A Markov approach to characterizing the PK-PD relationship of anti-migraine drugs

Maas, H.J.

6

Model-based quantification of the relationship between age and anti-migraine therapy

HJ Maas, M Danhof, OE Della Pasqua
Submitted to BMC. Clin. Pharmacol.

Migraine is a neurological disease that affects all age categories. However, the features of the headache attacks which are associated with migraine vary with age. As a consequence, the effectiveness of medication aborting these attacks also depends on a patient's age. Quantitative knowledge of the relationship between drug effects and age can guide the establishment of the most effective treatment regimens for the different age categories.

The current analysis aims to quantify such relationship for the oral formulation of the anti-migraine drug sumatriptan.

A time-inhomogeneous Markov model has been developed to describe the progression of a migraine attack over three clinically defined stages ("no relief", "relief" and "pain free"). The transition rates determining the progression along these stages are nonlinear functions of both the drug concentration in plasma and the age of the patient. Model parameters were estimated using data from clinical trials of oral sumatriptan in adolescents and adults (range 12 – 65 years).

The rates at which the pain relief and pain free states are attained are inversely related to age. The midpoints of these relationships are located at 23 (20 – 27) and 22 (17 – 27) years, respectively (mean and 95% confidence interval). In the absence of drug, the

mean transit time from "no relief" to "relief" is ∼3 h for adolescent patients and ∼6 h for patients aged 28 and over. Oral sumatriptan therapy reduces these transit times to 2 h, irrespective of age.

In conclusion, the Markov model captures the characteristics of the relationship between age and the effectiveness of oral sumatriptan therapy. This approach can be applied to predict the age-dependent response to other forms of anti-migraine.

6.1 Introduction

Migraine affects all ages. Although its peak prevalence is in the third to fifth decades [1], migraine is the most common cause of primary headache in children and adolescents with a prevalence between 2.7% and 10.6% [2]. The characteristics of childhood migraine differ somewhat from migraine in adults. It features a lower incidence of migraine attacks with aura and a headache that is bilateral instead of unilateral. With regard to the dynamics, the attack frequency is lower and the duration is shorter in the young.

The differences between the two age groups extend to the acute treatment of migraine attacks with 'triptan' agents (serotonin 1B/D receptor agonists). In particular, it has been difficult to demonstrate superiority of sumatriptan over placebo treatment. The main problem with randomised placebo-controlled trials of sumatriptan in children and adolescents is the high placebo response rate [3]. This may partially reflect the intrinsically shorter duration of attacks, yet it is also known that the anticipation of a treatment effect is especially important in paediatric pain studies.

An inverse relationship between placebo response rate and age has been demonstrated in recent papers [1, 3]. However, it is not clear whether the response rate following active treatment can be attributed to the underlying age-dependent placebo response or if it is independent of age. The matter of age-dependency is essential when wanting to predict the efficacy of new formulations.

For each age category, the part of the anti-migraine response that can be attributed to triptan treatment may be found by simply subtracting the placebo response rate from the response rate after drug treatment. Comparison of the remainders may then learn whether the treatment effect varies with age. However, this approach is based on the assumption that placebo effect and active treatment effect determine the response in an additive fashion. In reality, these effects need not be independent, but may share common pathways. Consequently, one effect may obscure or even exclude the other. In short, the response to treatment is expected to result from a certain degree of interaction between placebo and drug effects.

Clearly for any evidence of interaction to be extracted from clinical data, a technique more advanced than graphical analysis is needed. The aim of this paper is to develop a mathematical model to quantify the relationship between drug exposure, patient age and headache response in migraine attacks, allowing for interaction between placebo effects and drug effects. Model parameters are estimated from clinical efficacy studies in adolescents and adults covering both placebo treatment and active treatment with various oral doses of sumatriptan.

In clinical practice, migraine severity is assessed using headache intensity scores. The analysis of these scores requires an approach that can handle ordinal categorical data. At the same time, demographic and treatment explanatory variables affecting the time course of headache scores should be taken into account. The usefulness of Markov chains in the analysis of migraine data has been demonstrated [4, 5, 6]. Therefore, a Markov chain methodology was chosen to implement the relationship between age and the anti-migraine treatment effect.

