Personalised pharmacotherapy in paediatric epilepsy : the path to rational drug and dose selection

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CHAPTER 9

CONCLUSIONS AND FUTURE PERSPECTIVES

Conclusions and Future Perspectives

1. Conclusions

The objective of modern clinical pharmacology is to improve the effectiveness of current treatments and to provide new medicines to treat as many diseases and conditions as possible. In addition, its goal encompasses the development of methods and tools that allow for optimisation of evidence generation and evidence synthesis, ensuring appropriate prescription, delivery and use of medicines. Since the 1960s, with the Kefauver-Harris amendment to the Food Drug and Cosmetic Act in the USA in 1962 [1] and, with the European Directive harmonising requirements for marketing authorisations in 1965 [2], the action of national and supranational governments has established the need for appropriate scientific evidence on efficacy and safety of all new drugs before their approval for clinical use. These principles already take into account the concept of interindividual variability and recognise the fact the requirements to treat vulnerable patients may differ from the general population. Indeed, the recognition that therapeutic response is affected by intrinsic and extrinsic determinants of variability sets the foundations for personalised treatment, separating patients into different groups—with medical decisions, practices, interventions and/or products being tailored to the individual patient based on their predicted response or risk of disease. While the tailoring of treatment to patients goes back to the time of Hippocrates [1], the development of new diagnostic, mathematical and statistical approaches along with computer and informatics allows the implementation of dosing algorithms based on detailed understanding of disease and underlying exposure-response relationship.

In this thesis, we set out to show how understanding of pharmacokinetics, pharmacodynamics and exposure-response relationships may be used in conjunction with modelling and simulation to personalise antiepileptic drug treatment in paediatric epilepsy. In the first section we reflect on the key issues in the diagnosis and treatment of epileptic seizures. An extensive

review of current practices in paediatric epilepsy is presented together with the implications of different sources of variability for treatment outcome. A clear picture emerges regarding the consequences of empirical experimental evidence and the opportunities for the characterisation of exposure-response relationships using quantitative clinical pharmacology. It also becomes evident that knowledge regarding pharmacokinetics and pharmacodynamics is not being used to support clinical decisions, with titration, tapering and switching of drugs and dosing regimens as the method of choice to tackle inter-individual differences in treatment response. In the second section, we review the use of pharmacokinetic and pharmacokinetic-pharmacodynamic modelling for the most commonly used antiepileptic drugs. These data provides a baseline for the development and implementation of personalised treatment using model-based dosing algorithms, where we show that parameterisation of the impact of intrinsic and extrinsic factors (i.e., covariate effects) can already be used to guide dose selection and/or stratify patients. Focus was given to the role of demographic differences and drug-drug interactions, as they represent common causes of variability in drug exposure. These analyses have shed light into the gaps in knowledge, and in particular the lack of data regarding the exposure-response relationships of anti-epileptic drugs. In the third section, we make use of a paradigm compound, lamotrigine, to illustrate the requirements for the development of model-based dosing algorithms and their application in drug development and in clinical practice. We show how insight into covariate effects in pharmacokinetics and pharmacodynamics, along with the underlying exposure-response relationship allows further optimisation of treatment in children. We take the opportunity to highlight the experimental challenges associated with current research and propose possible solutions to overcome these issues. In this concluding chapter, we re-iterate the questions posed at the onset of this thesis, reflect on the results obtained, including some of the main limitations, and future steps required to implement personalised pharmacotherapy in paediatric epilepsy.

1.1 Knowledge integration

Neurologists have around 20 anti-epileptic drugs (AEDs) in their armament against epileptic seizures. Regardless, up to 30-40% of patients do not respond sufficiently to pharmacotherapy [2,3]. With the alternatives being invasive treatment such as vagus nerve stimulation or epileptic focus resection, there is a need for the optimal utilisation of existing AEDs as well as better experimental protocols for the evaluation of new compounds. Modelling and simulation techniques offer an opportunity for personalisation of treatment due to its ability to identify relevant sources of variability and integrate existing knowledge regarding the contribution of multiple factors to variation in exposure, pharmacological effect and clinical response. Of note is the possibility of using prior information, i.e. evidence synthesis, and exploration of hypothetical scenarios *in silico*, i.e., clinical trial simulations (CTS).

