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

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CHAPTER 2

SCOPE AND INTENT OF INVESTIGATIONS

Scope and intent of investigations

1. Introduction

Reference to epilepsy and epileptic seizures can be found in Assyrian texts, almost 2,000 B.C. [1]. However, it was not until the 18th and 19th century that medicine started the delineation of pathophysiology of epilepsy and the topographic localization of epileptic seizures. Unfortunately, at that time, the notion of interindividual and biological variation was far from the concepts defining the work on epileptogenesis, aetiology, and taxonomy of epilepsy. In fact, John Hughling Jackson's definition of epilepsy in 1873 was limited to the ictal phase of the disease ("Epilepsy is the name for occasional, sudden, excessive, rapid and local discharges of grey matter") [2].

The possibility of non-surgical interventions, based on pharmacological principles started only in 1857, when the anticonvulsant and sedative traits of potassium bromide were identified. Potassium bromide became a choice treatment for humans with epileptic seizures until the 1912 discovery of phenobarbital. The next drug introduced in the therapy of epilepsy was phenytoin in 1938. Phenytoin became the first-line medication for the prevention of partial and tonic-clonic seizures and for acute cases of epilepsies or status epilepticus, giving an alternative therapeutic choice for patients not responding to bromides or barbiturates. During the 1950s, new drugs came up such as carbamazepine in 1953 [3], primidone in 1954, ethosuximide in 1958 [4], and sodium valproate in 1963 [5]. Despite such a progress, none of these drugs have undergone the scrutiny of randomised clinical trials at the time of approval, or considered the need to establish different treatment options in children as compared to adults. By contrast, over the last two decades the field continued to evolve, with a considerable number of molecules introduced into clinical practice based on controlled clinical studies.

The so called newer antiepileptic drugs such as vigabatrin (1989), lamotrigine (1990), oxcarbazepine (1990), gabapentin (1993), felbamate (1993), topiramate (1995), tiagabine (1998), zonisamide (1989 in Japan and 2000 in the USA), levetiracetam(2000), stiripentol (2002), pregabalin (2004), rufinamide (2004), lacosamide (2008), eslicarbazepine (2009), and perampanel (2012), have all shown to meet regulatory criteria for efficacy and safety.

In parallel to the availability of novel drugs, various clinical guidelines have been introduced that are aimed at improved diagnostics, management and treatment of epilepsies, with a few of them considering the need to define a different treatment rationale in children [6–8]. However, a careful review of the history of epilepsy along with the evolution of treatment guidelines reveals that the focus on diagnostics and taxonomy of epileptic seizures may have distracted researchers from the principles that underpin modern clinical pharmacology and therapeutics, i.e., the relevance of characterising exposure response relationships and quantifying the impact of different (intrinsic and extrinsic) factors on exposure and response variability. In this context, it is not surprising that despite the notion that differences in drug levels may be associated with therapeutic failure or adverse events, limited attention has been given to the use of quantitative clinical pharmacology methods as a tool for dose selection. Therapeutic drug monitoring was introduced in 1960, when Buchtal and Svensmark introduced the measurement of antiepileptic drug levels in the blood [9], but its use in clinical practice has remained an undesirable requirement. Most importantly, data collected during therapeutic drug monitoring has been linked to an empirical decision process, with trough plasma concentrations often confounded by other covariate factors.

As discussed in **Chapter 1**, it is clear that inter- and intra-individual differences in pharmacokinetics and pharmacodynamics of AEDs need to be taken into account for the personalisation of treatment in paediatric epilepsy. Evidence of efficacy in a clinical trial, does not imply that individual patients will show optimal response in clinical practice or that the same dose and dosing regimen(s) will be appropriate for all patients, in particular, if one considers paediatric patients. In brief, the assumption

current limitations in the understanding of the exposure-response relationships can be mitigated by up and down-titration or tapering of the dose, appears to be flawed. Dose selection based on such procedures does not account for age-related changes in pharmacokinetics and pharmacodynamics in children, especially when dealing with polytherapy with two or more AEDs. In fact, dose recommendations in formularies, such as the Netherlands Kinderformularium or the British National Formulary for Children overlook the role of covariate factors and other sources of variability in pharmacokinetics and pharmacodynamics [10,11]. Moreover, in spite of the use of therapeutic drug monitoring (TDM), which is widely accepted in paediatric epilepsy compared to adults, AED levels are checked against a therapeutic window, which was originally determined in adults.

