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Personalised Medicines

Individualized dosing regimens in children based on population PKPD modelling: Are we ready for it?

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ABSTRACT

Despite profound differences in response between children and adults, and between children of different ages, drugs are still empirically dosed in mg/kg in children. Since maturation of expression and function is typically a non-linear dynamic process which differs between biotransformation routes and pharmacological targets, paediatric dosing regimens should be based on the changing pharmacokinetic–pharmacodynamic (PKPD) relationship in children. In this respect, the population approach is essential, allowing for sparse sampling in each individual child. An example is presented on morphine glucuronidation, for which two covariates were identified and subsequently used to derive a model-based dosing algorithm for a prospective clinical trial in children. Using this novel dosing algorithm, similar morphine concentrations are expected while, depending on age, lower and higher morphine dosages are administered compared to mg/kg/h dosing. As the covariate functions may reflect system-specific information on the maturation of a specific drug-disposition pathway, its use for other drugs that share the same pathway is explored. For this purpose, prospective clinical trials and cross-validation studies are urgently needed. In conclusion, PKPD modelling and simulation studies are important to develop evidence-based and individualized dosing schemes for children, with the ultimate goal to improve drug safety and efficacy in this population.

1. Medicines in children: the role of the dose

Despite profound differences in response between children and adults, and between children of different ages, drugs are still used in children in an empirical manner. Most paediatric dosing regimens are expressed in mg/kg and are empirically derived from, e.g. adult regimens. To date, only a small number of drugs used in children are licensed for use in this specific group. Up to 37% of the drugs used in community practice settings and up to 80% of the drugs used in neonatal intensive care, are prescribed in an off-label or unlicensed manner (Conroy et al., 2000; Ernest et al., 2007; t Jong et al., 2001; Tod et al., 2008).

The difference in response to drugs between children and adults and between children of different ages may be caused by changes in the pharmacokinetics (PK) and/or pharmacodynamics (PD) of drugs. While a child grows, among others, kidney function (i.e. glomerular filtration rate, expression and function of renal transport proteins) and liver function (enzyme systems) which are involved in drug disposition may evolve, leading to changes in the relationship between dose and exposure. Likewise, the expression and function of receptors and proteins which are involved in the pharmacodynamics and the safety of a drug, may also develop, leading to alterations in the relation between exposure and response (Kearns et al., 2003). An important factor in this respect is that the maturation of these functions may vary between organs, and within these organs between pathways and receptors. For instance, cytochrome P-450 (CYP) 3A activity involved in, e.g. midazolam metabolism is low at birth with a surge of activity in the first months of life and an activity that exceeds adult levels during infancy (de Wildt et al., 1999). In contrast, uridine diphosphate glucuronosyltransferase (UGT)-2B7 involved in morphine glucuronidation matures exponentially up to the age of 3 years (Knibbe et al., 2009). Since maturation of expression and function is typically a non-linear dynamic process which differs between biotransformation routes and pharmacological targets, a dosing paradigm in mg/kg may result in under or over-dosing in specific age groups. As a result, dose adjustments, particularly in very young age groups are often proposed in national paediatric guidelines. For vancomycin for example, lower doses in mg/kg body weight are to be adminis-

Abbreviations: CYP, cytochrome P-450; LC–MS/MS, liquid chromatography with tandem mass spectrometry; MAC, minimum alveolar concentration; PIP, paediatric investigation plan; PUMA, Paediatric-Use Marketing Authorisation; TI Pharma, Top Institute Pharma; UGT, uridine 5′-diphospho-glucuronosyltransferase.

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tered in neonates younger than 1 week (20 mg/kg/day) compared to 1–4 week-old neonates (30 mg/kg/day) and children between 1 month and 18 years (40 mg/kg/day).

2. What information in children is needed as a basis for rational dosing?

Instead of an empiric dosing regimen based on bodyweight in a linear fashion, paediatric dosing regimens should be based on an understanding of the changing pharmacokinetic–pharmacodynamic (PKPD) relationship of the drug in children. Therefore, to define effective and safe dosing regimens for children of different ages, detailed information is needed a drug's pharmacokinetics (the drug-concentration *versus* time relationship), the pharmacodynamics (the effect *versus* time relationship) and the relationship between the two (the drug-concentration *versus* effect relationship, PKPD).