In other fields such as oncology, infectious diseases, and diabetes, modelling and simulation has advanced to a stage where models are starting to approximate the relevant physiology and pathology to a significant degree, leading up to systems pharmacology. In epilepsy, however, the complexity of the disease, the lack of biomarkers along with the use of the discrete measures of the clinical symptoms have resulted in a status quo, in which there appears to be no alternative to treatment optimisation through trial and error, as defined by titration, tapering and treatment switch guidelines [4]. Evidence exists for the selection of some AEDs over others in specific seizure types, syndromes, or in few cases known aetiologies. Yet, these guidelines only provide very rough guidance in terms of first-, second- and sometimes third-line AED choices. There appears to be no need for insight into the underlying exposure-response relationships, as it is assumed that variability in response to treatment cannot be, at least in part, assigned to specific factors. Once an AED is selected, information regarding dose titration across a predefined range of doses is considered as sufficient to establish whether a patient will respond to treatment or not. Again, no quantitative guidance is linked to these procedures other than therapeutic drug monitoring, which is often used to

determine treatment adherence as opposed to its use for dose personalisation.

In chapter 1, we argued that PKPD and disease modelling are essential to cope with this complexity and to eventually achieve rational epilepsy pharmacotherapy. In this context, paediatric epilepsy stands out from adult epilepsy and other disease areas due to the existence of specific paediatric types of epilepsy, even larger lacunas in paediatric evidence, and the fact that some paediatric epilepsy phenotypes exhibit more severe disease progression than that typically observed in adults. These factors are often used to justify the choice for polytherapy in paediatric cases. As such, prescribing physicians need to make careful assessment of combinations and dose adjustments, but these are often based on adult doses expressed in mg/kg body weight. It is now common knowledge that drug clearance scales non-linearly with weight [5]. Moreover, doses in children younger than 2 years of age need to account for ontogeny processes and other developmental changes, which are not characterised by the effect of body weight. Likewise the role of drug-drug interactions cannot be overlooked. In Chapter I, we reviewed different sources of variability in treatment outcome in epilepsy.

One of the questions we aimed to answer in this thesis was whether ***inter-individual differences in exposure to AEDs and inadequate response in some patients can be explained by size and age-related covariate factors.*** To address this question, in **Chapter 3** we have summarised all available PK and PKPD models in the published literature for AEDs. By doing so, an overview was created of the different model parameterisations and covariate effects, such as drug-drug interactions (DDIs), effect of body weight and age, genotype, and other covariates. While size and age-related covariate factors explained differences in exposure to some degree, a considerable proportion of the overall variability in pharmacokinetics remains after adjusting for these factors. Typically, the variability in clearance, expressed as coefficient of variance (CV%), is roughly 50% for most models for most AEDs. The review in chapter 3 also showed that most AED PK models were in the form of one-compartment model with first-order absorption and elimination. Notable exceptions were models for the

correlation between bound and unbound concentrations of valproic acid and phenytoin, and the physiology-based PK (PBPK) models for valproic acid [6]. Not many PD models were found in literature, and those that are available model the correlation between exposure and parametrically secondary outcome measures such as the time to first seizure analysis for topiramate efficacy. A database of predictive models was created, which allows looking up possible approaches to model pharmacological data in epilepsy, it aids in identifying the most relevant covariates to screen for in an analysis, and it reveals the models that are currently available for clinical personalisation of treatment and dose.

1.2 Model-based dosing algorithms

In **Chapters 4 and 5** we address three other important questions proposed at the start of this thesis, namely whether evidence of ***drug-drug interaction studies in adults can be used to assume similar effects in the paediatric population*** and evaluate ***the implications of commonly recommended empirical dosing in mg/kg*** in children. Using simulations and a selection of literature models from chapter III, we show the impact of DDIs on clinically relevant measures of drug exposure. Through these simulations, we also demonstrate the implications of adding one or more other AEDs onto the existing therapy, i.e., dose adjustments are typically required to ensure maintenance of comparable exposure levels to the primary AED. Furthermore, under the assumption of similar exposure-response, our results show important differences in terms of the magnitude of the effect of DDIs in children. This evidence reinforced the relevance of model-based dosing algorithms as a tool for dose personalisation. In chapter V, we use simulations to explore the impact of integrating therapeutic drug monitoring (TDM) with model-based concepts to define the dose rationale for individual paediatric patients. Variability in the time to achieve a predefined target AED exposure, as well as the variability in exposure during the maintenance phase were significantly reduced by an approach based on a combination of models and TDM, when compared to other approaches. These findings provided the basis for an answer to the

fourth question included in the objectives of this thesis, namely that ***model-based dosing algorithms can minimise the need for treatment switch and combination therapy.***