A range of arguments has been used to explain the lack of such a systematic evaluation of the exposure-response relationships for antiepileptic drugs. First, treatment and dose recommendations make their way into clinical guidelines and formularies according to evidence-based principles (Figure 1). However, the approaches currently available to establish the level and quality of evidence supporting therapeutic and clinical choices do not consider the pharmacological basis for an intervention. Whereas phase II dose ranging studies are aimed at defining dose rationale in phase III trials, these studies are not necessarily optimised to account for potential covariate effects on pharmacokinetics and/or pharmacodynamics. Subsequently, after drug approval in the primary target population, empirical evidence from randomised clinical trials, systematic reviews and meta-analyses does not necessarily provide insight into the underlying exposure-response relationship or clinical implications of covariate effects for the dose rationale. Second, it is not possible to control and stratify all factors contributing to variability in a clinical trial. Given that evidence is limited to the sampled population, it is not difficult to anticipate the challenges in quantifying the impact of inclusion and exclusion criteria. Third, the lack of biomarkers or effective predictors of response to treatment. This shortcoming is often compounded by the definition of response itself (clinical endpoint), which is based on a binary measure: responder (i.e., patients who show at least 50% of reduction in seizures compared to baseline) vs. non-responder. Dichotomisation of the response

into two categories can be detrimental for the characterisation of dose-exposure-response relationships.

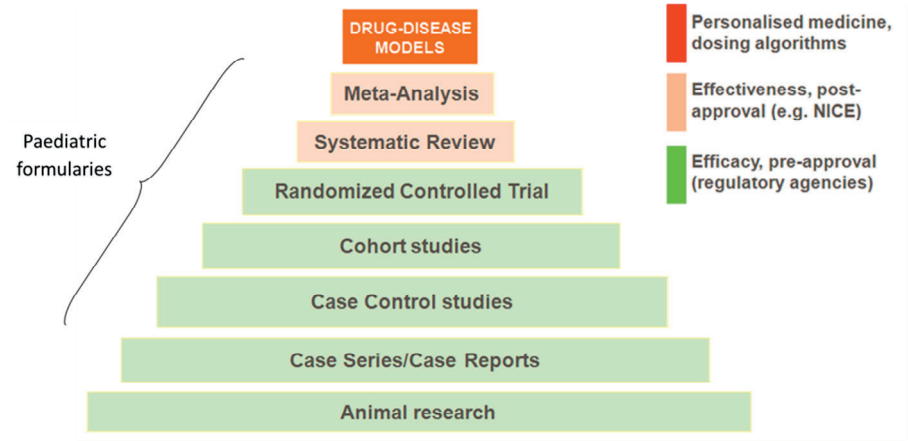

Figure 1. Evidence pyramid supporting treatment choice, target patient population and dose rationale. Different experimental data (evidence generation) and inferential methods (evidence synthesis) are used during the evaluation of efficacy and effectiveness of drugs in clinical practice. In contrast to systematic reviews and meta-analyses, drug-disease models provide a framework to assess the implications of multiple interacting factors, taking into account the underlying exposure-response relationships as well as drug-, disease and patient-specific characteristics. (adapted from Murad et al. [12])

Based on the aforementioned, any attempt to optimise treatment in paediatric epilepsy requires an integrated approach in which the implications of multiple interacting factors are taken into account. To that purpose, the theoretical concepts presented in **Chapter 1** will form the basis for the experimental work proposed in this thesis, which are described in the subsequent paragraphs in this chapter. Using a parametric approach along with data from a paradigm compound (lamotrigine), we aim to demonstrate how model-based dosing algorithms can be developed and implemented in clinical practice. For the sake of clarity, factors that determine treatment response and variability will be categorised into

disease, drug and patient-related factors. In order to illustrate the contribution of modelling and simulation as a tool for more effective evidence synthesis and better decision making regarding the dose selection, work presented in this thesis will be divided into three main sections, namely:

- **Section II (Knowledge integration)**, in which a compilation of the available pharmacokinetic and pharmacokinetic-pharmacodynamic models is presented along with details regarding the identification and parameterisation of the effect of intrinsic (e.g., disease, age-related) and extrinsic (e.g., drug interactions) factors on the exposure and response to AEDs.
- **Section III (Model-based dosing algorithms)**, where the magnitude of covariate effects and requirements for personalised regimens in paediatric epilepsy are evaluated using simulation scenarios under the assumption of comparable target therapeutic exposure ranges in adults and children.