At present it is appreciated that systematic information on the PK and PD of drugs in children is scarce. This has lead to the 'Paediatric Regulation' in the European Union (Pekkarinen and Fontelles, 2006) which came into effect in 2007. This law imposes pharmaceutical companies to perform research in the whole paediatric age-range for all drugs that are developed for the European market. This involves the submission of a paediatric investigational plan (PIP) in the early stages of the development of a new drug. In this PIP, a full description has to be given of the proposed clinical studies to optimize the dosing regimen in the paediatric population and to demonstrate efficacy and safety in this vulnerable group of patients. The development of novel drug formulations for the paediatric population is an integral part of this research. The reward for this effort is a 6 month supplementary production certificate for the pharmaceutical company. The European Union has also assigned funds for research in children for off-patent drugs (FP7 program) in order to get licensed paediatric formulations with proper evidence-based paediatric dosing guidelines to the European market for drugs that are already marketed for adults (Paediatric-Use Marketing Authorisation (PUMA)).

As a result of these new regulations and academic initiatives, there has been a large increase in PK and PD studies and analyses in children including young infants and neonates. Aims of these studies are to gather structural information on the pharmacokinetics and pharmacodynamics of novel and existing drugs in order to derive models that can be of predictive value.

3. Developmental changes in PK and PD in children and relation to other covariates

For the PK, age-related differences may be caused by differences in absorption, distribution, metabolism and/or excretion. For example, in neonates intra-gastric pH is elevated (>4) which may increase the bioavailability of acid-labile compounds (penicillin G) (Kearns et al., 2003). Additionally, gastric emptying in neonates is delayed, which influence the absorption of drugs (Grand et al., 1976). Other examples are changes in metabolizing enzyme capacity in children. Although most UGTs and CYPs are expressed during the first week of life, the activity at birth in comparison with adults is often low while the maturation of the different enzyme systems is known to occur at different rates. In addition, developmental changes in renal function can alter plasma clearance of compounds with extensive renal elimination (van den Anker et al., 1995). Furthermore, the body composition of children changes continuously, resulting in age-dependent changes in the relative proportions of body water and fat, which influences the distribution of drugs. For example, the total amount of body water is higher in neonates (80–90% of the bodyweight) compared to adults (55–60%). Hydrophilic drugs like aminoglycosides have a larger volume of distribution in neonates, which can be explained by larger extra-cellular fluid fraction (45% of the bodyweight) compared to adults (20% of the body weight) (Kearns et al., 2003).

Differences in PD can result from age-related changes in target receptor or tissue expression. For example, a lower minimum alveolar concentration (MAC) of isoflurane, required for induction and maintenance of anaesthesia, is observed in preterm neonates compared to full-term neonates and older children (Blussé van Oud-Alblas et al., 2009; LeDez and Lerman, 1987). Traditionally, studies on PD have received less attention than PK studies. As a result, limited information is available on maturation and variability in PD in paediatrics. This is an important limitation while it is generally accepted that the variability in PD is much larger than variability in PK (Levy, 1998). This underscores the need for pharmacodynamic investigations in children. A potentially complicating factor in this respect is the lack of validated PD endpoints in children (De Cock et al., 2010). The bridging between adults and children is further complicated by the fact that typically different endpoints are used in different age groups. For example, for depth of sedation in children under 3 years of age the COMFORT-behavior scale (van Dijk et al., 2000) is used while in neonates the COMFORTneo (van Dijk et al., 2009), in older children and adults the Bispectral index, a processed-EEG value, and in adults the Ramsay sedation scale (Ramsay et al., 1974) is applied as a PD endpoint. It is nevertheless of utmost importance that clinical trials in children focus on age-related variability in both PK and PD simultaneously as the basis to develop rational dosing schemes.

