Pharmacometric *in silico* studies used to facilitate a national dose standardisation process in neonatology – application to amikacin

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Summary

BACKGROUND AND AIMS: Pharmacometric *in silico* approaches are frequently applied to guide decisions concerning dosage regimes during the development of new medicines. We aimed to demonstrate how such pharmacometric modelling and simulation can provide a scientific rationale for optimising drug doses in the context of the Swiss national dose standardisation project in paediatrics using amikacin as a case study.

METHODS: Amikacin neonatal dosage is stratified by post-menstrual age (PMA) and post-natal age (PNA) in Switzerland and many other countries. Clinical concerns have been raised for the subpopulation of neonates with a post-menstrual age of 30–35 weeks and a post-natal age of 0–14 days ("subpopulation of clinical concern"), as potentially oto-/nephrotoxic trough concentrations (C_{trough} >5 mg/l) were observed with a once-daily dose of 15 mg/kg. We applied a two-compartmental population pharmacokinetic model (amikacin clearance depending on birth weight and post-natal age) to real-world demographic data from 1563 neonates receiving anti-infectives (median birth weight 2.3 kg, median post-natal age six days) and performed pharmacometric dose-exposure simulations to identify extended dosing intervals that would ensure non-toxic C_{trough} (C_{trough} <5 mg/l) dosages in most neonates.

RESULTS: In the subpopulation of clinical concern, C_{trough} <5 mg/l was predicted in 59% versus 79–99% of cases in all other subpopulations following the current recommendations. Elevated C_{trough} values were associated with a post-natal age of less than seven days. Simulations showed that extending the dosing interval to ≥36 h in the

subpopulation of clinical concern increased the frequency of a desirable C_{trough} below 5 mg/l to >80%.

CONCLUSION: Pharmacometric *in silico* studies using high-quality real-world demographic data can provide a scientific rationale for national paediatric dose optimisation. This may increase clinical acceptance of fine-tuned standardised dosing recommendations and support their implementation, including in vulnerable subpopulations.

Introduction

Neonatal dosing with anti-infective drugs is highly variable at both national [1, 2] and international levels [3] and across neonatal treatment guidelines [4]. In Switzerland, the Swiss database for dosing medicinal products in paediatrics (SwissPedDose, https://www.swisspeddose.ch/database) aims to standardise drug dosing in paediatrics at a national level. Recommendations consider the currently applied dosing regimens, the latest scientific evidence, clinical experience, and expert opinion [5, 6]. Pharmacometric modelling and simulation is a recognised approach to guiding dosage decisions in the development of new medicines and post-marketing drug optimisation [7, 8]. Modelling may also provide a scientific rationale for neonatal and paediatric dosing approaches in areas of uncertainty [9–12]. We present a motivational case study to illustrate and discuss the potential broader usefulness, prerequisites, and implementation in the context of a national dose standardisation effort.

Motivational case study

In Switzerland, amikacin is a frequently used aminoglycoside antibiotic with activity against gentamicin-resistant

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bacteria [13, 14]. Amikacin is mostly used in combination with a β-lactam antibiotic as a first-line empirical treatment for suspected neonatal sepsis [15]. During the national standardisation process, a dosing approach according to post-menstrual age (PMA, <30/30–35/35–44 weeks, defined as gestational age plus chronological post-natal age) and post-natal age (PNA, 0–14/≥14 days) was proposed by SwissPedDose after a literature review, defining six subpopulations (table 1) [6]. In the preterm subpopulation with a post-menstrual age of 30–35 weeks, a 24-hour vs 36-hour dosing interval was discussed, with the decision of a 24 hour dosing interval disregarding post-natal age for practical reasons. Clinical concerns regarding this approach were raised by neonatologists for the preterm subpopulation #3 (table 1) defined by a post-menstrual age of 30–35 weeks and a post-natal age <14 days (hereafter referred to as the subpopulation of clinical concern), as elevated trough concentrations (C_{trough}) were observed in a significant proportion of patients. For this reason, clinicians contacted SwissPedDose and requested an evaluation of extended dosing intervals such as 36 hours and 48 hours to mitigate the risk of elevated C_{trough} values associated with potential nephro-/ototoxicity, with a defined safety threshold as C_{trough} <5 mg/l [6, 16].

Challenges addressed by pharmacometric in silico studies

To the best of our knowledge, a dosing approach based on post-menstrual age and post-natal age has not been formally evaluated for amikacin regarding the suitability to achieve commonly used exposure targets [13, 17, 18], including safety targets associated with low risks of oto-/nephrotoxicity [17]. Although post-menstrual age and post-natal age have been shown to influence amikacin clearance in various population pharmacokinetic analyses, none of the reported models provides a description of clearance based on the combination of post-menstrual age *and* post-natal age [18, 19]. This is in line with characterisations of kidney function maturation that determines amikacin clearance: although post-menstrual age and post-natal age are important determinates of post-natal kidney function compared to other demographic factors, they have not been used in combination to describe the maturation

of renal amikacin clearance in preterm neonates [20–23]. Pharmacometric *in silico* studies can systematically predict pharmacological expectations of amikacin clearance as a function of birth weight and post-natal age to clinical exposure expectations. They can be performed (figure 1) leveraging a suitable model combined with a large representative neonatal demographic dataset (regarding the distribution of and correlation between weight, birth weight, post-natal age, and post-menstrual age). Various dosing approaches, including extended dose intervals, can be simulated, and the percentage of neonatal patients achieving the clinical target of interest derived for each subpopulation of interest. Model-informed drug development (MIDD) has become a standard approach in the pharmaceutical and biotech industries and is expected by health authorities such as the Food and Drug Administration (FDA) and European Medicines Agency (EMA), particularly in the context of development, approval, and utilisation of new medicines in paediatrics [24, 25]. In addition, applying a "model-informed dosing" approach to support efforts to optimise and standardise drug dosing in clinical paediatric practice has gained interest in other countries [26]. The pharmacometric approach used to support the Swiss neonatal dose standardisation of amikacin, our motivational case example, will be described in more detail in the following sections, which may serve as a proof-of-concept for further cases.

Methods

We applied pharmacometric approaches to assess overall expected exposure target achievement (percentage of neonates with C_{trough} <5 mg/l) under the initially proposed recommended dosage and to evaluate extended dosing intervals (36 hours and 48 hours instead of 24 hours) to quantify the improvement in target achievement in the neonatal subpopulation of concern.

As this was a virtual experiment, there was no clinical trial registration, and the study was deemed exempt from ethics approval.

Neonatal real-world dataset

Demographic covariate data were taken from the Antibiotic Resistance and Prescribing in European Children

Table 1:

Neonatal subpopulations (Pop$_{sub}$), dosing approach (according to initial SwissPedDose recommendations), and real-life demographic data from n = 1563 neonates receiving antibiotics (primary analysis population). n: number of neonates per subpopulation available (primary analysis population, including those with complete demographic data with respect to birthweight and postmenstrual age). Demographic data are given as median [interquartile range].