- **Section IV (Evidence generation and evidence synthesis)**, where a pharmacokinetic and a drug-disease model are developed using a population-wide approach for the characterisation of exposure and exposure-response relationships in adults and children. In conjunction with scaling and extrapolation principles, a model-based dosing algorithm is then proposed for the optimisation of treatment response in children.

The main features and steps of the approach that will be discussed throughout the different chapters in this thesis are summarised in Figure 2. As sketched out in the diagram, we attempt to reverse-engineer the process, by identifying the elements in the causal chain between treatment and response. We first explore the feasibility and impact of personalised treatment with AEDs using a model-based approach. These principles are illustrated for a range of drugs for which covariate effects have been identified and parameterised into pharmacokinetic models. This exercise aims to show the advantages of inferential methods over empirical dose selection. It also provides an opportunity to evaluate the impact of

combining different approaches to characterise interindividual differences, such as the use of therapeutic drug monitoring. Given the limited application of modelling and simulation in clinical research with AEDs, we select a paradigm compound to demonstrate how drug-disease models can be used with population-wide data to accurately characterise pharmacokinetics, exposure-response relationships and covariate effects in the target population. Taking into account its therapeutic indication in partial onset and primary generalised tonic-clonic seizures, the choice of lamotrigine as a paradigm compound offers insight into all the necessary elements required for the implementation of model-based dosing algorithms. It can be anticipated that the similar principles and parameterisation can be applied to other antiepileptic drugs.

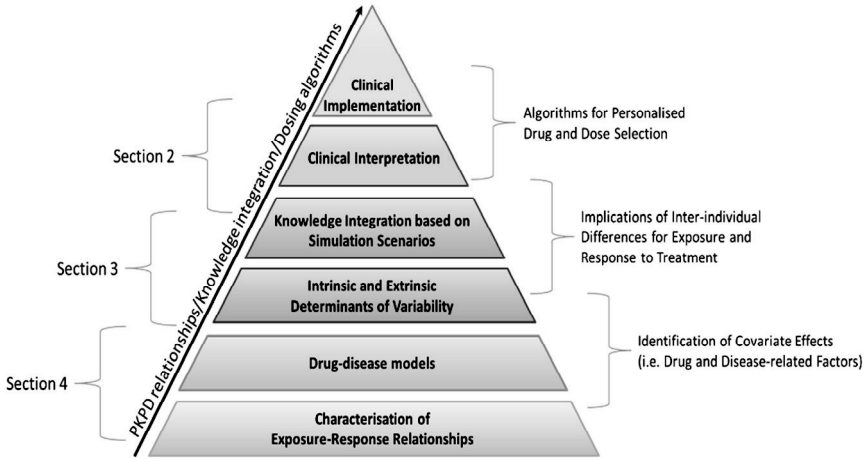

Figure 2. Diagram describing the different steps and themes presented in this thesis, which are required for the implementation of model-based algorithms aimed at the personalisation of the treatment of paediatric patients with epilepsy.

We anticipate that the concepts presented here offer more than just an opportunity for the optimisation of the treatment of paediatric patients. Our approach may provide answers to a range of clinical questions regarding the drug and dose selection. We endeavour to address the following:

1) Based on current clinical practice, ***can interindividual differences in exposure to AEDs and inadequate response in some patients be explained by size and age-related covariate factors?***

2) Assuming similar exposure-response relationships and target therapeutic range in adults and children, ***what are the implications of the commonly recommended empirical dosing in mg/kg?***

3) Given that the vast majority of drug-drug interaction studies are performed in adults ***can one assume similar effects in the paediatric population?***

4) ***Can model-based dosing algorithms minimise the need for treatment switch and combination therapy?***

5) Assuming comparable exposure-response relationships in adults and children, ***which data are required and which criteria should guide the selection and personalisation of paediatric doses?***

6) Assuming different exposure-response relationships in adults and children, ***which data are required and which criteria should guide the selection and personalisation of paediatric doses?***

An outline of the scope of the research and details on the implementation of the different sections are presented in the next paragraphs.