1.3 Evidence generation and evidence synthesis in epilepsy trials

In subsequent chapters VI, VII and VIII, we aimed to determine, amongst other things an answer to the two remaining questions included in the scope of this thesis, namely ***which data are required and which criteria should guide the selection and personalisation of paediatric doses.*** Using a paradigm compound we explored experimental requirements assuming comparable and different exposure-response between adults and children. A special case of prior information is allometry, a theory that states that certain PK parameters correlate to body weight according to pre-defined mathematical rules. Using allometry, we investigated our ability to predict paediatric PK of lamotrigine (LMT) using a model built on adult data. As previously suggested, below the age of 2 years, allometry does not adequately adjust for the observed changes in clearance and thus a maturation function was developed to adjust for these findings. The result was a model that is able to predict for patients ages 1 month to 91 years of age. The model was built on data from several major ethnicities (Black, Asian, Caucasian), for which no significant differences were found in PK. As a result, the developed model may be one of the most versatile models for LMT available. Due to its ability to predict for this wide range of populations, simulations were performed to optimise the typical dose for all ages, under the assumption of similar exposure-response. This is the first attempt to derive, through modelling & simulations, a dose of LMT in patients aged 1-24 months of age. While this dose will achieve average steady-state concentrations within the therapeutic range for most of these patients, large variability remains. Further personalisation and individualisation is still indicated to adjust for the unpredictable variance in the PK parameters, such as the 56.1% of variance in clearance after correcting for covariates. Furthermore, differences in exposure-response between adults and children may require setting a different target

exposure. Using the covariates presented with the PK model of chapter VI in combination with therapeutic drug monitoring and individual parameter estimation approach showcased in chapter V will allow further accuracy and precision in the personalisation of LMT dosing.

As discussed in chapter I, the definition of a clinical endpoint, and thus efficacy, determines the data required to accurately and precisely estimate parameters such as potency and maximum efficacy. Previous work described the estimation of pharmacodynamic models on clinical endpoints such as the ability to achieve at least a 50% reduction in seizure frequency, or the occurrence of a first seizure after start of treatment. These endpoints are binary and thereby the information from seizure diaries is reduced to simple yes and no outcomes. This simplification leads to a large loss in information, which is often compounded in the analysis of clinical trials by thereafter taking means and standard deviations of the study populations. These endpoints are in fact derived from the underlying endpoint which is seizure counts over time. With the description of seizure counts, one may determine the other, more often used, endpoints as they are the automatic result of it. Thus, it is recommended to model seizure counts, as it is closer to the pathophysiology and thus should be more sensitive to disease progression and treatment effect. Chapter VI outlined the use of a population Poisson model for the description of seizure counts in adult patients with partial onset (PO) and primary-generalised tonic-clonic (PGTC) seizures. Our investigation revealed that these patients differ in sensitivity to treatment, and we quantified the correlation between exposure and response. Apart from the typical inter-individual variability, as is normally taken into account by mixed-effects modelling, we also used Markov properties and stochastic differential equations (SDEs) to adjust for changes in the disease activity over time within the individual (intra-individual variability). Now that a PKPD model is available for LMT, individual sensitivity to treatment may be estimated in the clinical population, based on seizure diaries and TDM. More rudimentary dosing applications may be developed using nomograms or stratification of patient groups.

The Poisson model was further evaluated on a paediatric cohort of patients with PO seizures aged 1-24 months. These patients showed a higher

baseline disease activity, but also showed a higher sensitivity (as EC_{50}) to LMT compared to that previously found in adults with PO seizures. On the other hand, a small difference was found with regard to placebo and maximum treatment effect. We used clinical trial simulations to investigate the required number of patient to show efficacy in this population (power calculations), assuming similar PKPD as estimated from the data. It was found that a minimum of 200 patients were needed to achieve sufficient power, a number much higher than what was considered in the original trial. In other words, the original trial of LMT used in this analysis was found to be underpowered, even if LMT in this population can be quite effective. Future clinical trials of AEDs, especially in a patient group where patient inclusion is difficult such as in these young children, may want to use modelling & simulation approaches such as those showcased in chapter VIII to *a-priori* optimise the trial design for sufficient power.

