Review

Evidence-based drug treatment for special patient populations through model-based approaches

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ABSTRACT

The majority of marketed drugs remain understudied in some patient populations such as pregnant women, paediatrics, the obese, the critically-ill, and the elderly. As a consequence, currently used dosing regimens may not assure optimal efficacy or minimal toxicity in these patients. Given the vulnerability of some subpopulations and the challenges and costs of performing clinical studies in these populations, cutting-edge approaches are needed to effectively develop evidence-based and individualized drug dosing regimens. Five key issues are presented that are essential to support and expedite the development of drug dosing regimens in these populations using model-based approaches: 1) model development combined with proper validation procedures to extract as much valid information from available study data as possible, with limited burden to patients and costs; 2) integration of existing data and the use of prior pharmacological and physiological knowledge in study design and data analysis, to further develop knowledge and avoid unnecessary or unrealistic (large) studies in vulnerable populations; 3) clinical proof-of-principle in a prospective evaluation of a developed drug dosing regimen, to confirm that a newly proposed regimen indeed results in the desired outcomes in terms of drug concentrations, efficacy, and/or safety; 4) pharmacodynamics studies in addition to pharmacokinetics studies for drugs for which a difference in disease progression and/or in exposure-response relation is anticipated compared to the reference population; 5) additional efforts to implement developed dosing regimens in clinical practice once drug pharmacokinetics and pharmacodynamics have been characterized in special patient populations. The latter remains an important bottleneck, but this is essential to truly realize evidence-based and individualized drug dosing for special patient populations. As all tools required for this purpose are available, we have the moral and societal obligation to make safe and effective pharmacotherapy available for these patients too.

1. Introduction

Patients included in clinical trials during drug development are selected based on strict inclusion and exclusion criteria. Consequently, for the majority of drugs on the market, efficacy and safety are understudied and poorly characterized in various patient subpopulations, including pregnant women, paediatrics, the obese, the critically-ill, and the elderly. As a result, dosing regimens are not selected for optimal efficacy or minimal toxicity in these patients.

Evidence-based and individualized drug dosing regimens are tailored to individual needs by accounting for patient and treatment characteristics that influence the pharmacokinetics and pharmacodynamics of drugs. Trials needed to develop such dosing regimens are challenging, due to a myriad and ever changing landscape of rules and regulatory restrictions, and they are expensive to perform in all special patient populations. Therefore, approaches have been developed to expedite the development of evidence-based and individualized drug dosing regimens for these populations. Here we discuss five key issues regarding model-based approaches that are important to consider in this respect. These approaches have been successfully applied in the
paediatric population, the critically-ill, and obese patients, and can be extended to other special patient populations.

2. Population modeling

Special patient populations are often smaller than reference populations. Especially in children, practical and ethical constraints also limit the number of patients that can be included in studies as well as the number of invasive samples that can be obtained per patient. Moreover, studies in special populations are generally performed during routine clinical practice, which may negatively impact the information content of the obtained data. As a result, data obtained in special patient populations requires advanced methods with increased flexibility and statistical power to obtain a sufficiently high level of evidence from these data to derive drug dosing regimen.

Population modeling, also known as non-linear mixed effects modeling, is ideally suitable to study drug pharmacology in special patient populations (Admiraal et al., 2014; De Cock et al., 2011). This approach is based on the simultaneous analysis of pharmacological outcome data from multiple individuals and characterizes drug pharmacokinetics and/or pharmacodynamics on a population level, while also quantifying inter-individual variability. The quantification of inter-individual variability allows subsequent identification of patient-specific or treatment-specific predictors that can (partially) contribute to observed differences in drug exposure or exposure-response relationships in the studied population. These so-called covariates can serve as the basis for individualized drug treatment.

As population models for special patient populations are generally based on limited observations, the risk of drawing wrong conclusions is substantial. Therefore, although often overlooked (Brendel et al., 2007; Tod et al., 2008), the statistical validation of outcome predictions by models is essential before model-derived dose regimens can guide individualized pharmacotherapy. These statistical model validations should include at least an extensive internal validation, comparing model predictions to the observations used for model building (Admiraal et al., 2014; Krekels et al., 2011; Nguyen et al., 2016). An external validation, comparing model predictions to new external observations is also essential to perform. External data can be obtained in new clinical trials, but to limit resources and reduce the burden to patients, historic data or opportunistic samples may also be used for this purpose although the latter by nature are less reliable (Ince et al., 2009; Krekels et al., 2011).

