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Suggestions for Model Informed Precision Dosing to Optimize Neonatal Drug Therapy

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Abstract

Evidence for dosing, efficacy, and safety of most medications used to treat neonates is sparse. Thus, dosing is usually derived by extrapolation from adult and pediatric pharmacologic data with scaling by bodyweight or body surface area. This may lead to drug dosing that is unsafe or ineffective. However, new strategies are being developed and studied to dose medications in critically ill neonates. Mass spectroscopy technology capable of quickly analyzing drug levels is readily available. Software that integrates population pharmacokinetics and pharmacodynamics with data from sparse samples from neonates allows for timely adjustments of dosing to achieve the desired effect while minimizing adverse outcomes. Some genetic polymorphisms that affect drug response in neonates have also been reported. This review highlights aspects of drug response and how it is impacted by prematurity, assesses pharmacogenomic studies in neonates, and offers suggestions for innovative pharmacokinetic/pharmacodynamic model-based approaches which combine population or physiology-based pharmacology data, Bayesian analysis, and electronic decision support tools for precision dosing in neonates while illustrating examples where this approach can be used to optimize medical therapy in neonates. Barriers to implementing precision dosing in neonates and how to overcome them are also discussed.

Keywords

Neonate; Pharmacodynamics; Pharmacokinetics; Pharmacology; Precision Dosing; Population pharmacokinetics

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Conflict of Interest

Joshua C. Euteneuer, Suyog Kamatkar, Tsuyoshi Fukuda, Alexander A. Vinks, and Henry T. Akinbi declare that they have no conflict of interest.

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Introduction

Several federal agencies in the United States, including the National Institute of Health, the US Food and Drug Administration and the Office of National Coordinator for Health Information Technology have been charged with the implementation of individualized medicine in the clarion call for Precision Medicine Initiative[1,2]. In neonates, however, the task is daunting because of the lack of data despite the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA) legislation, European Medicines Agency, and International Neonatal Consortium encouraging more research into the safe and effective use of medications in children. Dynamic postnatal physiologic changes in neonates, together with an incomplete understanding of the ontogeny of important enzyme systems and pharmacogenetics/genomics that are responsible for interindividual variability in drug disposition and response are not accounted for with current dosing regimens. Dosing recommendations for most medications prescribed to neonates are not validated and do not address unique characteristics in this population. Thus, dosing schemes are either suboptimal or are fraught with avoidable adverse effects. Technological advances in bedside pharmacologic testing and electronic health systems provide an opportunity for evidence-based dosing of medications in neonates. Individualized dosing can best be achieved by integration of pharmacokinetic/pharmacodynamic (PK/PD) principles with developmental pharmacology, therapeutic drug monitoring, and model-based decision support using Bayesian adaptive control[3–6]. This strategy allows the realization for individualized dosing in order to achieve the desired drug exposure for efficacy while minimizing the risk of adverse effects.

In this review, we highlight aspects of drug response and how they are impacted by prematurity, assess pharmacogenomic studies in neonates, and provide suggestions for innovative PK/PD model-based approaches which combine population or physiology-based PK and PD data, Bayesian analysis and readily available decision support tools for precision dosing in neonates. Where relevant, we summarized some successful use of this model in neonates.

Why Neonatal Pharmacology is Unique

Pharmacology data are sparse in neonates because of the inherent difficulty in conducting conventional pharmacokinetic studies in vulnerable populations and the relatively small population of preterm infants from which to sample. Dosing of medications in neonates often relies on extrapolation from adult or older children data through scaling based on body weight or body surface area. Yet, successful application of adult or older children pharmacology data to neonates is hampered due to unique developmental physiological processes, changing body composition, and a non-linear relationship between growth and development in neonates which contribute to poor correlation between drug dosage and serum concentrations [1,7–11]. These developmental changes, and to a lesser extent, genetic variation, are important determinants of drug response. The absorption, distribution, metabolism, and elimination of medications are often quantified with PK parameters such as bioavailability, clearance, volume of distribution, and half-life. These determine PK measures such as peak and trough concentrations and area under the concentration versus