Pop$_{sub}$	Post-menstrual age (weeks)	Post-natal age (days)	Dosing approach	n	Weight (kg)	Post-natal age (days)	Birthweight (kg)	Post-menstrual age (weeks)
1	<30	<14	15 mg/kg every 48 hours	188	0.94 [0.74, 1.14]	4 [2, 7]	0.98 [0.75, 1.17]	27.9 [26.1, 29.1]
2	<30	≥14	15 mg/kg every 24 hours	70	0.84 [0.71, 1.01]	19 [16, 24]	0.74 [0.64, 0.92]	28.1 [26.8, 29.1]
3*	30–35	<14	15 mg/kg every 24 hours*	309	1.61 [1.34, 1.99]	4 [2, 7]	1.66 [1.38, 2.01]	32.4 [31.3, 33.4]
4	30–35	≥14	15 mg/kg every 24 hours	96	1.29 [1.06, 1.53]	20 [16, 23]	1.15 [0.95, 1.41]	31.9 [30.7, 33.4]
5	35–44	<14	15 mg/kg every 24 hours	705	3.03 [2.64, 3.53]	4 [2, 8]	3.04 [2.62, 3.54]	39.3 [37.4, 40.6]
6	35–44	≥14	15(–20**) mg/kg every 24 hours	195	2.88 [2.24, 3.51]	19 [15, 22]	2.72 [2.20, 3.31]	40.1 [38.0, 41.7]

* The suitability of alternative dosing intervals of 36 hours and 48 hours h was investigated by using *in silico* trials.

** Only the dose of 15 mg/kg every 24 hours was evaluated in the present simulations.

(ARPEC) point prevalence study [27, 28], an anonymous population of paediatric and neonatal in-patients treated with antibiotics at 8 A.M. in a one-day cross-sectional international web-based survey. For this study, only neonates with post-natal age <28 days and weight <5 kg (to exclude potential erroneous outliers) were included. Post-menstrual age (weeks) was calculated as gestational age (weeks) + post-natal age (days) / 7. The total selected neonatal population was stratified into six subpopulations according to post-menstrual age (<30 weeks, 30–35 weeks, 35–44 weeks) and post-natal age (0–14 days, and ≥14 days), in line with current dosage recommendation of SwissPed-Dose (table 1). A total of 500 individuals were randomly sampled with replacement from each neonatal subpopulation.

The primary pharmacometric analysis included only patients with complete information for relevant covariates (post-natal age, gestational age, weight, and birth weight). Sensitivity analyses were performed including all patients after imputation of missing covariates (birth weight, gestational age) as described below.

Pharmacometric model

An extensive externally evaluated and updated two-compartmental pharmacokinetic model [16] describing amikacin pharmacokinetics in neonates was used in which typical pharmacokinetic parameters were set as a function of demographic covariates: typical clearance (CL_{typ}) as a function of birth weight and post-natal age, and the typical central and peripheral volumes of the distribution ($V1_{typ}$, $V2_{typ}$) as a function of weight. The model also accounted

for clearance decreasing during whole-body cooling (therapeutic hypothermia [TH], binary with 1 = yes, 0 = no) and ibuprofen (IBU, binary with 1 = yes, 0 = no) treatment [16]:

CL_{typ} [l/h] = CL_{pop} [l/h] × (birthweight [kg]/1.75 kg)$^{1.34}$ × (1 + 0.22 post-natal age [days]/2 days) × 0.838^{IBU} × 0.594^{TH}, with CL_{pop} = 0.0495 l/h

$V1_{typ}$ [l] = $V1_{pop}$ [l] × (weight [kg]/1.75 kg)$^{0.93}$ = $V2_{typ}$, with $V1_{pop}$ = 0.832 l

Inter-compartmental clearance (Q_{typ}) was defined as proportional to CL_{typ} (Q_{typ} = 0.45 × CL_{typ}). The model further described the effects of ibuprofen and therapeutic hypothermia on amikacin clearance (associated with 16% and 41% decreases in clearance, respectively). These treatment-associated variables were not used in the primary analysis, as it was assumed that the population of interest generally does *not* receive ibuprofen or therapeutic hypothermia (i.e., IBU = 0 and TH = 0). The remaining random inter-individual variability (between-subject variability) was 0.32 (standard deviation on a log-scale) in clearance, and not quantified for other pharmacokinetic parameters.

Demographic characteristics of the neonatal populations on which the model was developed and externally evaluated are summarised in table S1 in the appendix. Briefly, an initial model [29] was developed using a total of 874 neonates [30, 31] and externally evaluated on a total of 239 neonates [32, 33]. The respective model parameter estimates were similar when re-estimated from another population of 573 neonates [34]. The structure of the initial model [29] was further refined by the inclusion of addi-

Figure 1: Implementation of pharmacometric *in silico* studies in neonatal dose standardisation. The general prerequisites for pharmacometric guided dose evaluation are (1) the availability of at least one suitable pharmacometric model for the population of interest (e.g., a population pharmacokinetic or pharmacokinetic/pharmacodynamic model), (2) the possibility of defining a representative patient population with relevant covariate information (i.e., for the pharmacometric model employed, and considered for different dosing approaches), and (3) the definition of a quantitative target or reference outcome (e.g., therapeutic area-under the curve [AUC], trough concentration [C_{trough}], peak concentration [C_{max}], or general adult reference exposure). The illustrated example represents dose-exposure simulations (as shown for the motivational example of amikacin), but these may be extended to dose-exposure-response simulations in the case of available pharmacodynamic models. Proposed *in silico* studies are not meant to be unidirectional, but are ideally part of a "learn, confirm, and update" cycle and should be weighted by expert opinion. PNA: post-natal age; GA: gestational age; CL: clearance.
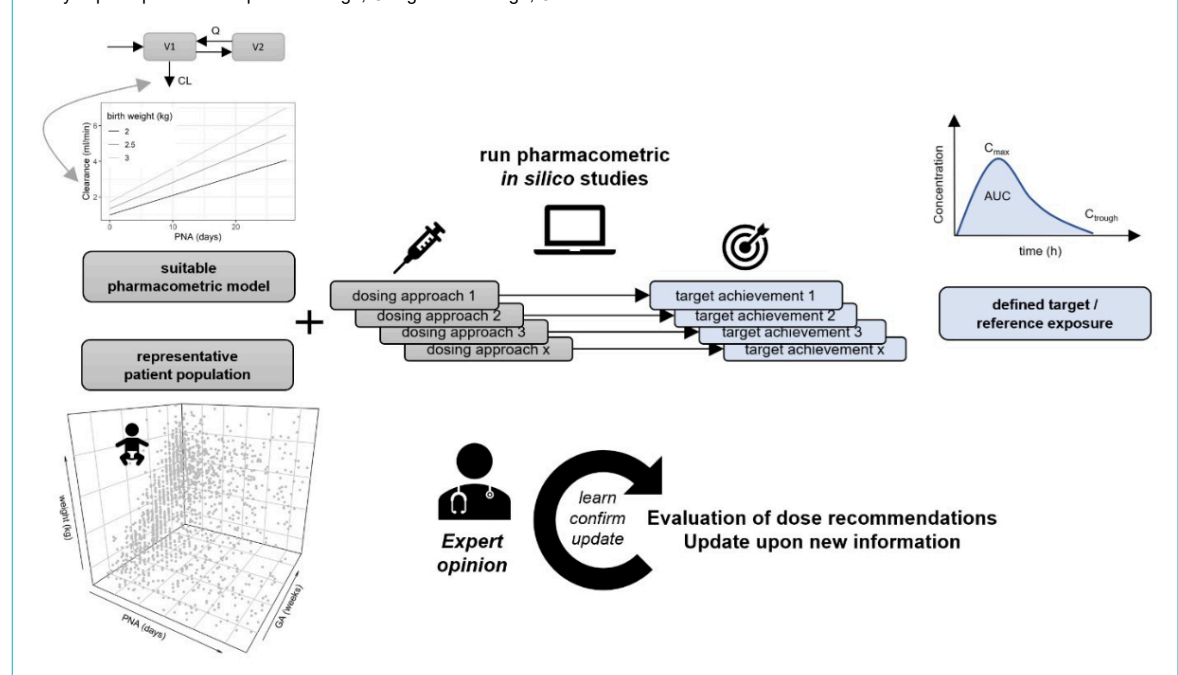
tional therapeutic drug monitoring data of 56 neonates (the model applied herein), which allowed consideration of the effect of therapeutic hypothermia on amikacin clearance [16], again yielding almost identical model parameter estimates as previously reported [29].