In practice it is important that developmental changes in PK and/or PD in paediatrics are considered in the context of all other sources of intra- and inter-individual variability resulting from genetic-, environmental- and disease related factors and drug interactions in a so-called 'comprehensive covariate analysis'. These sources of variability also include variability resulting from differences in dose-bioavailability between adults and children for which advanced techniques are readily available (Rinaki et al., 2003a,b). An example is the role of pharmacogenetic factors on treatment effect or PK which should not be evaluated independently, but should be studied together with all other clinical covariates (Krekels et al., 2007). In a recent example on CYP2D6 polymorphisms in newborns, the relative influence of age, body weight and CYP2D6 polymorphisms classified as 2D6 activity score were simultaneously quantified (Allegaert et al., 2008). In our opinion this study provides a sophisticated example on how to study different covariates such as age-related and genetic factors in a quantitative manner.

4. How can this PK and PD information for paediatric dosing be gathered and analysed?

Properly designed studies in children aiming at the development of PKPD models are difficult to perform. Specific challenges are not only the availability of limited patient numbers, but also ethical and practical constraints with regard to the frequency and the volume of blood sampling and the availability of a pharmacodynamic endpoint, particularly in young infants and/or neonates. Meanwhile modern technologies for blood sampling and laboratory analyses have been developed which facilitate studies in paediatric populations. LC–MS/MS, for example, is a highly sensitive analytical technique enabling the use of very small volume samples for drug concentration analyses (Ahsman et al., 2010, 2009). In addition to these novel technologies, the application of advanced data-analysis techniques, the so-called 'population approach' has opened new avenues for drug studies in children. Population PKPD modelling involves the application of concepts of 'non linear mixed effects

modelling', where PKPD models are identified and PK and/or PD parameters are simultaneously estimated in all individuals. The most important advantage of the population approach is that it allows for the utilization of infrequently obtained samples and observations from actual patients at irregular time points (i.e. time points compatible with clinical care), rather than scheduled time points according to a specific experimental protocol. The approach allows for the analysis of relatively dense data, combinations of sparse and dense data or combinations of observations from experimental settings and clinical practice. Therefore, as the population approach is able to handle 'missing data' in individual patients, it greatly facilitates pharmacokinetic and/or pharmacodynamic studies in young children. Finally, this approach ensures that the obtained information can indeed be directly applied in clinical practice and that the burden to the individual patient can be kept to a minimum (Boeckman et al., 1998; Johnson, 2005).

As a result, population PKPD modelling and simulation constitutes the basis for the development of rational and individualized paediatric dosing guidelines at different phases of the process: (1) simulations for optimization of clinical trial designs based on preliminary data, (2) development and internal validation of population PKPD models using sparse data, (3) external validation using independent data and (4) prospective clinical evaluation of optimized dosing regimens (Ince et al., 2009). While this approach can be considered a top-down approach by studying the net influence of various covariates on a drug's pharmacokinetics, physiologically based pharmacokinetic (PBPK) modelling (Johnson and Rostami-Hodjegan, 2011; Johnson et al., 2006; Pang and Durk, 2010) can be considered a bottom-up approach. Using the PBPK approach, information on in vitro drug characteristics and information on all underlying biological processes are combined to simulate pharmacokinetic profiles. With this methodology a substantial number of drugs pharmacokinetic profiles have already been successfully predicted in children (Johnson and Rostami-Hodjegan, 2011; Johnson et al., 2006) and therefore population PKPD modelling and PBPK modelling methodologies should be considered to complement one another. This also accounts for the application of the principles of nonlinear dynamics which can provide a tool for the analysis of variability in encountered in PK or PD (Dokoumetzidis et al., 2001).

