Scope and intent of investigation

2.1 Scope

The objective of the investigations described in this thesis was the development of novel PK-PD modelling for the characterisation and prediction of the effects of anti-migraine drugs in clinical investigations. Chapter 1 illustrated the many complexities of the characterisation of drug effects on migraine attacks. The episodic nature of the disease poses problems in relation to timing of the treatment of migraine attacks. The onset of an attack is not easily determined. Typically the headaches of patients entering the clinic vary widely in intensity, as does the time between onset and arrival. Furthermore, the diagnosis of migraine is based purely on clinical symptoms. Moreover the headache episodes are characterised by an enormous heterogeneity in duration and intensity, both within and between patients. The course of headache severity changes during the attack, first increasing, then decreasing upon (placebo) treatment, and often increasing again as a result of headache recurrence.

The pathophysiological processes behind these events are incompletely understood. Moreover, biomarkers of migraine are not sufficiently validated to be routinely used in trials. The course of migraine can therefore only be assessed using subjective rating scales. Subjectivity is a major component when dealing with pain assessment. This becomes especially clear when analyzing the responses following placebo administration. Up to 60% of the patients in a trial may experience pain relief after two hours [1]. The extent of the placebo response also depends on the route of administration, the placebo response to subcutaneous injection being some 7% higher than that following an oral placebo [2].
The development of 5-HT\textsubscript{1B/1D} receptor agonists (triptans) has meant a significant improvement to the treatment of migraine attacks. Triptans are better tolerated than the ergotamines and their mechanism of action makes them more specific than NSAIDS. Nevertheless, as with other anti-headache medications, triptan therapy carries the risk of overuse, which can result in progression of migraine into more chronic types of headache. On the other hand, administration of triptans early in the attack may prevent the onset of central sensitisation, which impedes fast resolution of pain.

These and other issues are usually addressed using routine statistical analysis of clinical trial results. In these types of analysis, the headache response at a given time is compared with the headache at baseline and the difference is taken as the treatment effect. Though this is a fast method for assessing drug efficacy, it does not contribute to an increased understanding of the action of anti-migraine drugs. In particular, it does not take into account the course of the disease itself. As mentioned before, headache intensity changes rapidly over the course of a migraine attack. Different phases of the attack are characterised by a variety of pathophysiological events. The development of allodynia has recently been described as a turning point in the attack. Therefore, when seeking to understand the action of anti-migraine drugs, the phase of the attack is an important aspect that should not be excluded from analysis.

Pharmacokinetic-pharmacodynamic modelling is a data analysis technique that studies the interrelationship between the treatment (pharmacokinetics, pharmacodynamics) and the physiology of the disease. By developing models that differentiate between these two aspects, properties of both drug and disease can be quantified. Drug-related parameters that are thus derived and estimated, provide more insight into the properties of the drug than the difference in headache response measured between two time-points. This is because these parameters are to a lesser degree dependent on the background process, the disease. The information obtained from PK-PD modelling can be exploited in various phases of drug development. The development of new anti-migraine compounds in any clinical phase benefits from the insight obtained by characterising the disease process of migraine. Drug properties determined in in vitro or in vivo experimental research can be integrated into the model to forecast the expected clinical effect. In later stages of drug development, the estimates from earlier analysis can be used to predict the drug effect on experimental clinical endpoints. Furthermore, the effect of pharmacokinetic parameters on the effect can be investigated by varying these parameters in a simulation study.

To date the application of PK-PD models to the analysis of anti-migraine drugs has been limited because of the categorical nature of the pain endpoints and the considerable heterogeneity in the response. Both limitations render analysis using differential equations and algebraic equations practically impossible. Any modelling effort will thus have to be based on probability theory. Especially in the case of longitudinal analysis, probability models are sparse. Proportional odds models have been applied to describe the decrease in pain intensity over time [3]. These models describe the odds of observing a certain score relative to another score as a function of drug concentration and time. An apparent disadvantage of this technique is that the course of the probability of a headache score in the drug-free situation is determined by a monotonically decreasing or increasing function of time. This means that as time increases, the probability of observing a
higher pain score will approach zero. However, it is not time that determines the next pain intensity, but rather the current phase or state of the attack. This is because the state of the attack represents the underlying disease process. In fact, many disease models are based on the assumption that the next state is independent of the time spent in the current disease state. This “memoriless” property is a unique characteristic of Markov models.

The Markov approach has first been applied to migraine data by Hassani and Ebutt [4]. They used a two-state approach that distinguished between headache and no headache. This approach is appropriate for describing the pain free response, but not the pain relief response, as this endpoint would require that an additional state be included. Moreover, this model does not consider a relationship between drug concentration and transition rate. Rather, dose was used as a predictor of pain resolution.

