		naratriptan	
x – y	parameter	estimate	95% C.I.	estimate	95% C.I.
1-2	$r(0)$ [h^{-1}]	0.16	0.15 – 0.18	0.12	0.10 – 0.13
	$EC50$ [nM]	32	10 – 105	9.6	5.7 – 16
	$Emax$	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
2-1	$r(0)$ [h^{-1}]	0.08	0.06 – 0.10	0.07	0.05 – 0.09
	T [h]	13	10 – 17	14	11 – 20
2-3	$r(0)$ [h^{-1}]	0.24	0.22 – 0.30	0.26	0.21 – 0.31
	$EC50$ [nM]	600	180 – 2000	11	2.9 – 39
	$Emax$	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
3-2	$r(0)$ [h^{-1}]	0.04	0.03 – 0.05	0.03	0.02 – 0.04
	T [h]	25	20 – 33	33	25 – 50

possible. Using the disease model to simulate pain scores short time intervals apart, 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 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 1h and 2h after administration of sumatriptan and naratriptan, allowing both drugs to be compared in terms of efficacy and overall clinical response (pain relief, Figure 4.6. For comparison of potency, drug concentrations are expressed in molar units (M). Sumatriptan is approximately three times less potent than naratriptan, whereas $Emax$ estimates was found to be similar for both drugs. One should note that $Emax$ increases over time because pain relief is determined cumulatively after dosing.

4.4 Discussion

The analysis of ordered categorical data such as headache intensity scores is not straightforward when the underlying measure, pain, is continuous. Two approaches can be used to deal with this incongruence. Either the data are treated as continuous and discretised after analysis or the data are treated as truly categorical and analysed in a model describ-

Table 4.3: *Comparison of potency and maximum effect ratios for sumatriptan (suma) and naratriptan (nara) as obtained in vitro, ex vivo and by the migraine model. CCA (h) = human cortical cerebral artery, MCA(c) = canine middle cerebral artery. "mean" denotes the mean values or estimates. 95% CI denotes 95%-confidence intervals.*

	$EC50_{suma}$ (nM)		$EC50_{nara}$ (nM)		$\frac{Emax_{suma}}{Emax_{nara}}$	
Source	mean	95% CI	mean	95% CI	mean	95% CI
in vitro 5-HT$_{1D}$ [22]	18	12 – 26	4.4	2.9 – 6.6	1.3	1.1 – 17.4
in vitro 5-HT$_{1B}$ [22]	230	180 – 310	23	12 – 43	1.2	1.1 – 1.4
ex vivo CCA(h) [23]	160	63 – 400	100	63 – 160	1.0	0.56 – 1.4
ex vivo MCA(c) [24]	210	120 – 360	70	50 – 100	0.85	0.62 – 1.08
model transition 1-2	32	10 – 105	9.6	5.7 – 16	0.74	0.55 – 0.97
model transition 2-3	600	180 – 2000	11	2.9 – 39	6.8	0.48 – 15

ing 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 quantify distances between categories.