6.2 Methods

6.2.1 Markov model

In clinical practice, the migraine response is assessed in terms of the fraction of patients attaining "pain relief" and "pain free" status [7]. These endpoints are based on a four-point scale of headache intensity of which the levels are "no pain", "mild pain", "moderate pain" and "severe pain". Given that a patient's initial score is moderate or severe, pain relief is reached when headache has decreased to mild or no pain. A patient is said to be pain free once the "no pain" score is reached. Within a migraine attack, the transitions from one response status to the next can be represented by the state-to-state transitions of a Markov chain [6]. The dynamics of the transitions in a Markov chain are governed by the Markov property which states that only the current state determines what the next state will be. The rates of the transitions may be constants or they may be expressed as functions of explanatory variables. This model consists of a three-state Markov chain expressing disease dynamics (Figure 6.1). Previous states do not influence the course of the process, making the Markov chain a powerful modelling tool. Furthermore, the transition time from one state to the next is a random variable. That is, the time spent in the current state x, before jumping to the next state y is exponentially distributed with rate parameter $Rate_{xy}$. Markov chains are best described by diagrams such as Figure 6.1, showing the allowed transitions between states.

In the migraine attack model, the choice of the states is based on the clinical differentiation between attaining pain relief (state 2) and attaining pain free status (state 3), starting from a full-blown migraine attack (state 1) [1]. Trigeminal pathophysiology may well be a biological substrate for this differentiation. A major advantage of this approach is the ability to estimate transition rates from one state to another, which makes the evaluation of treatment effects independent of sampling time and observation windows.

However, in trials of anti-migraine drugs the observed variable is not the clinical state (full-blown, pain relief, pain free) but rather the headache intensity score which is defined on a four-point scale. In this scale, scores 0, 1, 2 and 3 indicate "no pain", "mild pain", "moderate pain" and "severe pain", respectively. In order to relate the Markov states to the headache intensity scores, the states are coupled to a layer that gives the probability distributions of the headache scores for each of the states (Figure 6.1). The layer containing the probability distributions is referred to as the 'open' layer, as it contains the observed variable, which is the variable to be modelled. The Markov chain is referred to

as the 'hidden' layer of the model as it describes the unobserved clinical states. Together, the two layers form the hidden Markov model.

The expected probability distributions of the scores over the states can be deduced from clinical guidelines [1], which state that pain relief is defined as a decrease in headache from score 3 or 2 to 1 or 0, whereas pain free is defined as a decrease from a score 3 or 2 to 0. Therefore, the distribution of the first Markov state (representing a full-blown attack) consists of scores 2 and 3, the second state (similar to pain relief) will contain score 1, and the last state (pain free) will be occupied by score 0.

6.2.2 Age and treatment effects

As shown in Figure 6.1, forward transitions towards states of decreasing pain as well as backward transitions towards states of increasing pain are allowed in the Markov chain. Forward transitions reflect resolution of the attack after active treatment or placebo treatment. Measures of drug exposure such as plasma drug concentration have been shown determinants of these rates. However, the forward transitions are likely also affected by the demographic variable 'age', as the effect of placebo treatment has been shown to be strongly related to the age of the patient. A mathematical relation was constructed for the rate of the forward transitions that combines both observations. This relation describes the joint effect of drug concentration and age and is structurally based on models of drug interaction [8, 9]. The basic function defining the rates consists of a function (Equation 6.1, first line) scaling the rate ($Rate_{xy}(t)$) between a minimum ($Rate_{min}$) and maximum value ($Rate_{max}$).

$$Rate(t) = Rate_{min} + \frac{Rate_{max} - Rate_{min}}{1 + f(age, C(t))} \quad where$$
$$f(age, C(t)) = E_0 \cdot \exp\left(\frac{E\max_{age} \cdot \exp(age)}{\exp(E50_{age}) + \exp(age)} - \frac{E\max_{C(t)} \cdot \exp(C(t))}{\exp(E50_{C(t)}) + \exp(C(t))} \right) \tag{6.1}$$

By treating age and drug exposure as covariates that respectively decrease and increase the forward transition rates, the effect of age and active treatment can be modelled explicitly. Equation (6.1, lower line) describes the rates $Rate(t)$ of the forward transitions from some state x to another state y during active treatment (subscript xy has been omitted to simplify notation). The E_0 term and the Age term together represent the rates in the absence of drug (placebo model). $C(t)$ is the plasma drug concentration at time t. $Emax_{C(t)}$ represents the maximum contribution of the drug effect on the transition rate from state x to state y. $E50_{C(t)}$ is defined as drug concentration corresponding to the effect reached at half of the value of $Emax_{C(t)}$.