Pharmacometric in silico studies: dose-exposure simulations

Individual concentration-time profiles were generated by Monte Carlo simulations, given the covariates and random inter-individual variability in amikacin clearance. The individual predicted C_{trough} before the third dose was then extracted (the usual sampling time in clinical practice), and the percentage (%) of neonates with C_{trough} <5 mg/l was calculated for each of the six subpopulations (the goal being at least 80% with a desirable C_{trough} in all neonatal subpopulations).

Individually predicted C_{trough} values were plotted against patient demographics to evaluate their potential correlation with elevated C_{trough} >5 mg/l.

Initially proposed standardised dosing approach

A total of 500 neonates were simulated for each of the six neonatal populations to calculate the percentage of neonates with C_{trough} before the third dose with the initially proposed approach.

Evaluation of alternative dosing intervals

Two additional simulations were performed for the subpopulation of clinical concern to calculate the percentage of neonates with C_{trough} before the third dose with alternative dosing intervals of 36 h or 48 h.

Sensitivity analyses

The following sensitivity analyses were performed: (a) pharmacometric simulations using a dataset with missing covariates of birth weight and gestational age imputed and obtained by three methods: (a1) linear regression, and multiple imputation by (a2) predictive mean matching or (a3) random forest (supplemental methods in the appendix); (b) pharmacometric simulations, including residual intra-individual variability; (c) simulations adding hypothetical inter-individual variability in the distribution (standard deviation = 0.1 for log-transformed parameters) and a small

correlation of 0.3 between individual random effects of the distribution and clearance; (d) pharmacometric simulations for the same population treated with therapeutic hypothermia (TH = 1) to decrease the neurological sequelae of perinatal asphyxia; (e) simulations for the same population receiving ibuprofen (IBU = 1) treatment for a patent ductus arteriosus.

Software packages

In silico studies were performed using the software Simulx (Version 2021R2, Lixoft SAS, a Simulations Plus company). Data preparation and further statistical computing or figure creation were performed in R (version 4.2.1, R Foundation for Statistical Computing, https://www.R-project.org/).

Results

Neonatal real-world dataset

From the available demographic ARPEC database (comprising 3844 patients), 2590 neonates were eligible (postnatal age <28 days, post-menstrual age <44 weeks, weight <5 kg); among these, 1563 had complete demographic data with respect to gestational age/post-menstrual age and birth weight and were included in the primary analysis (table 1 and figure 2; overall median [IQR] post-natal age: 6 [3–13 days], weight: 2.3 [1.39, 3.15] kg). In most other patients with missing covariates (n = 1027, median [IQR] post-natal age: 8 [4–16], weight: 2.80 [1.80–3.40] kg), both gestational age and birth weight were missing (n = 918).

Pharmacometric model

Simulated individual pharmacokinetic parameters for each subgroup are depicted in figure S3 in the appendix. The corresponding simulated mean half-lives were 6.6 h and 5.3 h in subpopulations 1 and 3, respectively, and 2.2–3.7 h in the other subpopulations (initial exponential decline), suggesting that C_{trough} sampling before the third dose likely corresponds to a steady-state measurement in the plasma.

Figure 2: Illustration of real-life patient population demographic data used as a basis for simulations: birth weight versus postnatal age (PNA) as clearance-relevant covariates depicted by postmenstrual age (PMA) according to the SwissPedDose recommendations. Post-natal age values are slightly jittered for easier visual assessment. *Black dots*: complete data. *Grey dots*: imputed data with respect to post-menstrual age and birth weight (method a1).
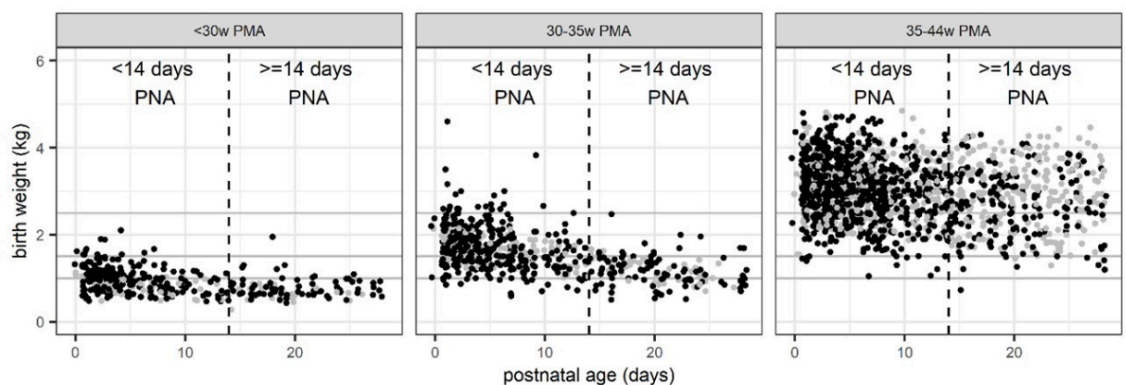
Pharmacometric dose-exposure simulations

The distribution of predicted amikacin exposure under the initially agreed harmonised dosing approach is shown in figure 3. The corresponding predicted distribution of C_{trough} before the third dose is shown in figure 4 and table 2.