Since study and patient characteristics in some populations may differ from those in traditional clinical trials, it is important to tailor the statistical model validation procedures to these characteristics (Krekels et al., 2011). It has for instance been shown that inapt validation of a published paediatric model for the pharmacokinetics of morphine failed to identify misspecification of the covariate model, resulting in a systematic under-prediction of morphine and metabolite concentrations in neonates and infants, which could have led to a disastrously high doses in these patients, in case that model had been used for dose predictions (Krekels et al., 2011).

3. Integration of data and use of prior pharmacological and physiological knowledge

As mentioned, the potential sample size of patients is limited in special patient populations. Moreover, the heterogeneity in these populations increases noise in the data, while the vulnerability of many sub-populations may limit the amount of invasive samples that can be obtained per patient. In addition to costs, these factors may considerably limit the feasibility of dedicated trials for each relevant drug in special patient populations. To cope with this limited data potential, strategies should be applied to most optimally use existing data and prior knowledge, both for study design, data analysis and the identification of drug-specific and system-specific properties.

For many drugs, historic data or scavenged samples and therapeutic drug monitoring (TDM) data can be valuable sources of information on patient subpopulations (Allegaert et al., 2008; Autmizguine et al., 2014; Gonzalez et al., 2014; Leroux et al., 2015a; Zhao et al., 2015). Even when these samples cannot be used to inform a full population model, they may be useful in the presence of more informative data from a reference population, to inform the covariate model for the special patient population and also allow model-based predictions in that population (Voller et al., in preparation).

Despite initiatives on data sharing or opportunistic sampling, the need for dedicated studies in special populations will never be negated. Software tools for simulations and optimal study design can be used to optimize sampling strategies based on prior knowledge or limited existing data, so that samples containing most information on the endpoint of interest can be obtained during clinical studies with a minimal burden to individual patients (Ince et al., 2009; Nyberg et al., 2015; Van Hasselt et al., 2013, 2014). Involvement of a pharmacometrician familiar with these techniques during study design is therefore of high value.

Another important strategy to cope with the limited data potential is increasing the information derived from study data through the integration of findings regarding drug pharmacology and patient physiology. Population models are empirical models yielding information on particular drugs in particular populations. The potential to extrapolate findings from one drug to another drug in the same population, or from one population to another population for the same drug, is restricted. This results from the fact that parameters in population models contain both system-specific and drug-specific information.

Currently several research efforts are focused on developing methodologies to disentangle system-specific information from drug-specific information, using for instance physiology-based pharmacokinetic modeling or systems pharmacology models (Danhof, 2016). Only when system-specific and drug-specific information are disentangled for a certain drug in a certain population, can extrapolations be made to inform on the pharmacology of other drugs or other populations. For example, a population analysis on the pharmacokinetics of midazolam showed systemic clearance of this drug to be similar in obese patients undergoing bariatric surgery and healthy volunteers, while oral bioavailability was lower in the bariatric patients (Brill et al., 2014a, 2014b). One year after surgery and considerable subsequent weight loss, systemic midazolam clearance in the patients had increased statistically significantly, whereas oral bioavailability remained unchanged (Brill et al., 2015). To better understand the physiological basis of these findings a physiology-based pharmacokinetic model was developed for midazolam and its hydroxymetabolite in the bariatric patients before and after weight loss, with specific focus on the CYP3A activity in the gut wall and liver. From this it could be concluded that hepatic metabolic clearance of midazolam increases after weight loss, while metabolic clearance in the gut wall is low and highly variable both before and after weight loss (Brill et al., 2016). After obesity-
related changes in hepatic blood flow and perfusion have been elucidated, the information obtained in this analysis can be used to predict systemic and pre-systemic clearance of other CYP3A substrates based on drug-specific properties.