Backward transition rates in the Markov chain represent the activity of a migraine generator, which may differ between states of response and is not affected by drug treatment. These rates do not vary in time and are parameterised as $Rate(t) = Rate_{min}$. $Rate_{min}$ is estimated separately for each backward transition. In total, the model con-

tains 2 forward and 2 backward transition rates, the parameters of which are to be estimated.

6.2.3 Data

Sumatriptan pharmacokinetic and efficacy data were obtained from the SNAP database. Details about the data source have been described elsewhere. Headache score measurements in adults performed at 0, 0.5, 1, 1.5, 2, 4 and 8 h post dose were included in the analysis. Whenever available, scores at 0.17, 0.33, 3 and 6 h were included as well. It has been shown that data up to 8 h can be described by Markov chain dynamics without losing accuracy in the early time points. As in adolescents headache was assessed only up to 4 h post dose. This was not considered to complicate analysis since due to the shorter duration of migraine attacks in young patients, sufficient data covering the three states of the attack. Whenever available, scores at 0.17, 0.33, 3 and 6 h were included as well.

For sumatriptan efficacy data included headache scores from 1231 migraine attacks, 449 of which were recorded in adolescents. The characteristics of the studied patient populations are summarised in Figure 6.2 and Table 6.1.

6.2.4 Pharmacokinetic analysis

The studies from which the headache scores were derived did not contain pharmacokinetic data. In order to provide all headache observations with sumatriptan concentration values, population-based concentration profiles were generated using data from pharmacokinetic studies. First, these data were fit to pharmacokinetic models. Sumatriptan concentration data were fit to a model proposed by Cosson and Fuseau [10] . This model consists of two compartments with a combined first-order and zero-order absorption rate, describing the irregular absorption characteristics of sumatriptan. In the PK analysis, it

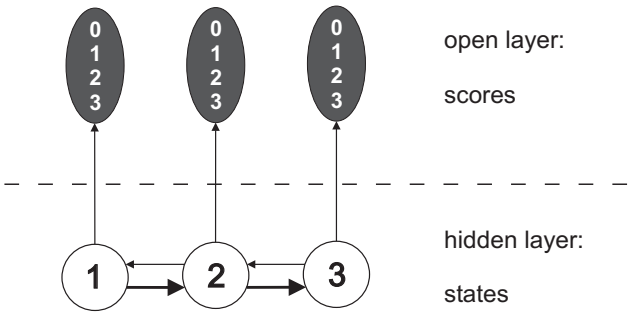

Figure 6.1: *Diagram of the hidden Markov model. The hidden states represent the clinical states "no relief", "relief", and "pain-free". The open layer represents the observed scores. Bold arrows indicate forward transitions. The associated transition rates are functions of both sumatriptan concentration and patient age.*

Table 6.1: *Characteristics of the age groups.*

age groups (range and mean in years)	Number of migraine attacks in each dose group					duration of studies (h)	% female
	placebo	25 mg	50 mg	100 mg	total		
12 – 17 15	73	122	133	121	449	≤ 4	57
18 – 65 34	139	46	44	553	782	≤ 48	89

was assumed that the pharmacokinetics in children are not significantly different from those in adults. Moreover it was assumed that the PK of patients during attack does not differ from healthy subjects. [11] and [10] provide indications that these assumptions do not invalidate the analysis. A data set was constructed containing both the observed headache scores and the simulated concentration data. This data set was then applied to estimate the parameters in the hidden Markov model.