Initially agreed harmonised dosing approach

The simulated proportion of neonates with C_{trough} <5 mg/l before the third dose was 59% (95%CI: 55–64%) in the subpopulation of clinical concern, and 79% (75–82%) to 99% (98–100%) in the other subpopulations. The correlations between elevated C_{trough} and patient demographics in the subpopulation of clinical concern are depicted in figure 5.

Evaluation of alternative dosing intervals

When extending the dosing interval in the subpopulation of clinical concern from 24 h to 36 h or 48 h, the simulated percentages of neonates with a desirable C_{trough} increased to 89% (86–91%) and 97% (95–98%), respectively.

Sensitivity analyses

The proportion of patients with predicted individual C_{trough} values <5 mg/l before the third dose are summarised in table S2 (a–c, see appendix) and table 2 (d–e). Briefly, predicted proportions from sensitivity analyses a, b, and c were similar to those of the primary analysis. In sensitivity analysis d (therapeutic hypothermia), all proportions of target achievement were lower, with only the subpop-

Figure 3: Illustration of a simulated amikacin concentration-time profile distribution for each of the six subpopulations of the primary analysis (where complete covariate data were available), following two administrations of the dose according to the initial national SwissPedDose recommendations. Shaded areas delimit the 50% prediction interval (percentile 25–75, *dark grey*) and 90% prediction interval (percentile 5–95, *light grey*). *Orange line*: C_{trough} target of <5 mg/l. PMA: post-menstrual age; PNA: post-natal age.
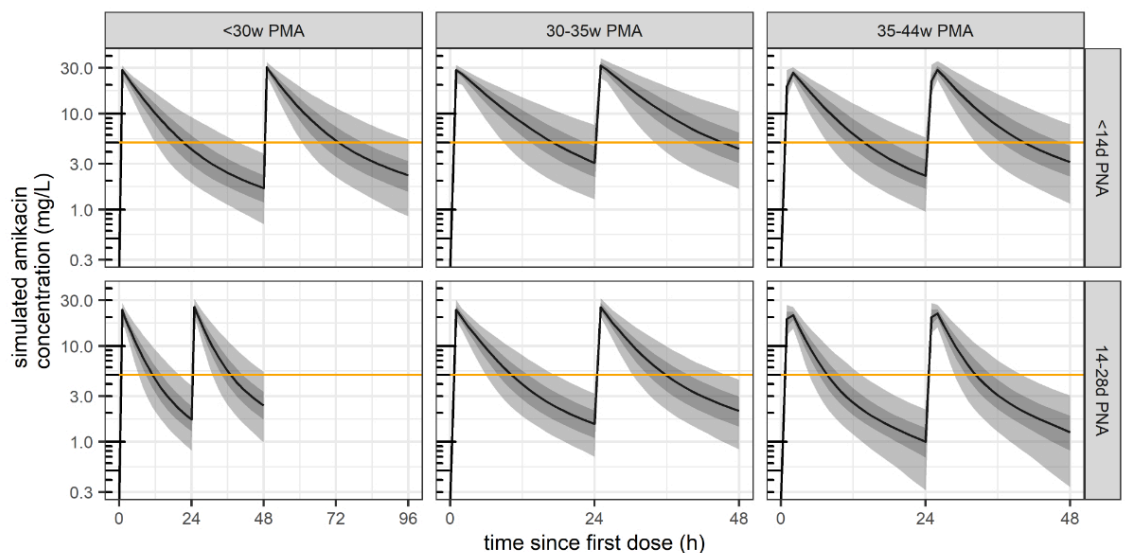

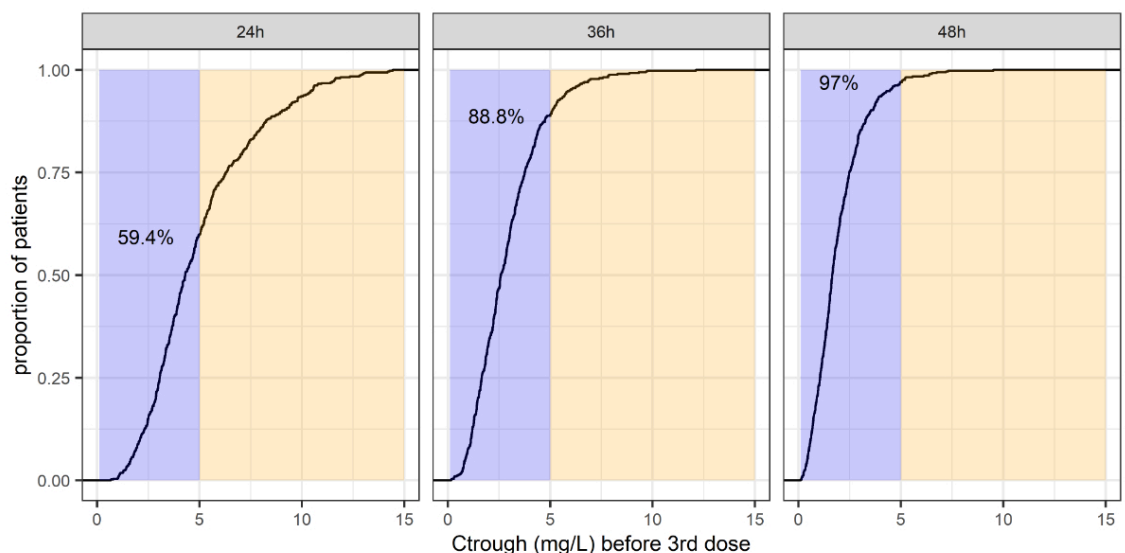**Figure 4:** Summary of the C_{trough} distribution before the third dose, and the predicted proportion of patients with C_{trough} <5 mg/l (i.e., the *violet* shaded area, with the proportions summarised by numbers).

ulation of late preterm or term neonates outside the newborn period (post-menstrual age 35–44 weeks, post-natal age ≥14 days) achieving C_{trough} <5 mg/l in at least 80% of neonates (89.9% versus 15.6–59.8% in the other subpopulations under the initially proposed dosing regimen). In sensitivity analysis e (ibuprofen treatment), all proportions of target achievement were lower, but most subpopulations still achieved C_{trough} <5 mg/l in at least 80% of neonates.

Discussion

We applied pharmacometric *in silico* approaches in the context of a national dose standardisation process in neonatology to illustrate their utility and prerequisites. For our motivational example of amikacin, all three prerequisites for performing a pharmacometric simulation study were met (figure 1). First, a suitable, externally evaluated population pharmacokinetic model was available for the drug and population of interest [16]. Second, representative demographic patient population data could be taken from a large real-world data set for neonates treated with antibiotics [27]. Third, the clinical target exposure of interest was quantitatively defined (C_{trough} <5 mg/l), as was the outcome of interest (percentage of neonatal patients achieving the target: ≥80%).

