Comparison of sumatriptan and naratriptan using a Markov model approach

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Introduction

Sumatriptan and naratriptan are $5HT_{1B/D}$ receptor agonists commonly prescribed for migraine headache. Their mechanism of action involves $5HT_{1B}$ receptor-mediated constriction of intracranial blood vessels and $5HT_{1D}$ receptor-mediated inhibition of pain signal transmission to central trigeminal neurons. It was recently suggested that the effectiveness of triptans can be limited after sensitisation of central trigeminal neurons (Figure 1). The assessment of treatment response in migraine ought therefore to consider drug access to target sites and timing of administration.
Sumatriptan and naratriptan distinctly differ in their pharmacokinetic properties. Sumatriptan has a lower elimination half-life than naratriptan and is less lipophilic. Determining the pharmacodynamic properties of these drugs is more complicated, as these are dependent on the underlying disease process.

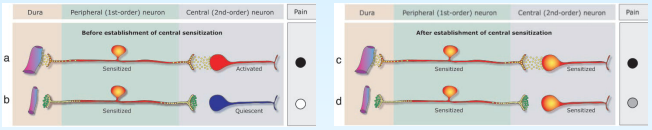

Figure 1. Proposed mechanism of action for triptans during migraine. Before sensitisation of central neurons (**a**, **b**) pain is abolished by binding of triptans to peripheral 5HT1B/1D receptors. In this stage of the migraine attack triptan treatment completely resolves pain. After sensitisation of central neurons (**c**, **d**) pain transmission depends less on peripheral input and triptans might only provide partial pain relief. Adapted from [Levy *et al*]

A hidden Markov model has been developed to predict the effects of triptans on anti-migraine treatment (Figure 2). The model comprises three states, the transitions between which are based on the clinical differentiation between attaining pain relief (from a headache score 3 or 2 to 1 or 0) and attaining pain resolution (from a headache score 3 or 2 to 0). As shown in Figure 1, trigeminal pathophysiology may well be a biological substrate for this differentiation. The hidden Markov model was applied to predict the concentration-effect relationship for sumatriptan and naratriptan. A major advantage of this approach is the the ability to estimate transition rates from one state to another, which makes the evaluation of treatment effects independent of time and observation windows.

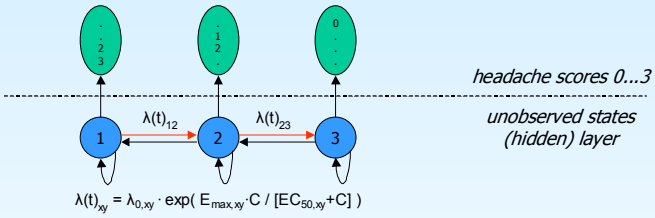

Figure 2. Hidden Markov model of a migraine attack. The red arrows indicate the transitions that are affected by the triptans. The relation between triptan concentration (C) and transition rate $\lambda(t)_{xy}$ is given in the equation.

Estimation & Prediction

Headache scores were derived from clinical studies (GlaxoSmithKline). Based on pharmacokinetic data and models, drug concentrations were simulated in NONMEM V (Globomax LLC) to match sampling times of headache observations. Training data sets were built for sumatriptan and naratriptan by combining headache scores and drug concentrations. Subsequently, the parameters of the hidden Markov model were estimated for both data sets separately in the Splus module HMM [Bureau *et al*].

Using the estimates of the drug-related parameters $E_{max,12}$ and $EC_{50,12}$ the effects of sumatriptan and naratriptan concentrations on the rate $\lambda(t)_{12}$ are plotted in Figure 3.

As pain relief is dependent on the time of observation, comparison between treatments are usually based on 'snapshots' (e.g., 1hr, 2hr and 4 hr). Therefore, evidence of differences or similarities between compounds from current clinical research practice is not fully informative. In addition to a time-independent concentration-effect relationship, the use of a hidden Markov Model allows estimation of treatment response at clinically relevant time points (Figure 4).