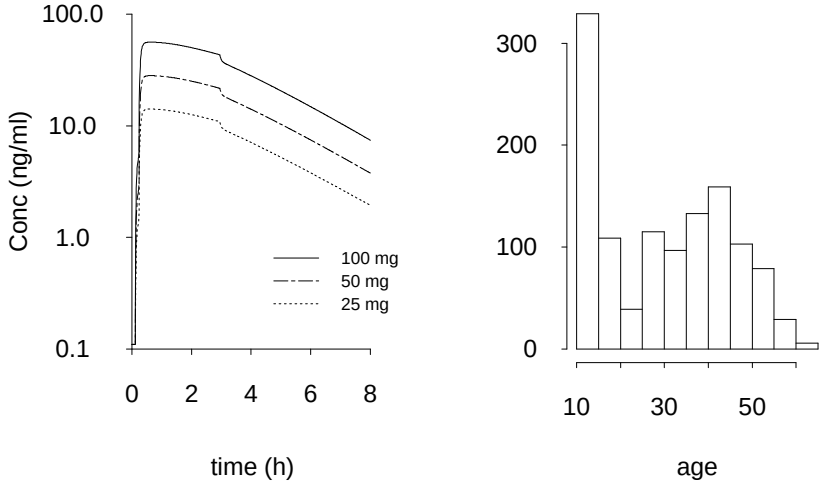

Figure 6.2: *graphical summary of explanatory variables "drug concentration" (left) and "patient age" (right). Three concentration versus time profiles are shown in the left plot. In the right plot, the distribution of patient ages is shown.*

6.2.5 Disease Modelling

The observed headache scores (the modelling variable) and triptan plasma concentrations (the time-varying covariate) were fit to the hidden Markov model. Data derived from the sumatriptan and naratriptan studies were analysed separately. In both analyses, placebo data and active treatment data were modelled simultaneously. The parameters included the parameters of the forward and backward transition rates of the Markov chain and the probability distributions of the headache scores in each of the states of the Markov chain.

6.2.6 Software

Pharmacokinetic modelling was performed using the non-linear mixed effects software package NONMEM (version V, Globomax LLC, Maryland, US). Models were written in subroutine ADVAN4 and the first order estimation algorithm was adopted.

The migraine attack model (hidden Markov model) was implemented in S-Plus for Linux and run on SuSE Linux 7.2 Professional, kernel version 2.4.4-4GB-SMP.

6.3 Results

Table 6.2 shows the estimates for the parameters of the Markov chain with interaction between drug concentration and age. Estimates for the open layer with headache score distributions are given in Table 6.3. The $Emax_{C(t)}$ values are clearly larger than the maximum responses for age. This implies that according to the model, in the presence of drug, the age effect decreases.

The goodness-of-fit of the model is evaluated in Figure 6.3, where observed and predicted responses versus time are compared for adolescents and adults, pain free and pain relief responses, and at placebo, 25 mg, 50 mg and 100 mg. In general, there is a good agreement between observations and predictions. The size of the markers in the plots represents the relative numbers of attacks available for the different dose levels. Most data was available for the adult study population at the 100 mg dose level. Due to the small amount of data at the other levels, goodness-of-fit is less. Note that at the 25 mg level in adults, the observed responses are higher than those at the 50 mg level. Obviously, the model cannot take into account higher responses at lower doses.

Figure 6.4 shows predicted response surfaces at 1 h post-dose. In the pain relief surface the age and concentration step-functions can be clearly recognised.

6.4 Discussion

A statistical model has been developed to describe and predict the headache response to placebo and anti-migraine drugs across patients of different age categories.

Distributions of scores in the open layer of the model are as expected. Previous models that did not consider the age effect showed similar distributions of scores over