An advantage of physiology-based pharmacokinetic models in the previous example is that the system-specific information mostly comprises quantifiable physiological parameters that only need to be obtained once. However, these models do require a wealth of information that is currently not available for each subpopulation. Therefore faster and less data-intensive methods are also being investigated for the integration of knowledge on physiology and drug pharmacology. It has for instance been hypothesized that covariate relationships in paediatric pharmacokinetic models reflect the net influence of all changes in the physiological processes underlying particular pharmacokinetic processes. If this were true, it should be possible to extrapolate paediatric covariate relationships for clearance from one drug to another that is eliminated through the same pathway. Although this has indeed been confirmed for some drugs, including drugs eliminated through glomerular filtration and drugs undergoing glucuronidation (De Cock et al., 2014a, 2014b; Krekels et al., 2012a, 2012b), recent findings show that these extrapolations should be used carefully. Indeed, it was found that properties of both the model drug and the target drug influence the extrapolation potential of covariate relationships, with the extraction ratio of both drugs being especially predictive (Calvier et al., 2014). Similar research also showed that drug properties influence the predictive properties of allometric scaling in the paediatric population (Calvier et al., 2016). As the user-friendliness makes these relatively simple approaches attractive, more research is needed to explore in which situations extrapolations are justified.

4. Prospective evaluation of model-derived drug dosing regimens

To implement model-derived dosing regimens in clinical practice, it is essential to perform a prospective clinical study that evaluates the drug concentrations as well as efficacy and safety profiles obtained with the newly proposed dosing regimen as proof of principle. Only after expected clinical outcome parameters have been confirmed, should a dosing regimen be implemented in clinical practice (Ince et al., 2009).

Prospective clinical studies may reveal new information that could not be derived from data from studies performed with former dosing regimens. Non-linearities in pharmacokinetics or physiological responses may for example yield unexpected outcomes with previously untested drug doses. Moreover, prospective studies may reveal additional factors contributing to inter-individual variability in drug responses that were not taken into account in the developed regimen. For instance for morphine, when a model-derived dosing regimen correcting for differences in the pharmacokinetics of this drug across a population of newborns and young infants was prospectively evaluated, it was revealed that age-related differences in sensitivity to pain and/or morphine concentrations were an additional cause for age-related difference in required rescue medication (Ceelie et al., 2013; Krekels et al., 2014). This prospective study confirmed that corrections for differences in pharmacokinetics yield improvement of the pharmacotherapy particularly for the youngest neonates who required much lower dosages. Yet it also emphasizes that further pharmacodynamic studies are required to identify age-appropriate morphine target concentrations for older infants.

This example illustrates that when untested dosing regimens are evaluated in prospective clinical studies, it is advisable to monitor patients and allow for protocol deviations, including dose adjustments, when necessary. Such dose adjustments can be guided by directly observable outcome measures or, if these are not available, by proxies like TDM. In a currently ongoing study on a new paediatric dosing regimen for anti-thymocyte globulin derived from detailed studies on the pharmacokinetics (Admiraal et al., 2015b) and pharmacodynamics (Admiraal et al., 2015a) in children, TDM is being performed to avoid unexpected under- or over-exposure, resulting from the considerable changes in the new regimen.

5. Drug dosing based on pharmacokinetics and pharmacodynamics

Special patient populations may deviate from the reference patient population included in clinical trials regarding both pharmacokinetics and pharmacodynamics. The latter may cover both desired effects and side-effects. Much pharmacological research in special patient populations has however focused on the pharmacokinetic differences only.

In a number of cases, dose regimens that correct only for inter-individual differences in pharmacokinetics may indeed suffice. The FDA has developed a decision tree to guide pharmaceutical industry on the requirements for paediatric clinical studies during drug development (http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm106614.htm), that can be extended to other special patient populations as well. According to this decision tree, pharmacokinetic bridging studies suffice if the following criteria are met: 1) the special patient population and reference population can reasonably be assumed to have similar disease progression and similar response to intervention, and 2) the exposure-effect relationship between the special patient population and reference population can be assumed to be the same for the drug of interest.