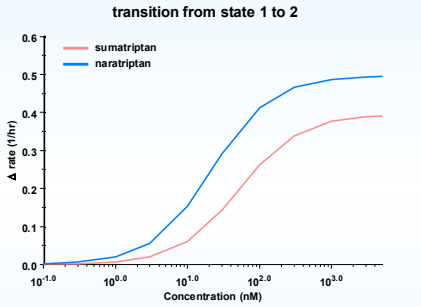

Figure 3. Estimated placebo-corrected drug effects on the transition rate from state 1 to state 2 in the model

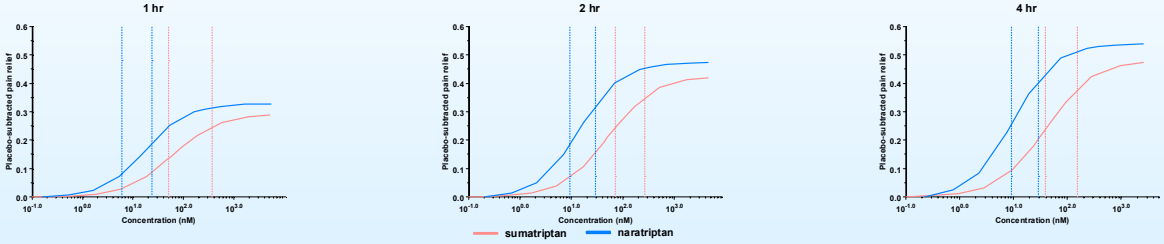

Figure 4. Triptan concentration versus model-predicted pain relief at different time points after drug administration. Pain relief is defined as the placebo-subtracted proportion of patients attaining headache score 1 or 0, starting from headache score 3 or 2. The broken lines enclose the pharmacokinetic ranges of the standard oral dose of sumatriptan (100mg) and naratriptan (2.5mg) at the time of observation.

Discussion & Conclusion

Table 1. Ratios of drug potencies and maximum effects (±SEM). Markov model parameters of sumatriptan and naratriptan are compared with values obtained from experimental models of anti-migraine activity. Ratios from experimental data were calculated using data from [Connor *et al*] and [Comer *et al*].

ratio \ *model*	*markov model transition 1-2*	*carotid constriction*	*middle cerebral artery constriction*
	clinical data	*in vivo* (dog)	*in vitro* (dog)
$EC50_{nara}/EC50_{suma}$	0.30 ± 0.08	0.44	0.38
$Emax_{nara}/Emax_{suma}$	1.25 ± 0.20	0.92	1.14

The anti-migraine activities of sumatriptan and naratriptan were compared by calculating the ratios of drug-related parameters $EC_{50,12}$ and $E_{max,12}$ (Table 1). According to these ratios sumatriptan is 3 times less potent than naratriptan. The maximum effects of the two drugs are not different.
The predictive value of these ratios was evaluated by comparing them to the ratios of experimentally obtained parameters of anti-migraine activity. As indicated in the table, the values are of the same order of magnitude.

The relationship between concentration and pain resolution (*i.e.* attaining headache score 0, or state 3 in the hidden Markov model) can also be characterised with the current approach. However, the sumatriptan-related parameters determining rate $\lambda(t)_{23}$ could not be independently estimated. This may be explained by the dose range available for sumatriptan, which was smaller than that of naratriptan. Alternatively, the biophase corresponding to transition $\lambda(t)_{23}$ may differ from that corresponding to transition $\lambda(t)_{12}$, as is suggested by Figure 1. Sumatriptan could exert its effect differently in this biophase.

In conclusion, a Markov model approach was used to compare the pharmacodynamics of sumatriptan and naratriptan. The concentration-effect relationships were expressed in terms of a time-independent transition rate ($\lambda(t)_{12}$) and a time-dependent clinical measure of efficacy (pain relief). Sumatriptan was found to be approximately three times less potent than naratriptan. The maximum effects of the two drugs were comparable.

References

Bureau *et al. J Comp Graph Stat* 9(4): 621
Comer *et al. Headache* 42(Suppl 2): S47
Connor *et al. Cephalalgia* 17:145
Levy *et al. PNAS* 101(12): 4274