time curve. These PK parameters and measures are usually stated as a mean with a standard deviation and are used to create dosing guidelines for an average patient. However, they typically fail to account for the often large inter-individual variability in PK and PD. The neonate's dynamic physiology impacts drug disposition and response, suggesting they could benefit tremendously from precision dosing. It also implies that utilizing data from other populations, such as adults or from older children, may not be appropriate for neonates. The need for neonates-specific data is also underscored by the heterogeneous population in which the bodyweight may vary more than 10-fold, gestational age could span between 24 and 42 weeks, postnatal age ranges from 0 to 30 days, and their size is affected by *in utero* environment that could result in growth restriction or small-for-gestational age infants in contrast to appropriate- or large-for-gestational age infants with implications for drug, particularly in weight-based dosing. For example, should a 30-day old former 24-week infant weighing 1 kg be dosed the same as a 1-day old 28-week infant who also weighs 1 kg? These are important questions that are not addressed by the current dosing schemes in neonates.

Pharmacokinetic-Pharmacodynamic (PK-PD) Modeling

Neonatal pharmacology is challenged by the fact that for a given drug dose there is a range of clinical responses related to interindividual PK and PD variability resulting in limited predictability. PK variability leads to differences in drug exposure between patients for a given dose and can be related to body composition, protein binding capacity, organ function maturity, cardiac output, or ontogeny of transporters and drug metabolizing enzymes [3,12–15]. Factors contributing to PD variability, which could explain the relationship of drug exposure to drug effect, are less well understood but examples include bacterial antibiotic resistance, severity of illness, or interindividual differences in receptor binding affinity[16]. The quest then is to take into account this PK/PD variability in selecting the appropriate drug dosing regimen. PK/PD modeling attempts to describe and predict the dose-exposure-response relationship for a given drug in a given patient. While a number of modeling techniques have been developed to account for this task, two of the most commonly-used approaches are the combination of either population PK or physiology-based PK models with the PD response[17].

Introduced in the 1980s, population PK uses descriptive equations to explain the relationship between physiology and PK, the interindividual variability in these relationships, and their residual intraindividual variability[18]. Population PK studies simultaneously use data from multiple subjects in a population who have drug concentrations collected at different time points. This allows for random sparse sampling which is desirable in the Neonatal Intensive Care Unit (NICU) population and results in a robust analysis describing the PK of the drug. By applying population PK through non-linear mixed effects modeling, covariates can be identified to determine PK parameters and their variability. Covariates include factors such as age, bodyweight, biomarkers of liver or renal function, or, to a lesser extent, pharmacogenetic markers are utilized to partially explain PK variability in this population. Once PK parameters, typically clearance and volume of distribution, are estimated then an initial dosing regimen can be designed. This is the first advantage of this patient-tailored dosing technique, where evidence-based guidelines can be used to account for

interindividual variability by incorporating the identified covariates in order to implement the most appropriate dosing regimen[19]. As an example, this model-based approach has been demonstrated to be useful in dosing vancomycin in neonates, safely increasing the rate of target concentration attainment from 41% to 72%[20]. The better-informed dosing scheme is then modified when the remaining variability is adjusted for through therapeutic drug monitoring combined with Bayesian analysis techniques described below.

Physiology-based PK (PBPK) models are mechanistic models combining anatomy and physiology data of the patient population with the biochemical characteristics of the drug that describe the absorption, distribution, metabolism, and excretion of the drug[21]. In this model a patient is represented by a large number of compartments corresponding to different organs and tissues which are connected by flow rates paralleling blood flow[22]. Typically, adult models are constructed first and medication parameters determined. Then patient-specific parameters can be modified for the neonate[23]. However, this may be challenging in neonates, and especially in preterm newborns, due to rapidly evolving enzyme systems and changing physiology[24,25]. As more is learned about the ontogeny of these enzyme systems, PBPK modeling can better predict drug exposure. Combined with PK-PD data, PBPK modeling can then facilitate precision dosing of drugs.