5. Perspectives of a PKPD analysis in children: an example using morphine

The results of a population PKPD analysis are (1) a structural PKPD model describing the time courses of the plasma concentration and the effect intensity, (2) estimates of the structural PK and/or PD parameters and (3) estimates for the interindividual variability (variance) in the structural model parameters as well as intraindividual variability or residual error (variance). A crucial element in any population PKPD analysis is the so-called covariate analysis, in which demographic and (patho)physiological (e.g. weight, age, liver and kidney function, disease severity, pharmacogenetics) predictors of the variability are identified. An example of a paediatric population PK analysis is our ongoing research on optimization of the dosing of morphine. When analysing the time courses of the concentrations of morphine and two metabolites in 250 children under the age of 3 years we found that the non-linear maturation of morphine glucuronidation was most adequately described using bodyweight in an allometric function with an exponent of 1.44 ($Cl_{individual} = Cl_{population} \cdot BW^{1.44}$). In addition to this relation with body weight, in neonates younger than 10 days it was found that morphine glucuronidation was reduced by 50% (Knibbe et al., 2009) (Fig. 1).

The predictors of variability that result from the covariate analysis, i.e. in this example both bodyweight and age younger or older

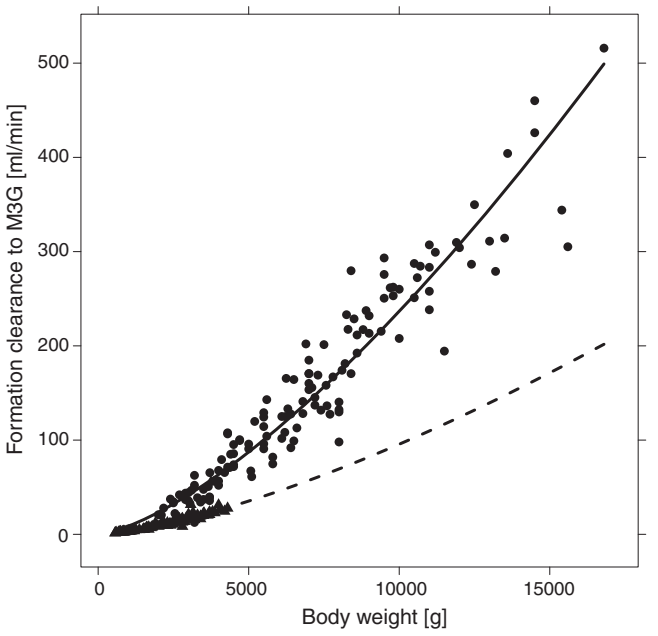

Fig. 1. Morphine glucuronidation clearance to morphine-3-glucuronide (M3G) *versus* bodyweight. Population predicted clearance in children younger than 10 days (dotted line) and older than 10 days (solid line) and individual clearance values in children younger than 10 days (triangles) and older than 10 days (circles). Log scale in insert. [Reproduced from Knibbe et al., 2009, with permission from Adis, a Wolters Kluwer business (©Adis Data Information BV [2009]. All rights reserved.)].

than 10 days, may serve as the basis for the design of individualized dosing schedules. Before these dosing schedules can be used, the models should be adequately validated internally and/or externally, which proved to be the case for only 28% and 26% of the population PK and PD models published between 2002 and 2004, respectively (Brendel et al., 2007). After internal (Knibbe et al., 2009) and external validation of the model (Krekels et al., 2011) and while assuming an unaltered pharmacodynamic relationship, a nonlinear dosing regimen (mg * bodyweight$^{1.5}$ per h) with a 50% reduction in neonates younger than 10 days for morphine in children up to the age of 3 years old was proposed (Knibbe et al., 2009) (Fig. 2). This model-based dosing algorithm (Table 1) is expected to result in similar morphine concentrations in children in the age range between preterm born neonates and 3 year old children while using the traditional dosing algorithm in mg/kg/h large variability in morphine concentrations is expected (Fig. 2). Table 1 shows the model-based dosing algorithm up to the age of 1 year of age as the final model has been validated externally against independent paediatric datasets up to this age limit of 1 year (Krekels et al., 2011). The table demonstrates that this algorithm results in the initiation of lower morphine doses in the youngest age ranges, i.e. in (preterm) newborns a maximum reduction of 75% of the morphine dose compared to traditional dosing regimens is proposed. In contrast, older children will initially receive a larger dose than currently is being used in clinical practice (Table 1). Both these proposed dose adjustments are in agreement with clinical observations that neonates require less additional morphine doses compared with other age groups (Bouwmeester et al., 2003b) and that neonates aged 7 days or younger require significantly less morphine postoperatively than older neonates when morphine is dosed in mg/kg/h (Bouwmeester et al., 2003a).