In summary, we have created a model library and overview of PK and PKPD models for AEDs, allowing easy implementation and adaptation of the available literature information. Furthermore, we have shown that personalised and individualised medicine based on modelling approaches is not only feasible, but has a significant impact on achieving pre-set exposure targets, thereby reducing variability in treatment outcome. Finally, new models for the PKPD of lamotrigine were provided, which, assuming their validity in clinical populations, may allow pharmacodynamic personalisation and individualisation, as well as clinical trial simulations for the optimisation of future trial designs.

2. Limitations

In addition to the discussed thesis results and conclusions, a discussion of its limitations is warranted. Our work on the impact of drug-drug interactions and dosing algorithms through PK simulations in chapters IV and V required us to make certain choices in the use of PK models for anti-epileptic drugs in literature from chapter III. Due to the nature of the investigation with regard to drug-drug interactions, models were selected in which many of these interactions were taken into account. Such selection

criteria limited us in the possibility of selecting models that were able to predict for different races and sometimes age groups (notably lamotrigine and valproic acid). Also, by selecting models for this purpose, their appropriateness for parameter estimation in chapter V may have been affected. A more thorough, but much more time-consuming approach would have been to perform a full meta-analysis of the available models listed in chapter III, or to first create an integrated PK model for each AED based on the available literature models and validate it against simulated data from the original models, or ideally, against actual data. This was, in part, performed in chapter VI for the PK of lamotrigine, where we used literature information regarding the relevance of allometric scaling, drug-drug interactions, and changes in PK according to age to construct a model that was validated on actual PK data from several clinical trials. Such an exercise was not feasible for all AEDs discussed in chapter III due to a lack of time and data, but may be performed in the future using the materials provided in the supplements of chapter III.

A further limitation of chapters IV and V is the use of plasma AED concentrations as a substitute marker for cerebral exposure. As mentioned in chapter I, cerebral PK is largely determined by the blood-brain-barrier, which limits the amount of drug that enters the brain. Moreover, evidence exists for steep concentration gradients between different brain compartments, which may lead to differences in the effect of an AED depending on where in the brain it distributes to, further complicating our ability to link AED exposure to effect [7,8]. These issues are a source of variability in correlations between systemic exposure (observed as plasma concentrations) and clinical effect, compounding the disbelief amongst many clinicians regarding the clinical relevance of TDM in anti-epileptic drug therapy. More physiology-based PK models may improve the correlation between the PK of AEDs in plasma and at the target site, resulting in the ability to better correlate exposure to effect. Steps are already being undertaken to the establishment of generic brain PK models to allow the characterisation of system-specific and drug-specific parameters [9,10].

When it comes to the pharmacodynamic analysis in chapters VII and VIII, some major hurdles may also be identified. It has been reported that self-reporting of seizures, as was performed in the clinical trials from which data was used in chapters VII and VIII, may be subject to large under-reporting of seizure counts of up to 50% [11]. If this under-reporting has occurred fully at random time-points and in random patients, i.e. no underlying mechanism drove the under-reporting, then the impact on our conclusions in these chapters may be small to negligible. Although parameter values may in that case be affected, the models as reported would still predict adequately for numbers of seizures observed and treatment effect, albeit that they do not predict for seizures unobserved or unreported. However, if there is some mechanism of seizure under-reporting, unbeknownst to us, that skews the under-reporting in certain moments or types of patients, we may not be able to accurately determine treatment effect in a subpopulation of our data. For example, if seizure reporting is affected more in patients with PO seizures compared to those with PGTC seizures, or vice-versa, our estimated treatment effect may not compare between the two groups as was our conclusion in chapter VII, even though the models may still predict reported seizure counts in both populations to an acceptable degree. Several devices exist for the direct registration of seizures based on EEG patterns, but the use of these is invasive. It is at this point unrealistic to make predictions on the impact of modelling seizure counts as registered by these devices compared to the patient-reported seizure count.