While PK models predict the time course of drug exposure for a given dose, PD modeling relates exposure to the effects of the drug on the body. Exposure can be measured in a number of ways including peak or trough concentration of a medication, area under the plasma drug concentration-time curve for a specific time period, or determining the duration of time a drug concentration is within a predetermined target exposure range. Characterizing the PD of drugs in neonates is significantly hampered by the lack of defined biomarkers or PD outcomes measures for neonatal disease processes and adverse effects. For instance, differing definitions of bronchopulmonary dysplasia[26] and delayed diagnosis of neurodevelopmental impairment[27] hinder the ability to associate drug exposure with changes in disease severity or outcomes. The impact of development on PD measures of drugs also still needs to be further investigated. For example, how does the exposure goal for caffeine in the treatment of apnea of prematurity change as a neonate develops? Is the goal the same at 26 weeks as it is at 32 weeks postmenstrual age? Answers to these important questions will help in advance precision dosing in neonates.

Effects of Pharmacogenomics/Pharmacogenetics on PK/PD

No review of personalized drug dosing is complete without a discussion about pharmacogenomics. The Human Genome Project has enabled technologies to probe diseases in order to refine clinical care for risk stratification, prevention, diagnosis, and treatment. Pharmacogenomics, the study of variability in drug response due to genetic factors, includes the prediction of a patient's response to a specific therapy, and susceptibility to toxicity and adverse events[7]. Pharmacogenetics deals with individual genetic variations that may explain some of the drug dose-exposure-effect relationship and its interindividual variability. These genetic variations may impact all aspects of drug response by altering drug distribution in the tissues, drug elimination from the body, or the PD of the drug[28,29]. Polymorphisms in genes encoding proteins that are important in drug transport and metabolism or in drug

receptors may be important covariates to consider with respect to drug dosing. Although a single polymorphism by itself may not be sufficient to explain the variability in drug exposure or response, a combination of variants from multiple genes may act synergistically to impact drug response. Poignant illustrations include genetic polymorphisms in the principal morphine metabolizing enzyme, UGT2B7, and the *mu* opioid receptor. UGT2B7 −900G>A polymorphism results in increased drug metabolism thereby contributing to lower morphine exposure after a single dose of intravenous morphine administration[30]. Similarly, a polymorphism in the gene encoding the *mu* opioid receptor (OPRM1 118A>G) combined with a polymorphism in catechol-O-methyltransferase (COMT 472G>A) has been associated with an increased need for a rescue dose of morphine in neonates requiring mechanical ventilation[31].

While some neonatal pharmacogenomic studies have confirmed several associations reported in adult or pediatric populations, some phenotype-genotype associations are anticipated to be unique to the newborn period[29]. Hence, pharmacogenomic studies being advocated through the Precision Medicine Initiatives by the US government[2] and the 100,000 Genome Project in the United Kingdom must be broadened to include neonatal clinical syndromes[28,29]. Unique neonatal conditions like neonatal abstinence syndrome can only be studied in the newborn population where outcomes have shown to be dependent on the genotype of the mother and the infant[32]. In addition, there is a dynamic temporal interplay between developmental and pharmacogenomic factors. Determining the age when genetic variations become the predominant factor for differences in drug response is crucial to evidence-based dosing algorithms in neonates. A recent study showed that morphine exhibits age-dependent extraction as a result of developmental increases in OCT1 and UGT2B7 protein expression/activity and hepatic bloodflow[33]. This temporal versus pharmacogenomics contribution to drug response in neonates is further demonstrated by CYP2C8*3, CYP2C9*2, and CYP2C9*3 polymorphisms that show lower ibuprofen clearance in adults[34]. It might be assumed genetic polymorphisms that reduce drug clearance would increase ibuprofen effectiveness but these polymorphisms have no effect in the ductus arteriosus response to ibuprofen in preterm infants[35]. The decreased enzyme activity of CYP2C8 and CYP2C9 in early life likely explains this[35,36]. Incorporating developmental and genetic data about drug metabolizing enzymes, transporter, and receptor systems along with age-related physiological changes in neonates into predictive PK/PD models is warranted to allow for more precise dosing.