The next step in this research program is the evaluation of the novel dosing regimen in a prospective clinical trial with the aim to evaluate whether the proposed dosing regimen indeed leads to the expected concentrations and/or effects. For the example on morphine, the model-based dosing regimen of mg * bodyweight$^{1.5}$ per

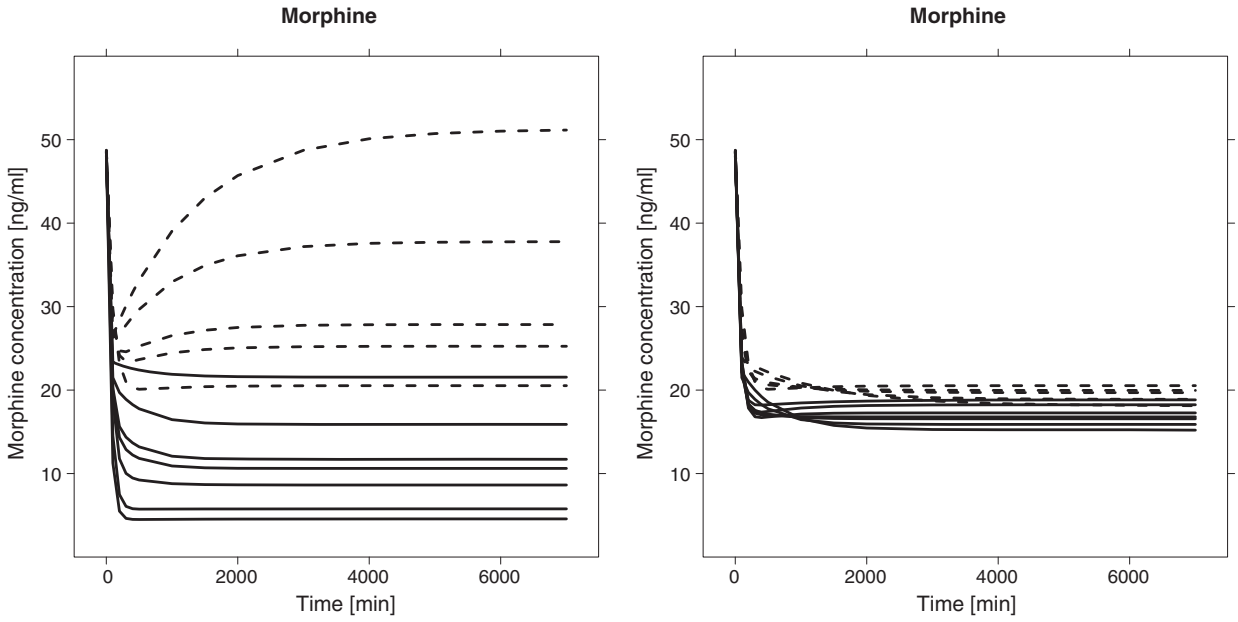

Fig. 2. Predicted morphine concentrations *versus* time following a traditional dosing algorithm in μg/kg/h (left panel) and a model-based dosing algorithm (μg*bodyweight$^{1.5}$ per h) (right panel). Morphine concentrations are predicted in children of 0.5, 1, 2, 2.5, 4, 10 and 17 kg and a postnatal age of less than 10 days (dotted lines) or more than 10 days (solid lines) based on a dosing regimen with a loading dose of 100 μg/kg and maintenance dose of 10 μg/kg/h (left panel) and based on a regimen with a loading dose of 100 μg/kg followed by an infusion of 10 μg*bodyweight$^{1.5}$ per h with a 50% reduction in maintenance dose for children younger than 10 days (right panel). The model-based dosing regimen in μg*bodyweight$^{1.5}$ per h is currently being prospectively studied in clinical trials NTR1438 and NTR2180 to evaluate the efficacy of this dosing regimen. [Reproduced from Knibbe et al., 2009, with permission from Adis, a Wolters Kluwer business (©Adis Data Information BV [2009]. All rights reserved.)].