In our case, this approach confirmed the clinically observed risk of amikacin accumulation with elevated C_{trough} (>5 mg/l prior to the third dose) in a neonatal subpopulation of clinical concern (preterm neonates with post-menstrual age 30–35 weeks, post-natal age 0–14 days) following the introduction of a new nationally standardised dose

recommendation (i.e., a 24 h-interval with a dosage of 15 mg/kg). Simulations provided a scientific, quantitative rationale indicating that extension of the dosing interval to 36 h would be sufficient for similar target achievement as in the other neonatal subpopulations for whom no safety concerns were raised. An extended dosing interval had already been discussed for a subgroup of preterm neonates during the SwissPedDose standardisation process but was finally set to 24 hours for practical reasons. To simplify dosing across different subpopulations and to guarantee sufficient peak plasma concentration (C_{max}), which is considered relevant for aminoglycoside efficacy [16], a reduction of the dose was not discussed. Figure 3 demonstrates that simulated C_{max} remained nearly constant despite the prolongation of the dosing interval. The results presented herein show that performing such pharmacometric simulations can facilitate scientific discussions by formulating and providing model-based pharmacological predictions. This can help to better define optimal dosing recommendations among clinical experts, in particular where study data are sparse or missing or when discussions are controversial or have not reached a consensus. Our simulations suggest that elevated C_{trough} values were indeed highly associated with post-natal age <7 days (<50% achieving C_{trough} <5 mg/l versus >80% for 7–14 days, figure 5) facilitating dose standardisation towards this cutoff, in line with the approach chosen for several other renally eliminated anti-infectives such as gentamicin and beta-lactam antibiotics [6].
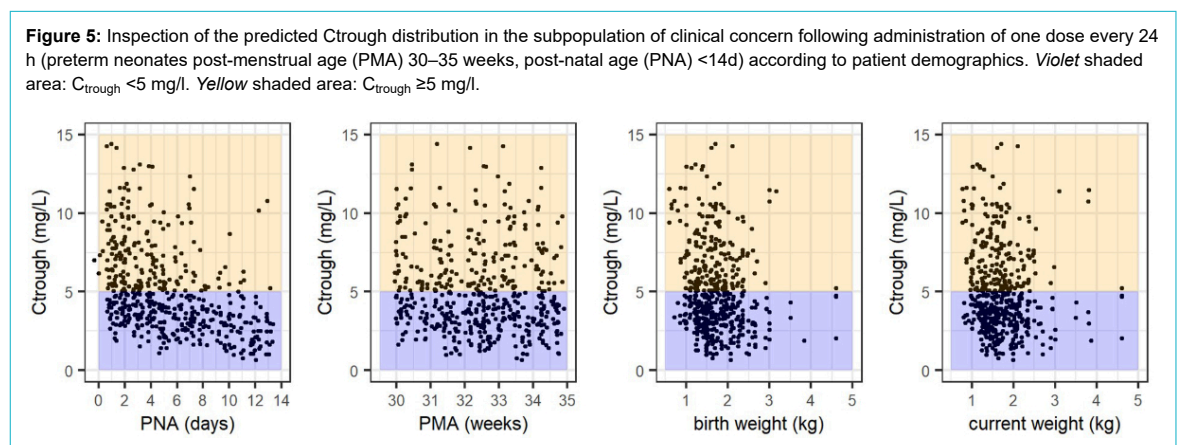
Table 2:
Predicted percentages with trough <5 mg/l before the third dose (primary and sensitivity analyses d and e*).

Pop$_{sub}$	Post-menstrual age (weeks)	Post-natal age (days)	Dosing approach	Primary analysis (complete data set)	Sensitivity analysis d (therapeutic hypothermia)	Sensitivity analysis e (ibuprofen)
1	<30	<14	15 mg/kg every 48 h	93.4	56	84
2	<30	≥14	15 mg/kg every 24 h	92.6	41	83
3**	30–35	<14	15 mg/kg every 24 h**	59.4	15	45
			15 mg/kg every 36 h	88.8	46	79
			15 mg/kg every 48 h	97.0	74	93
4	30–35	≥14	15 mg/kg every 24 h	98.6	62	89
5	35–44	<14	15 mg/kg every 24 h	79.0	30	66
6	35–44	≥14	15 mg/kg every 24 h	99.4	88	98

Pop$_{sub}$: Neonatal subpopulation according to the SwissPedDose dose recommendations.

* sensitivity analyses a, b, and c provided similar results as the primary analysis and are shown in the supplementary data in the appendix.

** Neonatal subpopulation of clinical concern, for which alternative dosing intervals of 36 hours and 48 h were evaluated

Figure 5: Inspection of the predicted Ctrough distribution in the subpopulation of clinical concern following administration of one dose every 24 h (preterm neonates post-menstrual age (PMA) 30–35 weeks, post-natal age (PNA) <14d) according to patient demographics. *Violet* shaded area: C_{trough} <5 mg/l. *Yellow* shaded area: C_{trough} ≥5 mg/l.

As a result of developmental and maturational processes, neonatal dosing is a complex process. On one hand, optimised dosing approaches in neonatology should consider not only safety and efficacy aspects but also quickly developing physiology and pharmacokinetics. On the other hand, it is crucial that dosing be practical and simple to mitigate the risk of medication errors in this vulnerable patient population [35–37]. In the development of new medicines, similar pharmacometric simulation approaches are regularly applied to translate initial complex approaches to dosing (e.g., based on body surface area) into simpler and more practical (e.g., stratified fixed dose) recommendations [7, 38, 39]. As our understanding of neonatal pharmacology is constantly increasing for many anti-infective drugs [40–43], it is time to bring such quantitative pharmacological knowledge into clinical practice, particularly in the context of national dose standardisation initiatives such as SwissPedDose.

Neonatal real-world dataset

Especially in the neonatal population, generating a virtual patient population with a representative multidimensional covariate distribution may be a challenge. Whereas the general neonatal population would show a uniform post-natal age distribution that can easily be simulated, our real-live demographic data show that post-natal age distribution in neonates treated with antibiotics is skewed to the left (i.e., an over-representation of neonates with post-natal age <7 days). Given the rapid improvement in kidney function and renal drug clearance with post-natal age, the predicted percentage of patients with amikacin C_{trough} <5 mg/l (the defined safety target) would increase if more neonates with older post-natal age were included. Utilizing a large real-world demographic dataset of a representative population has the advantage of fewer assumptions concerning a complex covariate distribution and correlations but may require the handling of missing demographic data [44]. In our case, neonates with missing information on birth weight and gestational age most likely represented neonates that were treated on a general paediatric ward (older gestational age and post-natal age, higher body weight as compared to "complete-information" neonates). Optimal dosing approaches may hence differ between neonates treated on general paediatric versus neonatal wards as well as in patients receiving additional potentially nephrotoxic drugs or therapeutic hypothermia (sensitivity analyses d–e).

In our simulations, we assumed that the covariates did not change over time. Our simulations may hence be considered conservative, as renal clearance improves with each day of life and increasing weight in neonates. A combination with neonatal weight-prediction models [45] could be of interest in other studies regarding questions as to when to adapt the dosing strategy in an individual patient.