Unfortunately, apart from seizure types PO and PGTC, no other covariates were found to influence baseline seizure counts, placebo effect, or LMT potency and maximum efficacy (although LMT exposure was found to predict for clinical efficacy). As a result, personalisation of treatment may only be done by a relatively small degree, and the current status-quo with regard to individualisation, i.e. adjustments of AED choice and dose after the start of treatment, will remain necessary until biomarkers may be identified that are sensitive to drug effect. Furthermore, our models were built on data of adults and children that were not treatment-naïve and were already under treatment when enrolled in their respective clinical trials. As mentioned in chapter I, this practice, which is the standard in

paediatric trials, does not allow us to estimate the parameters that determine treatment effect. The thereby increasingly therapy-resistant population that is subjected to these trials may bias drug development in the direction of drugs that work in a small resistant section of patients while the development of drugs that are safer in the general treatment-naïve population may be discarded. In essence, the treatment effect observed in clinical trials may not be directly translatable to the general clinical population, thereby possibly leading to an unfair advantage for the older AEDs that were tested in populations more representative of the typical clinical populations.

Apart from the issue of extrapolation of drug efficacy from add-on trials to the general patient population, there is the matter of drug-drug interactions (DDIs), both in terms of PK and PD. It has been shown in animal models that AEDs show significant PD DDIs [12–14]. While PK DDIs of AEDs are extensively described in literature (chapter III), these are only adjusted for to a limited degree in clinical trials. For example, in the evaluation of LMT in adult patients in our data, patients receiving valproic acid during the trial were given a lower dose, as it was already known that VPA decreases LMT clearance. There is however also variability in the DDIs themselves, i.e. not every patient shows DDIs to the same degree. When this is not taken into account during dose optimisation, observed drug interactions with regard to treatment outcome cannot accurately be attributed to PD. Further, the investigation of PD DDIs requires specific trial designs optimised for the ability to detect DDIs. This may include the start of the second AED after sufficient data has been collected to estimate the PD parameters of the primary AED, and the optimisation of dose levels to make sure sufficient DDIs will be found. Current trial designs do not consider such trial modalities and thus often do not allow the estimation of PD DDIs (if any) and the assumption in practice seems that, if it hasn't been found, it is simply not there. Future trials may be optimised by performing CTS and the application of optimal design criteria using specific software [15,16].

Finally, a major limitation exists with the use of seizures as a clinical endpoint, and by proxy its modelling. Disease activity often exists even when a patient has not had a seizure on a given day. In fact, some patients

only exhibit few seizures per month or even per year. Defining successful treatment in these cases becomes problematic due to a lack of data; how long do we need to wait in these types of patients before we can speak of treatment success? Similar to this issue, the Poisson model may only estimate lambda, i.e. the seizure frequency, if sufficiently long follow-up data is available.

Break-through seizures due to patient non-adherence may then easily be wrongly attributed to resistance to medication, resulting in unnecessary treatment changes. It also limits our ability to accurately estimate drug effect from clinical trials. Biomarkers that are able to accurately detect epileptic activity in patients with a low frequency of seizures may solve this issue in the future.

3. Future Perspectives

Given the conclusions and limitations, some possible future investigations may be discussed. An important question in epilepsy research is whether it is possible to predict disease progression. One notable example of disease progression modelling was undertaken by Berg *et al.* [17] In their work, three Markov states were defined, in remission, no longer in remission, and never in remission. Based on this model, they were able to describe the chance of achieving remission over time. They showed that, over the timespan of up to eight years, disease progression may be observed. In our investigations in chapter VII and VIII, we did not detect any noticeable direction of time-dependent changes in disease activity, nor did we find predictors for disease progression, even if many patients in our data showed large changes in seizure activity over time. This may be due to the limited time-scale in the data with regard to baseline, leading to the inability to differentiate disease progression from a small or negligible treatment effect. Contributing to our inability of measuring any significant disease progression may have been the relatively short follow-up of maximally two years, comparing to up to eight years in the Berg et al. data. Alternatively, predictors may exist, but these were not included in the data. Most probably however, predictors of disease progression will not be found

in demographic properties or easily observed variables. The question is then, how long does one need to have a base-line and follow-up data on a patient to adequately determine whether a started treatment is efficacious. In the following example, we investigate this using the Poisson models with and without SDE for PO type seizures from chapter VII.

AED therapy often results in the occurrence of side-effects. In this thesis, we focused on the modelling of PD in terms of efficacy alone, but similar approaches may be applied w.r.t. PD modelling of the number of side-effects, and their severity. Some novel methodologies are available, based on item response theory, that allow the simultaneous modelling of several clinical outcome markers including their severity scores, including the interaction between the scores [18,19]. Such methods may be further applied to the combined modelling of efficacy and side-effects, as it stands to reason that some correlations may exist between these outcomes.