Section II - Knowledge integration

The development and therapeutic use of anti-epileptic drugs (AEDs) is encumbered by a number of complex interactions, involving pharmacokinetics (PK), pharmacodynamics (PD), and disease heterogeneity [13]. Some of the complexities are related to the episodic nature of the disease, the non-continuous nature of clinical measures of efficacy (endpoints), whereas others arise directly from the poor understanding of exposure-response relationships, which is further compounded by variable disease progression. Some of these complexities have been discussed previously in **Chapter 1** and make evident the need for further knowledge integration if one aims to optimise treatment and dosing regimens. They also have implications for the design of clinical trials and the analysis of the resulting data.

If model-based dosing algorithms are to be developed for personalisation of treatment with AEDs, it is essential to establish which covariate factors (intrinsic and extrinsic sources of variability) contribute to changes in exposure and response to AEDs. Taking into account sample size requirements, we assume that nonlinear mixed effects modelling is a sufficiently robust methodology to characterise covariate effects and establish the correlations between model parameter and covariate factor. Therefore, our research starts in **Chapter 3** with a comprehensive review of the pharmacokinetic and pharmacodynamic models for anti-epileptic drugs in adults, children and neonates. Publications in which model-based methodologies have been applied to describe exposure and response to the most commonly used AEDs, including carbamazepine, clonazepam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine (and metabolite MHD), phenobarbital, phenytoin, topiramate, valproic acid, and zonisamide will be identified and summarised. During data extraction, focus will be given to details regarding model parameterisation and evidence of predictive performance for subsequent application of the model in the evaluation of personalised or individualised therapy. In addition, a full tabular overview of model parameterisation will be provided, including details on the modelling approach, relevant parameter values and code syntax. Those who are unfamiliar with the principles of pharmacokinetic

and pharmacokinetic-pharmacodynamic modelling are invited to review some key references, in which clinical applications and impact of model-based approaches are outlined [14–17]. Given the objectives of our investigation, data will be split into three categories, namely adults (> 16 years), infants, children and adolescents (paediatric patients, age 1 month - 16 years), and pre-term and term new-borns (neonates, age 0 – 1 month). It should become evident whether knowledge about parameter distributions and covariate effects is currently being used to select dosing regimens for an individual patient before the start of treatment, i.e., by taking into account patient specific characteristics.

Section III - Model-based dosing algorithms

Whilst it can be anticipated that limited evidence is available of the exposure-response relationships for AEDs in adults and children other than clinical data from efficacy trials, this does not need to represent a hindrance for the evaluation of the concepts underpinning the use of model-based dosing algorithms. In **Chapter 4**, we will assess the benefits and advantages of model-based dosing algorithms by exploring the clinical relevance of covariate effects, with special focus on the consequences of intrinsic sources of variability on pharmacokinetics. An assumption is made with regard to the therapeutic exposure ranges defined for adults, i.e., that these levels do reflect the desirable target levels in children. In addition, we hypothesise that for a given seizure type, the PKPD relationships are similar in adults and children. Using simulation scenarios and optimal design concepts we will attempt to identify suitable titration schemes and dosing algorithms and possibly personalise the treatment of seizures for the 11 most commonly used AEDs. In addition to a reference regimen based on a standard dose for all patients, a series of scenarios will be considered in which doses are adjusted according to i. individual clearance estimates (CL), as predicted by population PK models, and ii. individual clearance estimates, obtained by therapeutic drug monitoring according to different sampling schemes. Attainment of steady-state target exposure will be used as performance criterion. It can be anticipated that the implementation of model-based titration and dosing algorithms may be of particular relevance for 10-20% of patients who still show unresolved seizures when their target

dose has been achieved. This approach may also allow the identification of individuals within the group of patients who would respond to optimised regimens, but currently remain refractory to treatment and are said to have drug-resistant epilepsy.