Pharmacometric model

A suitable pharmacometric model may not be available for all dosing questions, or several candidate models may be available and compared regarding their predictions [46]. In cases where no suitable model is available for the drug and population of interest, physiology-based pharmacokinetic models may be considered to formulate semi-quantitative exposure comparisons for different neonatal or paediatric

subgroups, which then may be updated quantitatively upon the availability of actual pharmacokinetic data by population pharmacokinetic modelling [8]. Ideally, not only dose-exposure but also exposure-outcome simulations can be performed, such as for clinical cure, bacterial killing, and resistance development [47]. Pharmacodynamic studies in neonates, however, remain scarce due to practical and ethical difficulties [8].

In our case, we did not compare simulations from other models [18, 19], but the model we used represents by far the most extensively evaluated neonatal model, having additionally demonstrated favourable predictive performance regarding post-natal renal function maturation [20]. A large number of trough and peak amikacin concentration measurements were used to develop the model, suggesting its suitability for C_{trough} prediction.

Pharmacometric *in silico* studies

In general, many different exposure questions can be addressed, but clinical limitations with respect to formulated targets need to be kept in mind for final dosing decisions, as illustrated in figure 1 by expert opinion relevance (e.g., in our case uncertainty concerning the actual risk of oto-/nephrotoxicity associated with short-term high C_{trough}, an optimal C_{trough} cutoff to define "elevated" C_{trough} values under varying dosing intervals, and duration of post-antibiotic effect [48–50]). Simulations may be easily adjusted and updated if new evidence emerges regarding exposure targets, such as increasing minimal inhibitory concentration (MIC), as has been observed for gentamicin [12, 51]. Improved infrastructures allowing the collection and use of real-world data for scientific purposes [52] will further facilitate the development and evaluation of such model-informed dosing approaches and their implementation in a learn-and-confirm cycle (figure 1).

In our case, simulations may also be used to evaluate amikacin C_{max}, a key parameter related to aminoglycoside efficacy [16]; C_{max} >20 mg/l was achieved in the majority of patients (minimum efficacy target used in other studies [40]). As no random inter-individual variability was incorporated in the model applied, a factor that might be expected, this outcome may require a more cautious interpretation. Interestingly, however, the proportion of patients achieving C_{max} >20 mg/l was least in the "oldest" subpopulation (i.e., post-menstrual age 35–44 weeks, post-natal age 14–28 days) treated with single doses of 15 mg/mg, supporting the use of single doses up to 20 mg/kg in this subpopulation (table 1). Antibiotic coverage for efficacy (normally with a target ratio of C_{max} / minimal inhibitory concentration >8–10) may be more important in the first days of treatment compared to the risk of short-term drug accumulation [53].

Conclusion

In conclusion, pharmacometric *in silico* studies based on high-quality real-world demographic datasets can provide a quantitative scientific rationale and rating for dose optimisation and facilitate national dose standardisation, particularly in neonatology. In the present motivational example, this approach allowed us to translate pharmacological expectations for amikacin based on birth weight and post-

natal age to exposure predictions stratified by post-natal age and post-menstrual age for various dosing intervals. Further, computer simulations indicated that a post-natal age stratification ≤7 or >7 days may be considered in the future, in line with dosing recommendations for other renally eliminated anti-infective drugs employed in neonatology. Implementation of pharmacometrics into the decision-making process of neonatal dose standardisation should not be unidirectional, but rather part of a continuous learn-and-confirm process combining scientific evidence, clinical experience, and expert opinion (figure 1). In addition to facilitating the standardisation of existing neonatal dose recommendations, such an iterative approach will increase clinical acceptance of fine-tuned dose recommendations and support their implementation.

Data availability statement

All demographic and simulated data are presented in the manuscript/supplemental material. Further inquiries can be directed to the corresponding authors.

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Appendix

Supplemental methods

Sensitivity analysis a

As the proportion of missing covariate values was high with 36% for birthweight (bwt) and 39% for gestational age (GA) and hence postmenstrual age (PMA), three different imputation strategies were realized to obtain a for missing covariates imputed dataset for pharmacometric simulations in sensitivity analysis a:

(a1) linear regression

(a2) multiple imputation using predictive mean matching (PMM)

(a3) multiple imputation using random forest (RF)

(a1) A linear regression function based on cwt and PNA was developed on the complete dataset, and used to impute missing covariates bwt and GA as follows:

bwt = 0.147 + cwt · 0.697 - 0.011 · PNA

GA = 28.6 + log(cwt) · 8.57 - 0.0469 · PNA

In two neonates with resulting predicted PMA of 44 weeks (44.2 and 44.6 weeks, respectively), this was rounded down to <44 weeks (43.9 weeks) to keep the same number of patients. Observed and predicted relationships are illustrated in Supplemental Figure 1 and 2.

(a2 and a3) Predictive Mean Matching (PMM) and Random Forest (RF) imputation were each used as described before (Bräm DS, Nahum U, Aktinson A, et al. 2022) to generate 20 imputed data sets. The completed data sets were analyzed separately and the mean and standard deviation were calculated from the results.
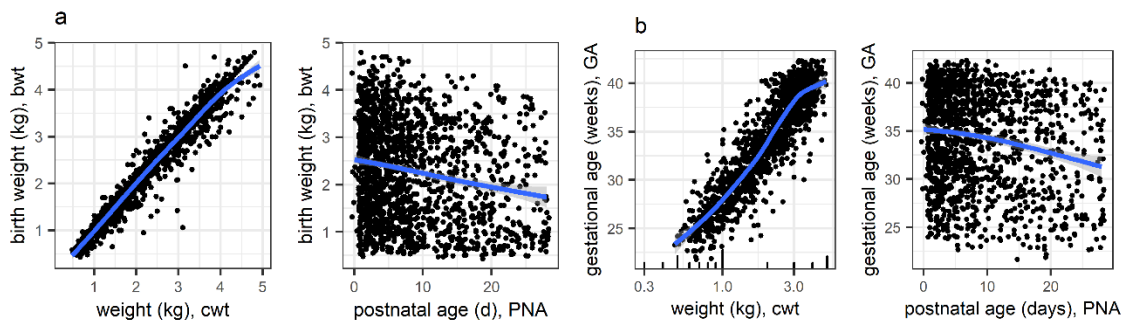
Supplemental figures