As described in chapter VII, a Poisson model was built that took into account time-dependent intra-individual changes in seizure activity using SDE. The SDE described random changes in seizure activity with no specific direction (i.e. the average change in seizure activity over the whole population remains 0), but 95% of individual changes in seizure activity (seizures/day, or frequency) were between -0.3 to +0.3 seizures/day (median: 0). In other words, starting at a seizure frequency of one per day, this could change to 1.3^7=6.3 seizures per day in one week. This is, however an extreme scenario, with most patients showing less dramatic changes over time. Efficacy of LMT was described using the typical sigmoidal curve dependent on maximum drug effect (Emax), potency (EC_{50}) and LMT average daily concentrations. Using this model, simulations were performed based on the characteristics of the patients from the original study with regard to demographics, seizure baseline frequencies, placebo effect, and lamotrigine potency and maximum efficacy. Seizure counts were simulated for two baseline weeks and six treatment weeks. Lamotrigine was titrated to a dose of 300 mg/day in steps of two weeks (up-titration to 50 and 100 mg/day) and one week (up-titration to 200 and 300 mg/day). During this treatment phase, one, two, or three pharmacokinetic therapeutic drug monitoring samples were simulated for subsequent PK

parameter estimation, using the methodologies from chapter V. Using the estimated PK parameters, or population-predicted parameters (no TDM samples), individual-predicted average LMT concentrations were derived for all days in all patients. Subsequently, PD parameters were estimated using the original model with and without SDE, and follow-up data of one, two, three, four, five or six treatment weeks. Relative error (RE) of PD parameters were then calculated using equation 1 and plotted between the different follow-up scenarios (between one to six weeks) and between number of TDM samples used (none to three). Plots were split between using the SDE model and non-SDE model.

$$Relative\ error\ (\%)\ = \frac{x-tv}{tv} * 100\% \qquad (1)$$

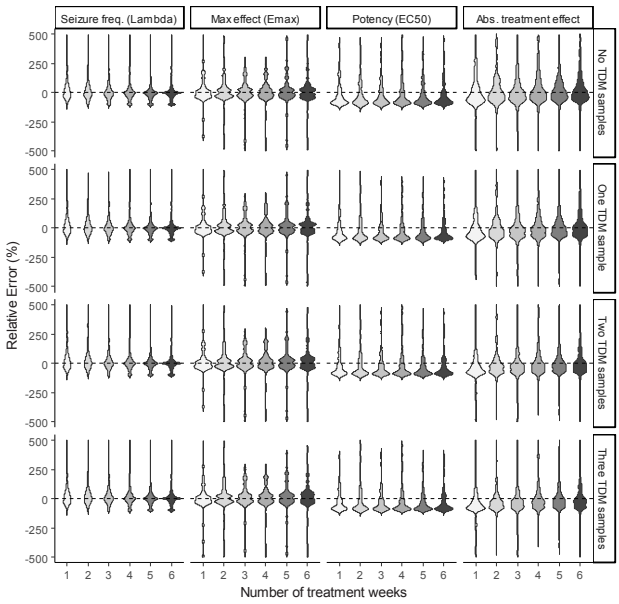

Figure 1. Results from application of the Poisson model with stochastic differential equations. Parameter estimation accuracy (RE%) of seizure frequency, maximum treatment effect, potency and absolute treatment effect between scenarios of different number of follow-up weeks, and differing number of TDM samples used for estimation. Positive values signify overestimation and negative values underestimation.

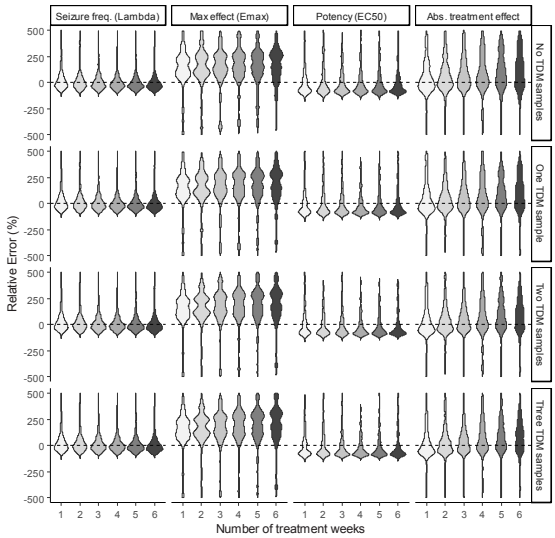

Figure 2. Results from application of the Poisson model without stochastic differential equations. Parameter estimation accuracy (RE%) of seizure frequency, maximum treatment effect, potency and absolute treatment effect between scenarios of different number of follow-up weeks, and differing number of TDM samples used for estimation. Positive values signify overestimation and negative values underestimation.

