Introduction

Sumatriptan and naratriptan are 5HT_{1B} 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.

Estimation & Prediction

Headache scores were derived from clinical studies (GlaxoSmithKline). Based on pharmacokinetic and models, drug concentration data 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 E_{max,12} the effects of sumatriptan and naratriptan concentrations on the rate \( \lambda_{12} \) 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., 1 hr, 2 hr, 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).

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 [Connor et al]. |

<table>
<thead>
<tr>
<th>ratio</th>
<th>model</th>
<th>parameter</th>
<th>clinical data</th>
<th>in vivo (dog)</th>
<th>in vitro (dog)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E_{max,nar}/E_{max,sum}</td>
<td>markov model</td>
<td>transition 1-2</td>
<td>0.30 ± 0.08</td>
<td>0.44</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>carotid constriction</td>
<td>1.25 ± 0.20</td>
<td>0.92</td>
<td>1.14</td>
</tr>
</tbody>
</table>

The anti-migraine activities of sumatriptan and naratriptan were compared by calculating the ratios of drug-related parameters E_{max,nar} and E_{max,sum} (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 \( \lambda_{12} \) 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 \( \lambda_{12} \) may differ from that corresponding to transition \( \lambda_{23} \), 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 \( \lambda_{12} \) 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 5(S2): 621
Connor et al. Headache 42(Suppl 1): 547
Connor et al. Cephalalgia 17:146
Liev et al. PMAS 10(10): 4374