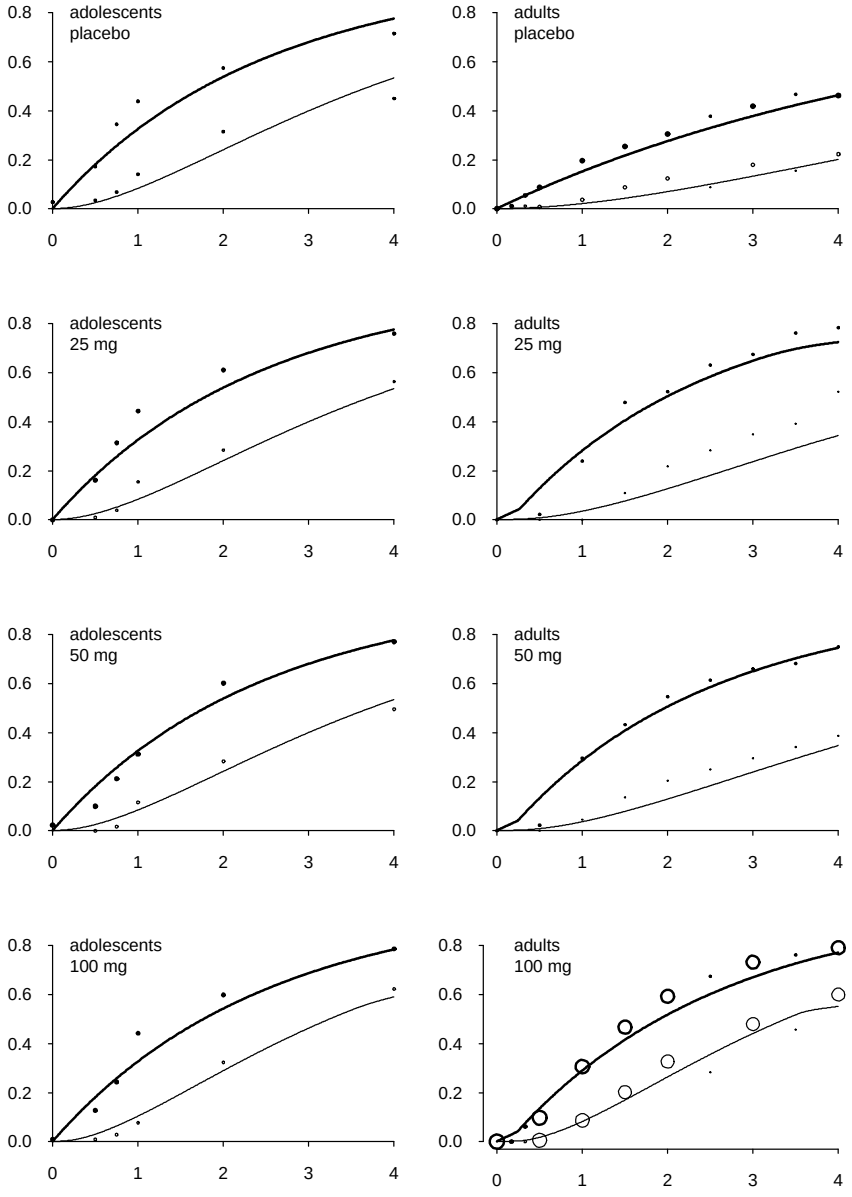

Figure 6.3: *Fraction of patients with headache response* vs *post-dose time in hours. Observed responses are shown as markers and predicted mean responses as lines. Bold face lines and markers represent pain relief response, normal face lines and markers represent pain free response. Predictions for both age categories (adolescents and adults) were obtained using the same model. The relative sizes of the markers indicate the proportions of the data that were used in the creation of each panel.*

Table 6.2: *Parameter estimates of the state layer of the model. Parameters are explained in Equation 6.1 and the text.*
* *indicates that no standard error (s.e.) could be calculated for these estimates.*

transition (from state – to state)	parameter	estimate	95% C.I.
1-2	$Rate_{min}$ [h^{-1}]	0.033	0.0037 – 0.32
	$Rate_{max}$ [h^{-1}]	0.39	0.30 – 0.74
	E_0	0.0018	0.00083 – 0.0040
	$E50_{C(t)}$ [ng/ml]	11 *	
	$Emax_{C(t)}$	39	38 – 40
	$E50_{Age}$ [y]	23	20 – 27
	$Emax_{Age}$	6.9*	
2-1	$Rate_{min}$ [h^{-1}]	0.051	0.033 – 0.078
2-3	$Rate_{min}$ [h^{-1}]	0.11	0.033 – 0.82
	$Rate_{max}$ [h^{-1}]	0.81	0.17 – 4.84
	E_0	0.43	0.0055 – 31
	$E50_{C(t)}$ [ng/ml]	34	32 – 35
	$Emax_{C(t)}$	19	21 – 23
	$E50_{Age}$ [y]	22	17 – 27
	$Emax_{Age}$	1.89	-0.46 – 4.31
3-2	$Rate_{min}$ [h^{-1}]	0.041	0.033 – 0.053

states [6]. As the second and third states almost exclusively contain “mild” and “no pain” scores, respectively, these states can be referred to as the “relief” and “pain free” states.

Results at convergence were scrutinised by testing the sensitivity to starting values. Parameter estimates did not appear to be sensitive to initial parameter values.

The functions relating age and sumatriptan concentration to transition rate (equation 6.1) are step-functions. Less steep transduction functions were also considered but these did not describe the data as well. Due to the complicated model structure not all standard errors could be calculated. For the same reason and also due to the lack of data in the low dose groups, some parameters could not be precisely estimated: in particular those on the transition from state 2 to state 3.