Another important aspect in clinical practice, which should be considered in the development of model-based dosing algorithms, is the need for combination therapies. Despite evidence on the role of pharmacoresistance and progression of the underlying pathological processes, the lack of response can be partly explained by inter-individual variability in the pharmacokinetics. The impact of such variability can be particularly important in the paediatric population, where exposure may vary due to maturation processes and developmental growth [13,18,19]. In addition, children who do not adequately respond to first-line treatment are given multiple AEDs in combination, which can lead to pharmacokinetic and pharmacodynamic drug-drug interactions (DDIs). Bearing in mind current clinical practice, in **Chapter 5** we aim to assess the impact of DDIs on the exposure to AEDs and establish the need for further dose adjustment for combination therapies. Using simulation techniques, a range of scenarios will be evaluated for 11 of the most commonly used AEDs, including different drug combinations and dose levels for both adult and paediatric patients. For each scenario, virtual patients will be simulated taking into account interindividual differences in clinical and demographic characteristics. We aim to identify the dose or dose levels that maximise the fraction of patients that reach and remain within the target exposure range for each drug. The impact of DDIs on the systemic exposure of the first-line or alternative first-line AED will be subsequently assessed based on clinically relevant dosing regimens and combinations. Here again we hypothesise that for a given seizure type, the PKPD relationships are similar in adults and children. In addition, we assume that differences in individual sensitivity to individual drug effects are captured by the proposed target range, whereas resistance to treatment would impose exposure to higher drug concentrations, which are likely to be associated with poor tolerability. We anticipate that our analysis will assist the review of clinical guidelines, taking into account the role of covariate factors in future dosing recommendations. Most importantly, it will provide clinicians further

insight into the role of PK variability in the overall efficacy and safety profile of AEDs.

Clearly, our ability to evaluate the implications of interindividual variability in pharmacokinetics and pharmacodynamics of AEDs and identify covariates or predictors of exposure and response depends on the quality of evidence. As the work described in the first two sections of this thesis relies primarily on the published literature, it should be highlighted that many of the studies involved non-controlled observational data obtained from clinical practice, whereas the collection of pharmacokinetic data in the case of clinical trials is usually a secondary or even exploratory objective.

In addition, with a few exceptions, the vast majority of the population pharmacokinetic modelling reported in the clinical literature lack stringent validation procedures, which support their prospective utilisation for simulations and/or prediction purposes. In fact, there appears to be no single example in neurology of the implementation of such concepts. In the next section of this thesis we will focus therefore on the use of approaches that ensure optimised evidence generation and improved assessment of the dose rationale for the paediatric population.

Section IV - Optimised evidence generation and evidence synthesis

The design and execution of clinical trials in adult patients with epilepsy is generally perceived as challenging. Restrictions exist on the type of patients that may be included; trials are required to apply a design where add-on medication is given to patients who have already unsuccessfully received multiple other treatments. Moreover, the pre-existing AEDs are generally not stopped before or during the trial. Consequently, these trial protocols are not designed to provide insight into exposure-response relationships or disentangle possible pharmacodynamic drug-drug interactions. As such, bias may occur regarding the efficacy and safety of the dose and dosing regimen under investigation. This situation usually complicates the extrapolation of study findings to a wider patient population.

In fact, the evaluation of pharmacokinetics and response is often limited to a statistical summary of the clinical endpoints along with the predefined statistical hypothesis test results. The primary endpoint is generally the percentage of patients that achieve treatment success, defined as a reduction in seizure frequency of at least 50% compared to baseline. Other (primary and secondary) endpoints include the time to first seizure, average population change in seizure frequency, probability of side-effects, etc. The analysis of seizure count data is complex and typical, non-parametric approaches are not suitable to describe individual patterns of response. These methods tend to weight response based on seizure frequencies over a time-period, which leads to the loss of information available for the characterisation of intra- and inter-individual variability, as well as eventual covariate factors or predictors. If a trial includes the evaluation of pharmacokinetics, data are usually summarised using non-compartmental methods, which limit the description of pharmacokinetic properties to total exposure with the area under the concentration vs. time curve (AUC), peak concentration, elimination by terminal half-life, etc. Interindividual variability in these analyses is captured by standard deviation of the parameters.