Antibiotics or antivirals for the treatment of infectious diseases are examples of drugs that are likely to meet these criteria. For pharmacokinetic bridging to work, it is imperative to study the pharmacokinetics at the relevant target site or a site that accurately reflects concentrations at this target site. It has for instance been shown that obese patients reach much lower subcutaneous tissue levels of cefazolin than their non-obese counterparts at the same serum concentrations. As this drug is intended to act in subcutaneous tissue to prevent post-operative wound infections, obese patients therefore require higher doses and higher serum concentrations for adequate prophylaxis (Brill et al., 2014a, 2014b).

The previous example of morphine suggests that in the paediatric population morphine does not meet the FDA criteria for bridging pharmacokinetic only. It can for instance be imagined that receptor expression or signal transduction for both pain and morphine are age-dependent. Alternatively, transport of morphine from plasma to the brain may be age-dependent (Lam et al., 2015). In these cases, pharmacodynamics studies using validated clinical endpoints in the pertaining patient population are essential to determine appropriate target concentrations in different subpopulations.

A number of pharmacodynamic studies have shown treatment indication or disease severity to be potentially important pharmacodynamic covariates that need to be taken into account for optimal drug dosing. A study in neonates with necrotizing enterocolitis (NEC) indicated increased morphine dose requirements compared to post-operative patients. This may result from prolonged and former pain experienced by NEC patients (Meesters et al., 2016), or from differences in the pain stimuli. Additionally, for the treatment of critically-ill adult patients it was found that the sensitivity to propofol sedation increased with increasing Sequential Organ Failure Assessment (SOFA) scores, suggesting that target concentrations for propofol decrease considerably with increasing disease severity (Peeters et al., 2008).

In addition to the pathophysiological and pharmacological requirements mentioned above, accurate bridging of findings between patient subpopulations requires the same endpoints in both populations. This may not be the case for drugs used for the treatment of outcomes that are quantified based on self-report. Ideally, surrogate endpoints that can be used as alternatives in such cases are biomarkers that can be directly and objectively measured. When such endpoints are not available, as is the case for pain, ratings by caregivers are often used in non-verbal populations, like the COMFORT-B scale in paediatric patients (Ista et al., 2005) or the REPOS scale in non-communicative
adults and cognitively impaired elderly (van Herk et al., 2009). For these endpoints it is essential that they are validated to be appropriate in the particular patient population before using them to investigate the pharmacodynamics of a drug.

Ratings by caregivers are often based on questionnaires and scales containing multiple items. It has been shown that advanced data analysis techniques can improve the statistical power of identifying drug effects in studies using these scales. Based on composite COMFORT-B scores, it was for instance not possible to support morphine treatment over placebo in neonates on artificial ventilation (Simons et al., 2003), but re-analyses using item response theory showed statistically significant benefits of morphine (Valitalo et al., Accepted). Furthermore, advanced statistical methods can be applied to increase the information content of scores from multi-item scales. Item response theory for instance also revealed which sub-items in the COMFORT and PIPP scale are most specific for pain and best reflect changes in pain behavior in neonates (Valitalo et al., 2016).

6. Clinical implementation of findings

Once evidence-based and individualized dosing regimens are available from validated models and following confirmation of the desired outcome in a prospective clinical trial, the dosing regimens need to be implemented in clinical practice, for which careful guidance is paramount.

To date, the clinical implementation of evidence-based drug dosing in special patient populations is still limited. For antibiotics treatment in the paediatric population, a recent study identified 444 different dose regimens for 41 different antibiotics in France (Leroux et al., 2015b). Similarly, for vancomycin dosing and TDM, 24 different protocols were identified in the UK (Kadambari et al., 2011). While an evidence-based regimen has been identified for vancomycin (Janssen et al., 2016), gentamicin and tobramycin (Valitalo et al., 2015), these regimens have not yet been fully included in (inter)national formularies. Successful examples in this respect are the adjustment of cefazolin prophylaxis doses for obese subpopulations which are to be implemented in Dutch SWAB guidelines as well as model-derived amikacin dosing in neonates (Smits et al., 2015) which is implemented in Leuven neonatal ICU and in the Dutch paediatric formulary.