Figure S1: Illustration of observed covariate relationships with (a) birth weight and (b) gestational age in the complete data, used to develop regression models for imputation of missing birth weight and gestational age. *Lines*: non-parametric regression lines (loess). In figures illustrating gestational age (GA) and/or post-natal age (PNA), data points are jittered for easier visual assessment of data density.
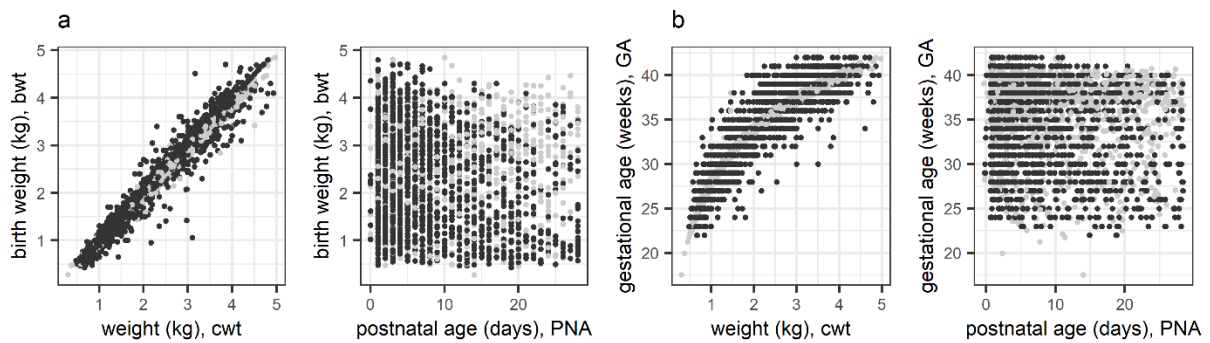

Figure S2: Illustration of observed covariate relationships with (a) birth weight and (b) gestational age in the complete data (black dots) and imputed data (grey dots). In figures b illustrating gestational age (GA) versus postnatal age (PNA), data points are jittered for easier visual assessment.
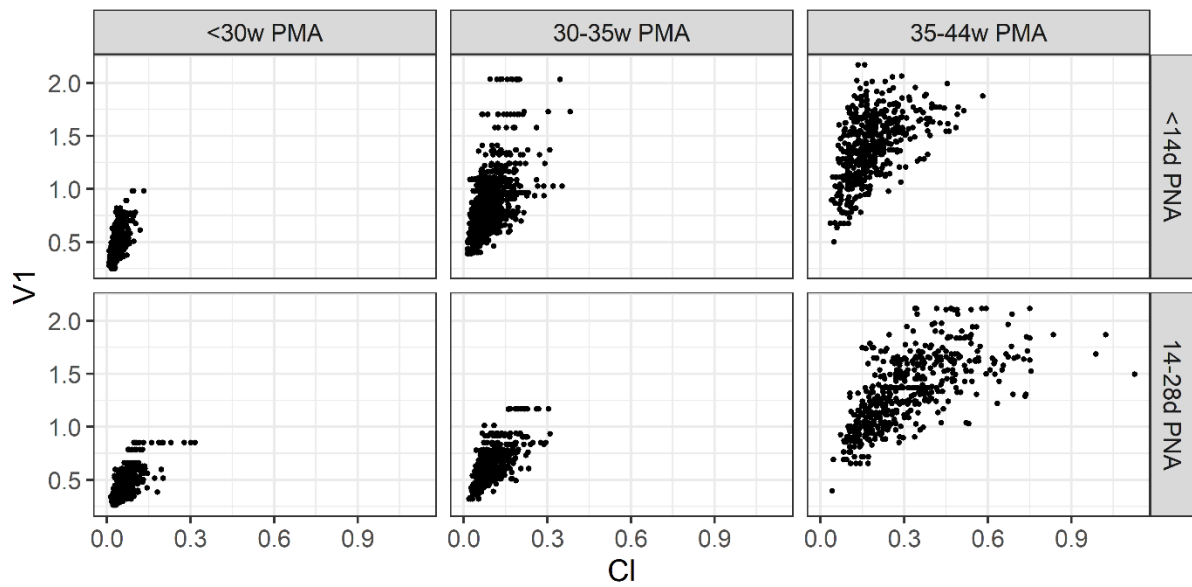
Figure S3: Simulated individual amikacin pharmacokinetic parameters (individual clearance, Cl, and individual central volume of distribution, V1). PMA: postmenstrual age. PNA: postnatal age.

Supplemental tables

Table S1: Patient characteristics of neonatal populations on which the applied amikacin population pharmacokinetic model was developed, evaluated and refined.

Reference	n	GA (weeks)	Birthweight (kg)	PNA (days)	Weight at PNA (kg)
Allegaert 2006[1]	162	28 [24–30]	1.052 [0.475–1.910]	2 (1-3)	1.052 [0.475–1.910]
Allgaert 2008[2]	721	33 [24–43]	1.990 [0.385–4.650]	2 [1–30]	1.990 [0.385–4.780]
Sherwin 2009[3]	80	26 [24–41]	0.880 [0.440–4.430]	16 [3–30]	1.060 [0.450–4.430]
Schreuder 2009[4]	159	31 [25–42]	1.740 [0.526–5.420]	1 [1–3]	1.665 [0.526–5.420]
Smits 2015[5]	579	34 [24-41]	2.28 [0.42-4.85]	2 [1-30)]	2.1 [0.42-5.04]
Cristea 2017[6]	56*	38 [35-41)]	3.18 [1.91-4.77]	2 [1-4]	3.18 [1.91-4.77]

*combined in the analysis with population from references[1, 2]. GA: gestational age. PNA: postnatal age.

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Table S2: Predicted percentage with trough < 5 mg/L before the 3rd dose from sensitivity analysis a 1-3 (imputation of missing covariate data)

Pop$_{sub}$	PMA (weeks)	PNA (days)	Dosing approach	Sensitivity analysis a1 (imputed dataset, linear regression)	Sensitivity analysis a2 (imputed dataset, PMM) Mean (sd)	Sensitivity analysis a3 (imputed dataset, RF) Mean (sd)	Sensitivity analysis b (complete dataset, with residual error)	Sensitivity analysis c (complete dataset, with BSV of 10% in Volume)
1	<30	<14	15 mg/kg every 48h	98.8	93.5 (0.9)	93.7 (0.9)	91.2	93.2
2	<30	≥14	15 mg/kg every 24h	96.8	92.1 (1.0)	92.0 (0.6)	90.2	93.2
3**	30-35	<14	15 mg/kg every 24h**	57.3	59.9 (1.7)	58.6 (1.9)	61.4	60.0
			15 mg/kg every 36h	89.0	89.9 (1.2)	89.3 (1.0)	88.4	89.8
			15 mg/kg every 48h	98.6	97.5 (0.7)	97.3 (0.6)	96.8	97.4
4	30-35	≥14	15 mg/kg every 24h	97.2	97.0 (0.7)	96.8 (0.8)	95.2	98.6
5	35-44	<14	15 mg/kg every 24h	79.6	77.5 (1.2)	79.4 (1.8)	77.6	79.2
6	35-44	≥14	15 mg/kg every 24h	100	99.5 (0.3)	99.8 (0.2)	99.4	99.8

PMM: predictive mean matching. RF: random forest. sd: standard deviation calculated from simulations with each 20 imputed datasets. Pop$_{sub}$: neonatal subpopulation according to current SwissPedDose dosing approach. PMA: postmenstrual age. PNA: postnatal age