Bayesian Analysis

While population and physiology-based PK/PD modeling and pharmacogenetics can provide improved dosing regimens in neonates, Bayesian analysis allows for truly individualized precision dosing. Bayesian analysis uses previously collected information (“a priori”), such as a PBPK model-based approach or population PK parameters (e.g., clearance and volume of distribution) of a drug for a defined population, subsequent patient-specific information (“a posteriori”), and biomarker data such as one or more measured drug concentrations at known time points[37]. With the knowledge of the dosing history, a time-exposure curve can then be constructed and graphically displayed for the clinician. Furthermore, this analysis then allows the clinician to simulate dosing regimens to predict drug concentrations

(Bayesian forecasting) or to determine a dosing strategy to best achieve the target concentration (Bayesian adaptive control)[38]. Infants have been included in some Bayesian adaptive control research to optimize drug treatment[39–41]; however, the use of this method has been understudied in neonates. Conventional guidelines for monitoring medications used commonly in neonates, such as gentamicin and vancomycin, recommend waiting to assure a steady state after multiple doses before checking a drug level. One major advantage of utilizing PK modeling coupled with Bayesian analysis is that the behavior of the drug in an individual patient can be modeled starting with the first dose and with obtaining just one drug level. In addition, this process obviates the need to wait for attainment of steady-state [42–44]. Thus, Bayesian analysis allows clinicians to achieve the optimal dose more quickly.

Therapeutic Drug Management with Decision Support Tools

For many drugs, dose is a poor predictor of serum concentration and outcome in neonates. There are no simple clinical or patient-related factors that reliably inform drug response and adverse effects. Replacing the current trial and error paradigm used in clinical practice with a model that tailors dosing to each individual neonate's profile is possible through the use of bedside drug concentration testing coupled with Bayesian modeling and integrated electronic decision support tool[45]. Tandem mass spectrometry has become widely available [46]. Its use in the analysis of minute amounts of specimens collected on dried blood spots (DBS) for accurate and reliable drug concentration analysis has been reported[47,48]. Advances in paper spray mass spectrometry technology have the enormous potential to enable rapid quantification of drug levels [49]. Assessing drug exposure in real time will allow feedback for appropriate dose adjustments. While PK/PD modeling can be used for initial drug dosing[50,51], to further refine exposure, Bayesian adaptive modeling techniques can be utilized to predict and control drug exposure at a target level (See Figure 1)[38]. However, exposure does not always equal response. Once a drug concentration has been quantified, these data can be compared to target dosing ranges and correlated to clinical response in order to determine the dosing adjustment needed to achieve desired response. Systems pharmacology platforms using Bayesian estimation are then utilized to determine dosing adjustment recommendations, as has been reported in neonates[52]. User-friendly software for PK/PD model-based precision dosing is available[53].

Clinical Examples: Optimizing Neonatal Fluconazole and Acetaminophen Dosing Using Model-Informed Strategies

Population PK modeling has been used to optimize the dosing of fluconazole in neonates[54]. From 55 infants, born between 23 and 40 weeks gestational age and less than 120 days old, fluconazole clearance and volume of distribution were determined via population PK analysis. [55]. Using liquid chromatography-tandem mass spectrometry analysis (LC-MS/MS) fluconazole serum concentration measurements were made. The ensuing new model suggested that weight-based fluconazole dosing should be based on both gestational age at birth and postnatal age. Thus, an eight-week old infant born at 24 weeks gestation may require a different dosing regimen from a one-day old infant born at 32 weeks despite a similar postmenstrual age of 32 weeks. Subsequent Monte Carlo simulations revealed higher

fluconazole doses were required in infants than is typically recommended[56]. Further PK and safety trial work provided recommendations for an appropriate loading dose of 25 mg/kg to achieve target concentrations more quickly in infants less than 60 days old[57]. Dosing in special circumstances, such as extracorporeal membrane oxygenation, was also explored. This revealed an increased volume of distribution thus requiring a further increase in the treatment loading dose to 35 mg/kg[58]. Despite these improvements, 10 – 20% of infants still do not reach a sufficient AUC target for treatment with fluconazole[56]. Implementing these recommendations clinically is challenging because it can be cumbersome for clinicians to appropriately adjust fluconazole dosing based on gestational age at birth, post-natal age, and other clinical factors. The decision support tool can automatically account for these variables and further adjust the dosing regimen so more infants are in the desired target range for fluconazole exposure. This work underscores the utility of the data in the decision support tool.