Finally, it is important to mention, that pharmacokinetic or pharmacodynamic covariates may not always be sufficient to support individualized dosing regimen, meaning that additionally monitoring may still be warranted for some drugs. Besides standard monitoring for safety and efficacy, especially for drugs with a relatively high unexplained variability in pharmacokinetics or pharmacodynamics and a small therapeutic window, TDM may remain necessary. This has for instance been the case for busulphan in the treatment of paediatric haematoepoietic stem cell transplantation patients where model-derived improvements in doses have been proposed (Bartelink et al., 2012). In these cases, TDM remains relevant to mitigate random unexplained doses in obese subpopulations which are to be implemented in Dutch SWAB guidelines as well as model-derived amikacin dosing in neonates (Smits et al., 2015) which is implemented in Leuven neonatal ICU and in the Dutch paediatric formulary.

7. Summary

While it remains challenging to develop evidence-based and individualized dosing regimens for special patient populations, the knowledge and tools to do so are available. We therefore have an obligation to make safe and effective pharmacotherapy available for these patients. Current efforts in integrating research information and further increasing statistical power of pharmacodynamic scales and data analysis techniques will help this field move forward even further. To date, it seems that implementation of findings in clinical practice still remains one of the biggest challenges that requires sustained efforts.

Conflict of interest

All authors declare no conflict of interest.

References

Admiral, R., van Kesteren, C., Boelens, J.J., Bredius, R.G.M., Tibboel, D., Knibbe, C.A.J., 2014. Towards evidence-based dosing regimens in children on the basis of population pharmacokinetic pharmacodynamic modelling. Arch. Dis. Child. 99, 267–272.

Admiral, R., van Kesteren, C., Jol- van der Zijde, C.M., Lankeste, A.C., Biering, M.B., Egberts, T.C.G., van Tol, M.J.D., Knibbe, C.A.J., Bredius, R.G.M., Boelens, J.J., 2015a. Association between anti-thymocyte globulin exposure and CD4+ immune reconstitution in paediatric haemopoietic cell transplantation: a multicentre, prospective pharmacokinetic-pharmacodynamic analysis. Lancet Haematol. 2, e194–e203.

Admiral, R., van Kesteren, C., Jol- van der Zijde, C.M., van Tol, M.J.D., Bartelink, I.H., Bredius, R.G.M., Boelens, J.J., Knibbe, C.A.J., 2015b. Population pharmacokinetic modeling of thymoglobulin® in children receiving allogeneic-hematopoietic cell transplantation: towards improved survival through individualized dosing. Clin. Pharmacokinet. 54, 435–446.

Allegaert, K., Scheers, I., Adams, E., Brajanoski, G., Cosse, V., Anderson, B.J., 2008. Cerebrospinal fluid compartmental pharmacokinetics of amikacin in neonates. Antimicrob. Agents Chemother. 52, 1934–1939.

Autmizguine, J., Benjamin, D.K., Smith, P.B., Sampson, M., Ovtchikine, P., Cohen-Wolkowiez, M., Watt, K.M., Watt, K., 2014. Pharmacokinetic studies in infants using minimal-risk study designs. Curr. Clin. Pharmacol. 9, 350–358.

Bartelink, I.H., Boelens, J.J., Bredius, R.G.M., Egberts, T.C.G., Wang, C., Biering, M.B., Shaw, P.J., Nath, C.E., Hempel, G., Zwaveling, J., Danhof, M., Knibbe, C.A., 2012. Body weight-dependent pharmacokinetics of busulfan in paediatric haemopoietic stem cell transplantation patients. Clin. Pharmacokinet. 51, 331–345.

Brendel, K., Darzi, C., Cormet, E., Lemenaul-Blot, A., Lavelle, C., Tranchard, B., Girard, P., Laffont, C.M., Mentre, F., 2007. Are population pharmacokinetic and/or pharmacodynamic models adequately evaluated? A survey of the literature from 2002 to 2004. Clin. Pharmacokinet. 46, 221–234.