The issues highlighted above are compounded by additional practical and ethical constraints when considering the design and execution of clinical trials in children with epilepsy. Consequently, the value of new data is tremendously higher than in a standard protocol involving adults. Yet, little attention has been paid to the role of methodologies that support evidence synthesis, whilst keeping the burden for the children to a minimum. Therefore, we propose to integrate evolving concepts in paediatric clinical pharmacology into the evaluation of the dose rationale for children. In a very simplistic manner, it can be said that three scenarios can be used to determine the rationale for paediatric clinical trials: 1) if differences between adults and children exist in disease and its progression, which cannot be predicted from data obtained in adults, then pharmacokinetic and efficacy data must be generated in children to establish the effective dose and dosing regimen; 2) if the disease and its progression can be deemed comparable across populations (or are considered different in children, but can be predicted from data obtained in adults) and the same

clinical endpoints are used to assess response in adults and children, then bridging concepts can be applied. In this situation, collection of pharmacokinetic and eventually pharmacodynamic data in children in conjunction with evidence of exposure-response relationship (and consequently of the efficacious exposure levels) in adults should be sufficient to define the dose rationale for the paediatric population; 3) in some cases it is also conceivable that pathophysiological processes and pharmacological mechanisms are sufficiently understood to allow full extrapolation of efficacy findings from the adult population without the need to generate efficacy data in children. In these circumstances, pharmacokinetic data in children should be used in conjunction with evidence of exposure-response relationship (and consequently of the efficacious exposure levels) in adults to adjust for differences in drug disposition and formulation to be used in the paediatric population. In all three cases the quality of the data collected is crucial to establish not only the effect size of a treatment, but also to define the dose rationale.

Whilst historically, evidence of different types of epileptic seizures and consequently differences in the diagnosis of epilepsy have been used justify the need for efficacy trials in children, limited efforts have been made to establish whether exposure-response relationships are indeed different between the two populations. Consequently, this has hampered the evaluation and potential implementation of bridging and extrapolation concepts. Using lamotrigine as a paradigm compound, we attempt to characterise exposure-response relationship of lamotrigine in adults and explore the feasibility of extrapolating efficacy based on the attainment and maintenance of target exposure.

First, in **Chapter 6**, we propose the use of a population-wide approach, in which pharmacokinetic data from patients from 0.2 - 91 years of age are pooled together, for an integrated analysis of the effect of covariates on the pharmacokinetics of lamotrigine. From a methodological perspective, allometric concepts will be used to describe the effect of age- and size-related differences on the pharmacokinetics of lamotrigine. If needed, a maturation function will be considered to describe changes in CL in infants and toddlers. Given the limited range of dose levels used for companion

drugs in combination therapy, drug-drug interactions will be parameterised as discrete covariates. Assuming a common target therapeutic range in adults and children, we illustrate how the covariate effects can be characterised and validated using a model-based approach. In addition to standard diagnostics and goodness-of-fit criteria, the predictive performance of the model will be evaluated using internal and external validation procedures, including numerical predictive checks, normalized prediction distribution error (NPDE) and nonparametric bootstrapping of the parameter estimates obtained with the final model. This is a critical aspect of the implementation of model-based dosing algorithms, as evidence of predictive performance has not been the focus of publications aimed primarily at the estimation of relevant model parameters. Metrics of predictive performance provide insight into other important validation criteria for the proposed dosing algorithms, such as sensitivity and specificity [20–22].

After having identified relevant covariate effects on the pharmacokinetics of lamotrigine, the next obvious step is the assessment of the exposure-response relationships of lamotrigine. In **Chapter 7**, we attempt to evaluate innovative modelling approaches to describe drug effects on episodic seizure events and identify clinically plausible influential factors affecting response in adult patients. Given the possibility to explore parameterisations in which drug- and disease-specific properties can be assigned to distinct parameters, we also aim to assess whether different exposure-response relationships are required to predict treatment response in partial onset and primary generalised tonic-clonic seizures. To this purpose data from clinical trials of lamotrigine, in which pharmacokinetics and efficacy were assessed in adults, will be pooled and analysed. In spite of the limited number of doses used during the maintenance phase, data obtained during the titration phase will be included in the analysis. It will be assumed that drugs effects are not delayed relative to the onset of treatment, i.e., that difference in response during titration is driven primarily by changes in exposure.