Unlike previous applications of the hidden Markov model for migraine attacks [12, 6, 5], the current model structure did not allow confidence intervals to be calculated for the mean-predicted headache responses. This is likely due to the large values of the exponentiated drug concentrations (see Equation 6.1). The differences between subsequent values of this covariate are too large to be evaluated in the recursive algorithm that was developed in [12].

Table 6.3: *Estimates of the score layer: percentages of pain scores in each state. Percentages per state (columns) add up to 100%.*

score	state 1	state 2	state 3
no pain	0	0	100%
mild	0	95%	0
moderate	58%	5%	0
severe	42%	0	0

The midpoints of the step function for age effect were 23 and 22 years for the transitions from state 1 to state 2 and from state 2 to state 3, respectively. It should be noted that these positions do not equal the age (*i.e.* 18 years) that separates studies in adolescents from studies in adults. On the basis of these results, it can be argued that the decrease of placebo effect with age represents a continuum and does not merely reflect differences between the designs of both types of study. The midpoints ($E50_{C(t)}$) of the concentration step function are within the concentration range of the 100 mg oral dose of sumatriptan. The values for $Emax_{C(t)}$ on both forward transitions are relatively large when compared

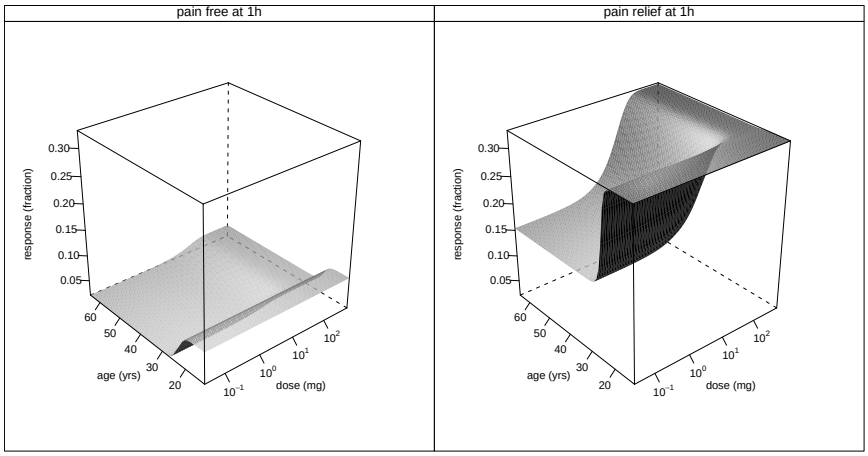

Figure 6.4: *Predicted response surfaces for pain free and pain relief responses at 1 h post-dose.*

with the maximum effects of age ($Emax_{age}$). The result of this difference is that when sumatriptan concentrations become similar to or above $E50_{C(t)}$, the forward transition rates are exclusively determined by drug concentration and age is of no influence. This can be seen very clearly in the predicted responses in Figure 6.3, where during the first 20 minutes before any drug is absorbed, the slope of the pain relief response is smaller in adults than it is in adolescents. After drug is absorbed, any differences in response between the age groups disappear. Although age and drug concentration are interacting variables according to the mathematics of Equation 6.1, they almost independently determine the response. Thus in adolescents, the response at placebo naturally does not depend on concentration, but reversely, the responses at 25 mg and higher do not depend on age. A stronger opinion on whether or not these explanatory variables are interactively determining the response may be gained by performing a (meta-)analysis of data from studies investigating administration routes other than oral. If indeed such studies show that the drug response in adolescents is higher than their placebo response, but equal to the response in adults, Interestingly, intranasally administered sumatriptan is more effective in children than the oral formulation. Furthermore, a significant treatment effect was found when oral sumatriptan medication was given early in the migraine attack rather than at the time of maximum pain intensity.

The utility of this Markov model with explanatory variables is not limited to the study of migraine attacks. Due to its structure, the model is thought to be more generally applicable to scenarios where a demographic variable bearing relation to disease progression interacts with treatment effect. Questions that should be addressed in a quantitative manner include i) can an effective doses be found for all age categories? ii) can treatment be improved by changing the treatment regimen? and iii) what is the influence of drug formulation on the age-efficacy relationship?