Brill, M.J.E., Houwink, A.P.L., Schmidt, S., Van Dongen, E.P.A., Hazebroek, E.J., van Ramshorst, B., Denere, V.H., Mouton, J.W., Knibbe, C.A.J., 2014a. Reduced subcutaneous tissue distribution of cefazolin in morbibly obese versus non-obese patients determined using clinical microdialysis. J. Antimicrob. Chemother. 69, 715–723.

Brill, M.J.E., van Rongen, A., Houwink, A.P.L., Burggraaf, J., van Ramshorst, B., Wieuwer, R.J., van Dongen, E.P.A., Knibbe, C.A.J., 2014b. Midazolam pharmacokinetics in morbibly obese patients following oral administration: a comparison with healthy volunteers. Clin. Pharmacokinet. 53, 931–941.

Brill, M.J.E., van Rongen, A., van Dongen, E.P., van Ramshorst, B., Hazebroek, E.J., Darwin, A.S., Rostami-Hodjegan, A., Knibbe, C.A., 2015. The pharmacokinetics of the CYP3A substrate midazolam in morbibly obese patients before and one year after bariatric surgery. Pharm. Res. 32, 3927–3936.

Brill, M.J.E., Valitale, P.A.J., Darwin, A.S., van Ramshorst, B., van Dongen, H.P.A., Rostami-Hodjegan, A., Danhof, M., Knibbe, C.A.J., 2016. Semiphysiological based pharmacokinetic model for midazolam and CYP3A mediated metabolite 1-OH-midazolam in morbibly obese and weight loss surgery patients. CPT Pharmacometrics Syst. Pharmacol. 5, 20–30.

Calver, E.A.M., Krekels, E.H.J., Knibbe, C.A.J., 2014. Extrapolation potential of semi-physiological covariate models to newborns: a simulation-based study. In: PAGE 24, Abstr 3595.

Calver, E.A.M., Krekels, E.H.J., Valitale, P.A.J., Rostami-Hodjegan, A., Tibboel, D., Danhof, M., Knibbe, C.A., 2016. Allometric scaling of clearance in Paediatric patients when does the magic of 0.75 fade? Clin. Pharmacokinet.

Cleele, I., de Wildt, S.N., van Dijk, M., van den Berg, M.M.J., van den Bosch, G.E., Duivenvoorden, H.J., de Leeuw, T.G., Mathôt, R., Knibbe, C.A.J., Tibboel, D., 2013. Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery. JAMA 309, 149.

Danhof, M., 2016. Systems pharmacology — towards the modeling of network interactions. Eur. J. Pharm. Sci. 94, 1–14.

De Cock, R.F.W., Piana, C., Krekels, E.H.J., Danhof, M., Allegaert, K., Knibbe, C.A.J., 2011. The role of population PK-PD modelling in paediatric clinical research. Eur. J. Clin. Pharmacol.

De Cock, R.F.W., Allegaert, K., Bruins, J.M., Sherwin, C.M.T., Mulia, H., de Hoog, M., van den Aker, J.N., Danhof, M., Knibbe, C.A.J., 2014a. Simultaneous pharmacokinetic modeling of gentamicin, tobramycin and vancomycin clearance from neonates to adults: towards a semi-physiological function for maturation in glomerular filtration. Pharm. Res. 31, 2643–2654.

De Cock, R.F.W., Allegaert, K., Sherwin, C.M.T., Nielsen, E.L., de Hoog, M., van den Aker, J.N., Danhof, M., Knibbe, C.A.J., 2014b. A neonatal amikacin covariate model can be used to predict ontogeny of other drugs eliminated through glomerular filtration in neonates. Pharm. Res. 31, 2716–2722.

Gonzalez, D., Melloni, C., Voge, R., Poindetx, B.B., Mendley, S.R., Delmore, P., Sullivan, J.E., Autmizguine, J., Lewandowski, A., Harper, B., Watt, K.M., Lewis, K.C., Capparelli, E.V., Benjamin, D.K., Cohen-Wolkowiez, M., Best Pharmaceuticals for Children Act – Pediatric Trials Network Administrative Core Committee, 2014. Use of opportunistic clinical data and a population pharmacokinetic model to support dosing of clineamycin for premature infants to adolescents. Clin. Pharmacol. Ther. 96, 429–437.