From a methodological perspective, instead of evaluating treatment response based on a dichotomous or binary measure (e.g decrease > 50% seizure rate), we propose to use mathematical concepts that are appropriate for the description of count data, as is the case for seizure frequency, which are usually described as numbers of events per interval. Naturally, zero event/count is also a possibility, especially in the case of efficacy, where antiepileptic drugs suppress all seizures [23–25]. Mathematically, a useful place to start modelling event-count data is the Poisson distribution. Count events can also be described by hazard functions. Hazard describes the instantaneous rate of the events and determining whether and how this hazard varies with covariates, including treatment effect, is typically the aim of the data analysis. However, in the case of epileptic seizures it is likely that time affects the hazard, i.e., the hazard is not constant, a repeated time to event analysis may be required.

The most important count model is the Poisson model, but the assumption of a Poisson distribution implies equality of the mean and the variance [26]. This property does not seem to apply to seizure events. Using a hierarchical modelling we attempt to address the so-called overdispersion phenomenon and estimate parameters that describe the event rate. Conceptually, the treatment effect is handled as a covariate effect, i.e., treatment alters the parameter(s) describing the probability and rate of events.

Given the chronic, episodic nature of epileptic seizures, we will also attempt to explore alternative methodologies, which enable characterisation of the underlying pathophysiological process and its progression (i.e., period of ictal activity followed by non-ictal intervals). Such an episodic process may also be described by multi-state models. In medicine, and more specifically in epilepsy, the states can describe conditions like healthy (non-seizure), seizure, worsening or complication of disease. Markov models and in particular hidden Markov models allow us to link the disease states (hidden layer) to the observed clinical symptoms (open layer) by means of statistical distributions. Hence, each state may be assigned to a clinically defined endpoint and may well have a pathophysiological analogue. Hidden Markov models (HMMs) have been successfully applied to model chronically recurring infections, such as herpes [27], and episodic diseases such as

migraine [28–30]. If necessary, stochastic methods will also be evaluated to ensure accurate characterisation of intra-individual variability over the course of treatment. Ultimately, these techniques provide us with the appropriate tools to assess whether differences in exposure only explain variability in response, or whether there are real differences in the underlying exposure-response relationship due to the different seizure types.

Lastly, in **Chapter 8**, we will illustrate the application of modelling and simulation concepts for the evaluation of treatment response and possible extrapolation of the dose from adults to infants and toddlers [31]. Data from children aged 1-24 months with partial type seizures receiving lamotrigine as adjuvant therapy will be used in this analysis. Based on the parameters describing the underlying exposure-response relationship and on covariate effects known to affect drug disposition we will apply clinical trial simulations to define the dose rationale for this population and explore opportunities to optimise prospective clinical trials in this population [8,32]. Of interest in this group of patients is the possibility to establish whether potential (biologically plausible) differences in disease alter the underlying exposure-response relationship or whether other factors explain differences in the clinical response phenotype, such as baseline seizure frequency, placebo effect or prior treatment failure. Our final goal is to show that model-based dosing algorithms can also be used as a design tool during drug development, supporting clinical pharmacology efforts such as bridging and extrapolation studies [33–35].

The last section of this thesis provides an integral summary of the findings and conclusions from the investigations presented throughout the previous chapters. In **Chapter 9**, we focus on the consequences of inaccurate dose selection and the implications of model-based dosing algorithms to guide the dose rationale for paediatric patients, In this concluding chapter, we revisit the concept of personalised medicine and attempt to shed light on the need to assess exposure-response relationships during the evaluation of efficacy and safety of novel molecules. We make clear that the current clinical paradigm (in which evidence generation is based solely on statistically significant separation from placebo or comparator arm) is

inefficient for the personalisation of treatment, and in particular for establishing the dose rationale for children. In addition, concrete recommendations are made for improving protocol design and data analysis of paediatric trials with antiepileptic drugs in which pharmacokinetics and efficacy are evaluated. We acknowledge that many methodological aspects remain to be explored, which relate to the heterogeneity of the disease in adults and children. This is presented along with the limitations imposed by the lack of intermediate measures or markers of pharmacology, which restrict the opportunities for characterising antiepileptic activity in humans before embarking into expensive and often complex clinical trials.

We anticipate that advancement of pharmacotherapy with antiepileptic drugs will require a different regulatory framework and a shift in the current clinical reasoning, with further attention to the so-called *level of evidence* needed for the assessment of pharmacokinetics, safety and efficacy and how model-based inferential methods can be applied to the analysis and interpretation of clinical findings.

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