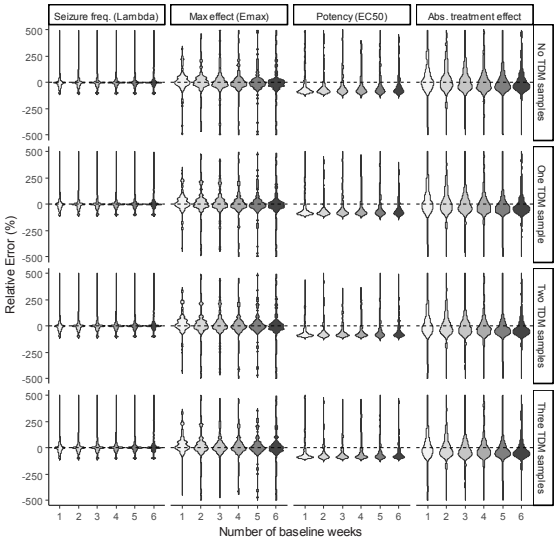

Figure 3. Results from application of the Poisson model without stochastic differential equations. Parameter estimation accuracy (RE%) of seizure frequency, maximum treatment effect, potency and absolute treatment effect between scenarios of different number of baseline weeks, using 6 treatment follow-up weeks, and differing number of TDM samples used for estimation. Positive values signify overestimation and negative values underestimation.

Results of these simulations are not very encouraging. Neither the model with SDE nor that without SDE is able to accurately estimate the potency. Furthermore, using the model without SDEs resulted in large errors in estimation of absolute treatment effect, showing that the issue of individual parameter estimation is one based on parameter identifiability and not on model complexity. This finding may have grave implications in the analysis of clinical trial data, where trial design choices should take into account the long follow-up times required to accurately estimate these parameters. The simplification of analysis by disregarding the changes in seizure frequency over time may result in improper assessment of drug effect in some trials, although if a trial were to be repeated infinite times, the mean estimation of drug effect should still approach the true value (Figure 1). Conversely, depending on duration of treatment follow-up, the absolute treatment effect, i.e. the treatment effect observed in the patient may be estimated to an adequate degree using the model that includes SDEs, with a follow-up of six weeks showing good agreement with the absolute treatment effect that was simulated (Figure 2). Parameter estimation was not significantly improved by increasing the baseline period from 2 to 6 weeks (Figure 3). However, maximum treatment effect and potency are required to make for prediction of treatment outcome, as it is these two parameters in combination with actual exposure (as average daily concentration) which determine the absolute treatment effect. It seems that therapeutic drug monitoring did not improve our ability to estimate pharmacodynamic parameters, but it should not be dismissed, as accurate pharmacokinetic parameters will still be needed to derive the optimal target maintenance dose once the optimal target exposure has been determined. Possibly, it may be required to perform so-called probing tests, in which the potency and maximum effect of the individual patient are explored by testing multiple dose levels or lower doses of multiple drugs. By perturbing the system and collecting data through sensitive biomarkers, we may derive system-specific parameters that inform on the sensitivity of the system to changes induced by AEDs. When this is applied in a systematic manner that evaluates the relevant physiology, a rational decision of pharmacotherapy may be made on the basis of sensitivity of the individual patient.

This example highlights the need for biomarkers to provide a window into the pathophysiology. Such biomarkers may then provide early predictors of the maximum efficacy of the available AEDs, thereby allowing selection of the most probable efficacious treatment *a-priori*, and selecting the appropriate exposure level for the patient, after which techniques as shown in chapters IV and V may be used to optimise for dose. With relation to the Poisson model, these biomarkers (or perhaps other predictors) would adjust the value of lambda, where possible over time. With enough accurate biomarkers, the value of lambda will simply approach the number of seizures for that day. Such biomarkers would also solve the issue discussed in the limitations, regarding difficulties in the estimation of treatment effect in patients with low seizure frequencies. In this sense, the use of a Poisson model, or any of the related models (negative binomial, zero-inflated binomial, etc [20,21]), to model seizure counts is a middle-outward approach to the problem. Using biomarkers, we may explain inter- and intra-individual variation in the lambda due to differences and changes in pathophysiology. Lambda may then be used to predict seizures in the future, from which the two major clinical endpoints seizure freedom and a reduction of at least 50% in seizure frequency may be derived. It is expected that pathophysiological biomarkers will be mostly relevant for 1) predicting sensitivity to treatment, and 2) the probability and amount of seizure frequency changes. On the other hand, biomarkers are required that inform on all links between basic pharmacology and clinical outcome.