Ince, H., de Wildt, S.N., Tibboel, D., Danhof, M., Knibbe, C.A., 2009. Tailor-made drug
treatment for children: creation of an infrastructure for data-sharing and population PK-PD modeling. Drug Discov. Today 14, 316–320.
Ista, E., van Dijk, M., Tibboel, D., de Hoog, M., 2005. Assesment of sedation levels in pediatric intensive care patients can be improved by using the COMFORT “behavior” scale. Pediatr. Crit. Care Med. 6, 58–63.
Janssen, E.J.H., Valtiolo, P.A.J., Allegaert, K., de Cock, R.F.W., Simons, S.H.P., Shervin, C.M.T., Mouton, J.W., van den Anker, J.N., Knibbe, C.A.J., 2016. Towards rational dosing algorithms for vancomycin in neonates and infants based on population pharmacokinetic modeling. Antimicrob. Agents Chemother. 60, 1013–1021.
Kadambari, S., Heath, P.T., Sharland, M., Lewis, S., Nichols, A., Turner, M.A., 2011. Variation in gentamicin and vancomycin dosing and monitoring in UK neonatal units. J. Antimicrob. Chemother. 66, 2647–2656.
Krekels, E.H.J., van Hasselt, J.G.C., Tibboel, D., Danhof, M., Knibbe, C.A.J., 2011. Systematic evaluation of the descriptive and predictive performance of paediatric morphine population models. Pharm. Res. 28, 797–811.
Krekels, E.H.J., Johnson, T.N., den Hoed, S.M., Rostami-Hodjegan, A., Danhof, M., Tibboel, D., Knibbe, C.A.J., 2012a. From pediatric covariate model to semiphysiological function for maturation: part II-sensitivity to physiological and physiochemical properties. CPT Pharmacometrics Syst. Pharmacol. 1, e10.
Krekels, E.H.J., Neely, M., Panoïla, E., Tibboel, D., Capparelli, E., Danhof, M., Mirochnick, M., Knibbe, C.A.J., 2012b. From pediatric covariate model to semiphysiological function for maturation: part I—extrapolation of a covariate model from morphine to zidovudine. CPT Pharmacometrics Syst. Pharmacol.
Krekels, E.H.J., Tibboel, D., de Wildt, S.N., Ceelie, I., Dahan, A., van Dijk, M., Danhof, M., Knibbe, C.A.J., 2014. Evidence-based morphine dosing for postoperative neonates and infants. Clin. Pharmacokinet. 53, 553–563. http://dx.doi.org/10.1007/s40262-014-0135-4.
Lam, J., Baelo, S., Iqbal, M., Kelly, L.E., Shannon, P.T., Chitayat, D., Matthews, S.G., Koren, G., 2015. The ontogeny of P-glycoprotein in the developing human blood-brain barrier: implication for opioid toxicity in neonates. Pediatr. Res. 78, 417–421.
Leroux, S., Turner, M.A., Guellier, C.B.-L., Hill, H., van den Anker, J.N., Kearns, G.L., Jacqz-Aigrain, E., Zhao, W., TINN (Treat Infections in NeoNates) and GRiP (Global Research in Paediatrics) Consortiums, 2015a. Pharmacokinetic studies in neonates: the utility of an opportunistic sampling design. Clin. Pharmacokinet. 54, 1273–1285.
Leroux, S., Zhao, W., Bétrémieux, P., Pladys, P., Saliba, E., Jacqz-Aigrain, E., French Society of Neonatology, 2015b. Therapeutic guidelines for prescribing antibiotics in neonates should be evidence-based: a French national survey. Arch. Dis. Child. 100, 394–398.
Meesters, N.J., van Dijk, M., Knibbe, C.A.J., Keyzer-Dekker, C.M.G., Tibboel, D., Simons, S.H.P., 2016. Infants operated on for necrotizing enterocolitis: towards evidence-based pain guidelines. Neonatology 110, 190–197.