Table 1
Dosing table for initial maintenance dose (μg/h) of intravenous morphine in children younger than of 1 year of age based on a model-based dosing algorithm (Knibbe et al., 2009; Krekels et al., 2011) and a traditional dosing algorithm. The model-based dosing algorithm is currently being studied in two paediatric clinical trials (NTR1438 and NTR2180). PNA = post natal age in days.

Bodyweight (kg)	Model-based dosing algorithm		Traditional dosing algorithm
	PNA < 10 days 2.5 mg * bodyweight$^{1.5}$ per h (μg/h)	PNA > 10 days 5 mg * bodyweight$^{1.5}$ per h (μg/h)	10 μg * bodyweight per h (μg/h)
0.5	0.88	–	5
1	2.5	5.0	10
1.5	4.6	9.2	15
2	7.1	14.1	20
2.5	9.9	19.8	25
3	13.0	26.0	30
3.5	16.4	32.7	35
4	20.0	40.0	40
4.5	23.9	47.7	45
5	28.0	55.9	50
5.5	32.2	64.5	55
6	36.7	73.5	60
6.5	–	82.9	65
7	–	92.6	70
7.5	–	102.7	75
8	–	113.1	80
8.5	–	123.9	85
9	–	135	90
9.5	–	146.4	95
10	–	158.1	100
11	–	182.4	110
12	–	207.8	120

h (Table 1) instead of mg/kg/h is now being studied in two clinical trials (NTR1438 and NTR2180) to evaluate the efficacy of this dosing regimen and as a consequence also the prospective value of the model and model-derived dosing regimens. These prospective trials are performed using a highly detailed dosing table (Table 1) for each bodyweight and age of a child in the intensive care. This dosing table is provided in order to prevent dosing errors when dosing by mg * bodyweight$^{1.5}$ per h. Within these prospective trials, clinical endpoints can be considered. For the example on morphine, it is expected that the lower dosage that results from this modelling exercise in preterm and term neonates, leads to less side effects such as withdrawal symptoms upon cessation of the morphine infusion. Specific advantages are expected upon prolonged use.

Obviously, if this approach needs to be applied to every single drug in paediatrics, large costs and significant time will be needed to develop evidence-based dosing schedules for each drug. An important question is therefore, to what extent a PK(PD) model constitutes a basis for the development of dosing guidelines for drugs other than those that have actually been studied. A specific

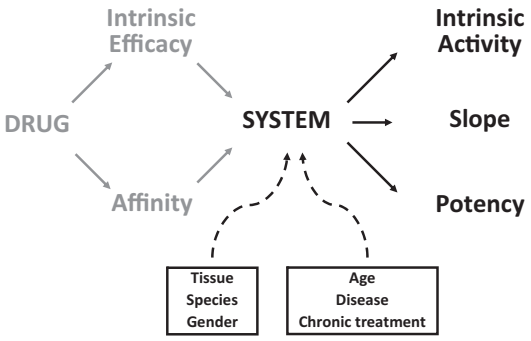

Fig. 3. Drug-specific and system-specific properties of the PKPD model. Drug-specific (grey) and biological system-specific (black) properties, with covariates influencing system-specific properties, in mechanism based PKPD models to characterize the time course of the drug effect. [Reproduced from Van der Graaf, Danhof. Int. J. Clin. Pharmacol. Ther. 1997;35:442–46, with permission of Dustri-Verlag (© 2007 Dustri-Verlag Dr. Karl Feistle)].