Markov models and other state-space models have always enjoyed much appeal in the analysis of disease progression. However, they have seen little application in PK-PD modelling. The current series of studies attempts to evaluate the usefulness of Markov models in determining the PK-PD relationships of 5-HT$_{1B/1D}$ receptor agonists.

2.2 Intent of investigation

In Chapter 3, the development is described of a hidden Markov model (HMM) for the prediction of the anti-migraine response. The question is addressed whether the PK-PD paradigm can be applied to Markov models of migraine. Thereto, the HMM is ‘trained’ using data from efficacy studies in which oral doses of placebo, 25, 50 and 100mg of the 5-HT$_{1B/1D}$ agonist sumatriptan were administered to migraine patients. As the pharmacokinetic profiles for these patients were not available, the pertinent pharmacokinetics are derived from population PK analysis of early clinical phase studies. In this setting, the results of model training are evaluated. Parameter estimates and their levels of uncertainty are reported. The results are interpreted in the light of clinical experience and pathophysiological knowledge about migraine.

Chapter 4 tests the predictivity of the hidden Markov model across drugs as it is applied to data from clinical studies of naratriptan. The parameter estimates, headache predictions and corresponding confidence intervals are compared between sumatriptan and naratriptan. The drug-related parameter estimates are also evaluated against values obtained from ex vivo and in vitro experiments. If these are similar, this suggests that the model may be used as a bridging tool for early clinical development. Also, the model-based predictions of the secondary endpoint ‘headache recurrence’ are discussed. In particular, the question is addressed whether the modelling assumptions are congruent with pathophysiological theories that explain the phenomenon of recurrence.

The value of the HMM in the development of new formulations for sumatriptan is explored in Chapter 5. Given the erratic absorption profile of oral sumatriptan in migraine patients experiencing an attack, formulations are being developed that aim to improve this. PK-PD modelling provides a method for predicting the expected influence of changed absorption characteristics on the clinical response. In particular, by varying the absorption rate constant and lag time, an impression can be obtained of the poten-
tial of improved formulations. The results of a series of HMM-based simulations are shown and the expected therapeutic gains of new formulations are evaluated, taking into consideration the assumptions upon which the model is based.

Chapter 6 addresses the issue of heterogeneity in migraine. Clinical symptoms are known to vary widely, both in duration and intensity, between patients. According to diagnostic criteria, the duration of migraine headache ranges between 4 and 72 hours [5]. In children and adolescents, headaches with durations shorter than 4 hours may also be diagnosed as migraine [6]. Simultaneously, patients in this age group show high placebo response rates [1]. Since young migraineurs add considerably to the heterogeneity of the disease, it is attempted to model the influence of age on the dynamics of the migraine attack. Applying a modification of the HMM described in Chapter 3, a paediatric study of sumatriptan is analysed together with studies in adults. Based on the parameter estimates, headache responses are predicted for different age categories and for different doses of oral sumatriptan. It is then discussed how an age model for migraine can help in establishing efficacious dosing regimens for children.

As migraine is an episodic disorder, the aim of drug treatment is not limited to aborting individual events (attacks). Treatment can also aim to prevent the generation of new events. On the other hand, acute treatment might inadvertently alter the dynamics of the disease, resulting in a higher attack frequency.

There has been little attention given to modelling the effect of anti-migraine drugs on the progression of the disease. Therefore, in Chapter 7, a Markov model is developed to characterise the dynamics of migraine as an episodic disorder. Based on states that represent migraine attacks and attack-free periods, the Markov model is used to estimate the transition rates between the states, both in the presence and in the absence of treatment. The results of the Markov approach are compared with those obtained by using an analysis of distributions, in which the durations of attacks and attack-free periods are characterised by statistical distributions. The advantages of both approaches are discussed in the light of model predictivity and application to prophylactic drug development.

In Chapter 8 the results of the investigations described are reviewed and discussed.

Appendix A describes in more detail the HMM and is concerned with the development of confidence intervals for Markov models. When applying a new approach to PK-PD modelling, adaptations to the approach are often necessary in order to make it to comply with the modelling practice. Although confidence intervals for individual parameter estimates can be relatively easily obtained with available software, they are not readily derived for the time course of the probability of response. As this time course encompasses more than a single parameter estimate, any calculation deriving the confidence interval of this time course also needs to take into account multiple parameters. In this appendix, a fast, iterative method is described that allows the construction of confidence intervals on mean response profiles. The results of this method are presented and compared with intervals obtained by a resampling technique. Based on the comparison,
guidelines are given as to the scenarios in which the use of the fast method is advised. Appendix B describes in more detail the general properties of a HMM and the statistical algorithm that is used in the present studies to obtain parameter estimates. Furthermore, it is explained which parts of the original source code were edited to allow for the modelling of clinical migraine responses. These parts of the source code are included in this appendix, as is a link to the complete code of the original S-Plus and R libraries.

References