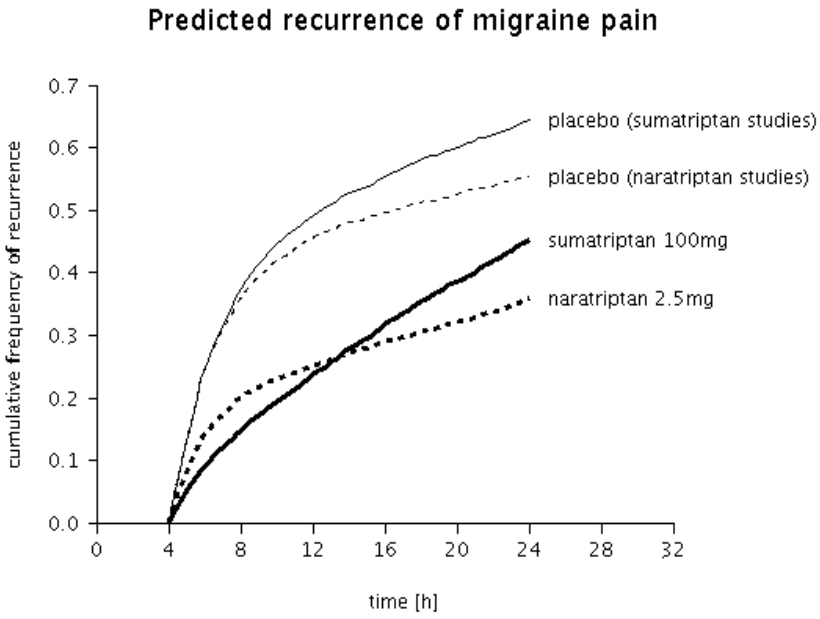

Figure 4.5: *Predicted recurrence rates for sumatriptan, naratriptan and placebo arms in the available clinical studies. Estimation is based on analysis of data up to 24 h after dosing.*

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 was 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

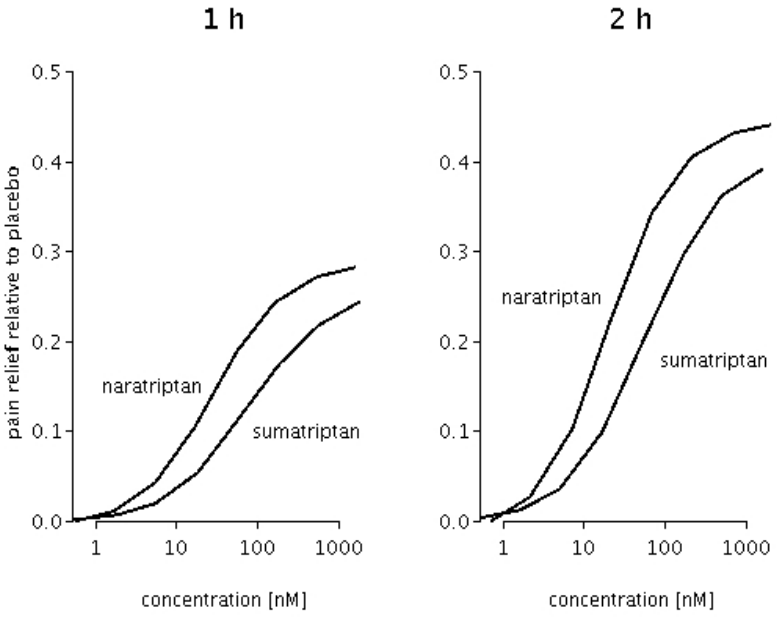

Figure 4.6: *Concentration vs pain relief responses after oral administration of sumatriptan and naratriptan. The role of disease dynamics on drug effect is described by the differences in the PK-PD relation at 1 h and 2 h after dosing.*

estimates, the course of pain relief (mean and 95% confidence interval) was simulated for a large population of migraineurs and then predicted responses were compared with those observed. As shown in Figure 4.4, most observations fall within the predicted 95% confidence interval. The observed placebo response in the naratriptan analysis however deviates somewhat from the predicted response. This is 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 is attached to the accurate estimation of the maximum effect and potency than to the estimation of baseline transition rates. Although balancing the data set 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 correspond 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) is predictive of activity at the 5-HT$_{1D}$ receptor, whereas the transition from state 2 to state 3 (*i.e.*, pain free) is more indicative of 5-HT$_{1B}$ activity. It should be noted that insufficient sumatriptan doses were available to reliably identify sumatriptan potency 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 sensitisation [11]. 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 [25]. Thus, the potency of sumatriptan on the second transition may not have been identifiable even if more data were available.

The vasoconstrictor activity of 5-HT$_{1B/1D}$ agonists are mediated via activation of 5-HT$_{1B}$ receptors [26]. Recent investigations suggest that the main anti-headache effect of triptans arises from activation of pre-synaptic 5-HT$_{1D}$ receptors located at central terminals of trigeminal neurons [8, 11]. 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 below 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 outcomes [21, 27]. 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% [28, 29, 30, 31, 32, 33, 34, 35]. 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 5-HT_{1B} receptor [4], the mechanisms causing recurrence after placebo treatment remain unknown and do not correlate with 5-HT_{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 4.6) were established for both drugs at different times after oral dosing. To our knowledge, no other approach seems to accurately quantify drug effect under non-stationary 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 4.6 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 anti-migraine 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 for 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 pre-clinical studies.

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