feature of mechanism based PKPD models is the strict distinction between drug-specific and biological system-specific parameters to characterize the time course of the drug effect (Danhof et al., 2007) (Fig. 3). In this respect the kinetics of age-related changes in renal function, the functionality of drug metabolizing enzymes, drug transporters, or the expression function of pharmacological receptors are considered system-specific properties. These biological system-specific or patient-specific properties, derived from one 'model' drug, could in principle serve as a basis for the prediction of age-related changes in the PK and PD of other drugs (so-called cross validation). Using simulations for drugs other than those used to generate system-specific information may significantly reduce the time and costs needed to develop drug dosing guidelines for individual drugs. These concepts are very similar to those that provide the basis for PBPK modelling (Pang and Durk, 2010; Johnson and Rostami-Hodjegan, 2011; Johnson et al., 2006) and both methodologies should therefore be considered to complement one another. In the example on morphine, currently the value of the derived paediatric covariate model for morphine is now studied in a cross validation study with a drug that is metabolized through the same UGT route (zidovudine). In this cross validation study, of the covariate model ($Cl_{individual} = Cl_{population} \cdot BW^{1.44}$), $BW^{1.44}$ is considered system-specific information while the actual value for morphine clearance or zidovudine clearance for a typical individual of the population, $Cl_{population}$, is drug-specific information. This proof of concept study will show whether a covariate model obtained for one drug, can be used for other drugs, sharing similar pathways. This is of potentially high value for new drugs that are currently being developed, as these models can then be used to better choose the (first) dose in children (of varying body weight), and to better design clinical studies through clinical trial simulations in European PIPs.

6. Our approach in practice: current project in The Netherlands

In The Netherlands, a multidisciplinary research platform on population PKPD modelling has been established by the foundation of the Top Institute Pharma (TI Pharma) mechanism-based PKPD modelling platform. Partners in this platform are four academic institutions and six leading international pharmaceutical industries who have agreed to the sharing of data, models and biological system specific information in a secure environment. The objective of platform is the development of a mechanism-based PKPD model library and a database of biological system-specific information for use in drug discovery and development. At present the modelling focuses on (1) translational pharmacology, especially in relation to drug safety, (2) developmental pharmacology especially in relation to paediatrics and (3) disease systems analysis (www.tipharma.com).

Within the platform, there are five projects on the modelling of developmental pharmacology in order to generate system-specific information and ultimately design individualized dosing regimens in children: (1) glucuronidation (UGT activity), (2) oxidation (CYP3A activity), (3) renal function (glomerular filtration and tubular secretion), (4) hepatic blood flow, and (5) immunosupppression. In these projects large data sets have been gathered through the partners while expertise on modelling and simulation is mainly provided by the Divison of Pharmacology of the Leiden-Amsterdam Center for Drug Research (LACDR) at Leiden University. Current status of the project is that initial models have been built, while external validation and cross validation studies are currently being performed. Additionally, new initiatives for sharing data between academic groups are being established.

7. PKPD model based dosing regimens in children: are we ready for it?

In conclusion, PKPD modelling and simulation studies are important to develop evidence-based and individualized dosing schemes for children, with the ultimate goal to improve drug safety and efficacy in this population. The population approach will allow for sparse sampling in children and reduce the burden for the individual child, thereby also allowing for studies in (preterm) neonates in which very little information is yet known while developmental changes are very large. The model-based dosing regimens will most probably be non linear based on bodyweight or age, thereby requiring dosing tables and formulations that can be used to individualize the dose. In order to actually implement these dosing guidelines in clinical trials and/or clinical practice, there is specific need for support by (hospital) pharmacists on the ward, e.g. by providing dosing tables in electronic prescription devices. Beside the novel paradigms for individualized dosing in children, the PKPD data-analyses will also allow for the characterization of the biological system, by a distinction between drug-specific and system-specific determinants of drug effect. Ultimately, results of a 'model drug', reflecting system-specific developmental drug disposition and effect pathways, can be used as a scientific basis to develop evidence-based dosing regimens for other existing or newly developed drugs, that share the same pathway. For this purpose, prospective clinical trials and cross validation studies are urgently needed. This approach will improve the efficacy/safety balance of dosing guidelines which will be of benefit to the individual child.

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