Nguyen, T.H.-T., Moukassi, M.-S., Holford, N., Al-Huniti, N., Freedman, I., Hooker, A.C., John, J., Karlsson, M.O., Mould, D.R., Pérez Ruixo, J.J., Plan, E.L., Savic, R., van Hasselt, J.G.C., Weber, B., Zhou, C., Comets, E., Mentré, F., Model Evaluation Group of the International Society of PharmacometricSop Best Practice Committee, 2016. Model evaluation of continuous data pharmacometric models: metrics and graphics. CPT Pharmacometrics Syst. Pharmacol.
Nyberg, J., Bazoli, C., Oungbenko, K., Aliev, A., Leonov, S., Duffull, S., Hooker, A.C., Mentré, F., 2015. Methods and software tools for design evaluation in population pharmacokinetics-pharmacodynamics studies. Br. J. Clin. Pharmacol. 79, 6–17.
Peeters, M., Bras, L., De Jongh, J., Weselink, R., Aarts, L., Danhof, M., Knibbe, C., 2008. Disease severity is a major determinant for the pharmacodynamics of propofol in critically ill patients. Clin. Pharmacol. Ther. 83, 443–451.
Simons, S.H., van Dijk, M., Van Lingen, R.A., Roothooft, D., Duivenvoorden, H.J., Jongeneel, N., Bunkers, C., Smioek, E., Anand, K.J., van den Anker, J.N., Tibboel, D., 2003. Routine morphine infusion in preterm newborns who received ventilatory support: a randomized controlled trial. JAMA 290, 2419–2427.
Smits, A., de Cock, R.F.W., Allegaert, K., Vanhaeckebrourck, S., Danhof, M., Knibbe, C.A.J., 2015. Prospective evaluation of a model-based dosing regimen for amikacin in preterm and term neonates in clinical practice. Antimicrob. Agents Chemoter. 59, 6344–6351.
Tod, M., Jullien, V., Pons, G., 2008. Facilitation of drug evaluation in children by population methods and modelling. Clin. Pharmacokinet. 47, 231–243.
Valtiolo, P.A.J., van den Anker, J.N., Allegaert, K., de Cock, R.F.W., de Hoog, M., Simons, S.H.P., Mouton, J.W., Knibbe, C.A.J., 2015. Novel model-based dosing guidelines for gentamicin and tobramycin in preterm and term neonates. J. Antimicrob. Chemother. 70, 2074–2077.
Valtiolo, P.A.J., van Dijk, M., Krekels, E.H.J., Gibbins, S., Simons, S.H.P., Tibboel, D., Knibbe, C.A.J., 2016. Pain and distress caused by endotracheal suctioning in neonates is better quantified by behavioural than physiological items. Pain 157, 1611–1617.
Valtiolo P.A.J., Krekels E.H.J., Van Dijk M., Simons S.H.P., Tibboel D., Knibbe C.A.J., 2016. Pain and distress caused by endotracheal suctioning in neonates is better quantified by behavioural than physiological items. Pain 157, 1611–1617.
Accepted. Morphine pharmacodynamics in mechanically ventilated preterm neonates undergoing endotracheal suctioning. CPT Pharmacometrics Syst. Pharmacol. Van Hasselt, J.G.C., van Eijkelenburg, N.K.A., Beijnen, J.H., Schellens, J.H.M., Huijtema, A.D.R., 2013. Optimizing drug development of anti-cancer drugs in children using modelling and simulation. Br. J. Clin. Pharmacol. 76, 30–47.
Van Hasselt, J.G.C., van Eijkelenburg, N.K.A., Beijnen, J.H., Schellens, J.H.M., Huijtema, A.D.R., 2014. Design of a drug-drug interaction study of vincristine with azole antifungals in pediatric cancer patients using clinical trial simulation. Pediatr. Blood Cancer 61, 2223–2229.
Van Herk, R., Boerlage, A.A., van Dijk, M., Baar, F.P.M., Tibboel, D., de Wit, R., 2009. Pain management in Dutch nursing homes leaves much to be desired. Pain Manag. Nurs. 10, 32–39.
Zhao, W., Zhang, D., Storme, T., Baruchel, A., Declèves, X., Jacqz-Aigrain, E., 2015. Population pharmacokinetics and dosing optimization of teicoplanin in children with malignant haematological disease. Br. J. Clin. Pharmacol. 80, 1197–1207.