Simulation code

- simulx project file name = project010.smlx
- pharmacokinetic model file name = model.txt
- covariate file names = pop1_xxx.csv to pop6_xxx.csv

simulx project

```
<MODEL>
file = '../model.txt'

<SIMULX>

[SETTINGS]
GLOBAL:
exportpath='project010'

[DEFINITION]
POPULATION:
parameters={Clpop, V1pop, sdCl, sdV1, corr_Cl_V1, thBW, thCW, thPNA}
'PopParameters' = {{{values={0.0495, 0.832, 0.32, 0.0001, 0.0001, 1.34, 0.926, 0.22}}}}

OUTPUT:
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'regularCc_72h' = {output=Cc, {{start=0, interval=1, final=72}}}
'regularCc_96h' = {output=Cc, {{start=0, interval=1, final=96}}}
'Cmin_ipred_24h48h' = {output=Cc, {{times={24, 48}}}}
'Cmin_ipred_36h72h' = {output=Cc, {{times={36, 72}}}}
'Cmin_ipred_48h96h' = {output=Cc, {{times={48, 96}}}}

INDIVIDUAL:
parameters={Cl, V1}
'indivManual1' = {{{values={0.05, 0.8}}}}
'indivmanual' = {{{values={0.05, 0.83}}}}

COVARIATE:
continuousCovariates={bwt, cwt, PNA, PMA, GA}
'Covariates' = {{{values={1, 1, 1, 1, 1}}}}
'pop1' = {file='../Data/Arpec/covdat_complete/pop1_20221026.csv'}
'pop2' = {file='../Data/Arpec/covdat_complete/pop2_20221026.csv'}
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'pop6' = {file='../Data/Arpec/covdat_complete/pop6_20221026.csv'}

TREATMENT:
'15mgkg_24h' = {{{start=0, interval=24, nbDoses=2, amount=15, duration=0.5}}, adm=1, scale={duration, covariate=bwt, intercept=0}}
'15mgkg_36h' = {{{start=0, interval=36, nbDoses=2, amount=15, duration=0.5}}, adm=1, scale={duration, covariate=bwt, intercept=0}}
'15mgkg_48h' = {{{start=0, interval=48, nbDoses=2, amount=15, duration=0.5}}, adm=1, scale={duration, covariate=bwt, intercept=0}}

[SIMULATION]
GROUPS:
```

'tau48_pop1'={size=500, parameter='PopParameters', remaining={}, covariate='pop1', outputs={'regularCc_96h', 'Cmin_ipred_48h96h'}, treatment={'15mgkg_48h'}}
'tau24_pop2'={size=500, parameter='PopParameters', remaining={}, covariate='pop2', outputs={'regularCc_48h', 'Cmin_ipred_24h48h'}, treatment={'15mgkg_24h'}}
'tau36_pop3'={size=500, parameter='PopParameters', remaining={}, covariate='pop3', outputs={'regularCc_72h', 'Cmin_ipred_36h72h'}, treatment={'15mgkg_36h'}}
'tau24_pop3'={size=500, parameter='PopParameters', remaining={}, covariate='pop3', outputs={'regularCc_48h', 'Cmin_ipred_24h48h'}, treatment={'15mgkg_24h'}}
'tau48_pop3'={size=500, parameter='PopParameters', remaining={}, covariate='pop3', outputs={'regularCc_96h', 'Cmin_ipred_48h96h'}, treatment={'15mgkg_48h'}}
'tau24_pop4'={size=500, parameter='PopParameters', remaining={}, covariate='pop4', outputs={'regularCc_48h', 'Cmin_ipred_24h48h'}, treatment={'15mgkg_24h'}}
'tau24_pop5'={size=500, parameter='PopParameters', remaining={}, covariate='pop5', outputs={'regularCc_48h', 'Cmin_ipred_24h48h'}, treatment={'15mgkg_24h'}}
'tau24_pop6'={size=500, parameter='PopParameters', remaining={}, covariate='pop6', outputs={'regularCc_48h', 'Cmin_ipred_24h48h'}, treatment={'15mgkg_24h'}}

SETTINGS:
samplingMethod=withReplacement

[EXPLORATION]
GROUPS:
'explorationGroup1'={remaining={}, parameter='indivmanual', outputs={'regularCc_96h'}}
'explorationGroup2'={remaining={}, parameter='indivmanual', outputs={'regularCc_96h'}}
'explorationGroup3'={remaining={}, parameter='indivmanual', outputs={'regularCc_96h'}}

[ENDPOINT]
OUTCOME:
'CminLT5_before3rd_tau24h' = {outputElement='regularCc_48h', statistic=last, sample=value, threshold='value<5'}
'CminLT5_before3rd_tau36h' = {outputElement='regularCc_72h', statistic=last, sample=value, threshold='value<5'}
'CminLT5_before3rd_tau48h' = {outputElement='regularCc_96h', statistic=last, sample=value, threshold='value<5'}

OUTPUT:
referenceGroup='tau24_pop3'
decisionCriterion=false
'percentLT5_tau24h' = { outcome='CminLT5_before3rd_tau24h', function=percentTrue, criterion={type=statisticalTest, test='value!=1', pValue=0.05} }
'percentLT5_tau36h' = { outcome='CminLT5_before3rd_tau36h', function=percentTrue, criterion={type=statisticalTest, test='value!=1', pValue=0.05} }
'percentLT5_tau48h' = { outcome='CminLT5_before3rd_tau48h', function=percentTrue, criterion={type=statisticalTest, test='value!=1', pValue=0.05} }

[TASKS]
simulation()
endpoint()

pharmacokinetic model file code

[COVARIATE]
input = {bwt, cwt, PNA, PMA, GA}

[INDIVIDUAL]
input = {Clpop, V1pop, sdCl, sdV1, corr_Cl_V1, bwt, cwt, PNA, PMA, GA, thBW, thCW, thPNA}

EQUATION:
Cltyp = Clpop * (bwt/1.75)^thBW * (1+thPNA*PNA/2)
V1typ = V1pop * (cwt/1.75)^thCW

DEFINITION:
Cl = {distribution=lognormal, typical=Cltyp, sd=sdCl}
V1 = {distribution=lognormal, typical=V1typ, sd=sdV1}
correlation = {level=id, r(Cl, V1)=corr_Cl_V1}

[LONGITUDINAL]
input = {Cl, V1, b, a}

EQUATION:
Q = 0.45*Cl
V2 = V1

PK:
; Parameter transformations
V = V1
k12 = Q/V1
k21 = Q/V2
; PK model definition
Cc = pkmodel(V, Cl, k12, k21)

DEFINITION:
y = {distribution = normal, prediction = Cc, errorModel=combined2(a, b)}

OUTPUT:
output = Cc

covariate file structure – example

ID	bwt	cwt	PNA	PMA	GA
6	1.31	1.16	6	28.86	28
12	1.06	0.94	3	27.43	27
29	0.68	0.67	5	26.71	26