Biomarkers can be divided into several categories, based on their place in the cascade from low-level determinants of drug effect up to clinical outcome [22]. The currently available biomarkers were recently categorised according to this system [23]. Based on this categorisation, several important gaps in epilepsy biomarkers were identified. Many of the biomarkers found in literature are qualitative, i.e. based on the need to categorise patients into one of several convenient and easy-to-grasp groups such as responders and non-responders. However, for rational polytherapy, biomarkers are required that inform *quantitatively* on aspects such as target occupancy and activation. These types of biomarkers are essential to the estimation of AED sensitivity of the individual patient, corresponding to the EC_{50} in our Poisson models. When biomarkers enable the accurate

estimation of the individual patient's EC_{50} before treatment, or early after initiation, a target maintenance dose can be set early and titrated towards. Conversely, if the EC_{50} is simply too high, a switch may be indicated to an AED that the patient will be more sensitive to. Similarly, such methodologies may be used to prevent the occurrence of side-effects. For the prevention of epileptogenesis, one needs quantitative information on pathophysiological processes occurring in the patient at risk of developing seizures. Assuming anti-epileptogenic efficacy exists for some AEDs, such information, combined with biomarkers on target sensitivity may be used to derive a low but sufficiently bioactive dose to prevent epileptogenesis while minimising the risk of side-effects. At the moment, determining whether a patient's seizures are simply suppressed or their epilepsy has remitted is based on clinical presentation. Some patients will show renewed seizure activity after treatment cessation, resulting in severe risk of harm. Biomarkers on disease status may prove a rational decision tool for the cessation of treatment. The occurrence of seizures and exposure to AEDs can have significant impact on mental ability in children, which may result in worse school performance and stinted development. When biomarkers are available allowing us to predict epileptogenesis, disease progression and sensitivity to AEDs, seizures may be optimally prevented and AED exposure minimised by providing the minimum-required dose and stopping treatment as early as possible.

Based on the methodologies described in this thesis, we may develop clinical trials more robustly; we may perform clinical trial simulations for power calculations, trial population selection (in terms of disease severity), duration of the trial and duration of baseline and treatment periods. Furthermore, we may be able to better investigate whether a drug is an actual anti-epileptic drug (i.e. does it treat the disease?) or an anti-convulsant (i.e. does it suppress seizures?). Although we have used the term anti-epileptic drug throughout this thesis, no results from chapters VII and VIII suggested that lamotrigine has any disease-modifying effects. To accurately answer whether a compound has disease-modifying properties, study designs need to be very carefully considered. Another important question in epilepsy research is whether pharmacodynamic drug-drug interactions exist, and whether these are beneficial (i.e. synergy) or

detrimental (i.e. antagonism) to treatment outcome. Through CTS, we may develop special trials that are sufficiently powered and designed to answer these, and other questions. To be able to do so, it is required to first estimate the parameters of the Poisson model with regard to mono-therapy in treatment-naïve patients. For now, the models provided in chapters VII and VIII showed no interactions between lamotrigine and the other existing AEDs involved in the studies. Whether these findings may be extrapolated to treatment-naïve patients remains to be shown in external validation studies.

Our introduction was named “Pharmacotherapy in paediatric epilepsy: from trial and error to rational drug and dose selection – a long way to go”. This thesis provides signposts that highlight the path towards rational anti-epileptic pharmacotherapy with the help of modelling and simulations. It is our hope that future investigations in paediatric epilepsy will recognise the importance of exposure-response relationships and take into account the methods, and approaches proposed and implemented throughout this thesis. The use of PKPD principles and drug-disease models will lead to rational pharmacotherapy of AEDs in paediatric epilepsy. Our current prescription paradigm needs to evolve. Exposure considerations are important for assessing efficacy and safety. This point was raised by Paracelsus in 1538, and is stated in the adage, the dose makes the poison. Model-based dosing algorithms may make the medicine.

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