As shown in Figure 2, fluconazole dose is initiated based on the neonate's gestational and postnatal ages. So for a 28-week infant who is 2 weeks old, a loading dose of 25 mg/kg is administered. Because clinical response is difficult to assess early on in fungal infections a drug level must be obtained. If the fluconazole level is suboptimal per the PK/PD model then a new dosing regimen can be determined and the level checked again. If there is a change in clinical status, such as impaired renal function, concurrent administration of medication that might impact PK or PD, or during critical illness, follow-up samples can be obtained and the Bayesian dose optimization process repeated (learn and confirm). This strategy can also be used to study the exposure-effect relationship to better define the target exposure range thereby maximizing the likelihood of response while minimizing the risk of adverse effects[59].

Using a PBPK model-based approach as the "a priori" information to describe the dose-exposure relationship in neonates is also possible[4,60]. Rather than using the population PK data to determine the initial dosing regimen, the PBPK model would inform the targeted dosing regimen. The prescribed dosing regimen would be adjusted in a similar fashion as described above to attain the desired exposure target or response. For acetaminophen which is used in the NICU for pain control and ductus arteriosus closure, a published neonatal PBPK model exists[61]. This model could be used to minimize the risk of liver toxicity to optimize therapy to close the ductus arteriosus when used with Bayesian adaptive modeling techniques.

Clinical Example: Using Bayesian Methods to Optimize Morphine Dosing

At Cincinnati Children's Hospital Medical Center, we have developed an electronic health record-linked decision support platform for precision dosing of morphine in neonates(Alexander A. Vinks. Cincinnati Children's Medical Center. Electronic Health Record (EHR)-embedded Decision Support Platform for Individualized Precision Drug Treatment in Neonates. Gerber Foundation. http://www.gerberfoundation.org/pediatric-health.). This population PK/PD model-informed precision dosing platform using Bayesian estimation allows the clinician to adjust the dosing regimen to optimize the drug therapy in real time. The example in Figure 3 shows the predicted morphine PK profile (blue line on

the left panel and dashed red line in the right panel) based on the infant's weight and gestational age and dosing regimen administered (continuous infusion plus bolus doses as needed, based on the pain scores). Two measured morphine levels (open circles in the right panel) revealed the concentration to be less than the expected value. Based on the feedback from these measured morphine concentrations, a new individually-predicted PK profile is developed (blue line in the right panel) using Bayesian analysis. The dotted lines represent the potential target range of 10–30 ng/mL (mean 20 ng/mL in red) as suggested by Anderson and van den Anker[59]. This example was reported retrospectively to develop this technology but it illustrates its power to tailor morphine therapy in neonates in real time. The lower than expected observed concentrations suggest this study subject has a higher clearance than the "average" neonate and the dosing regimen could have been adjusted accordingly to safely provide analgesia (blue line in the right panel). Could the number of painful experiences for the neonate be decreased using this tool? Could the tool be used to better control pain without putting the infant at increased risk for adverse effects from morphine? Is the target morphine concentration range correct and how does it change over time? How does the clinician incorporate this information to make clinical decisions? The platform is undergoing prospective evaluation as a decision support tool to answer these questions.

Overcoming Limitations to the Implementation of Therapeutic Drug Management

The clinical utility of population models is not intuitive and before Bayesian analysis techniques are fully adopted a number of impediments must be overcome. Lack of knowledgeable and well trained staff in modeling and simulation makes this technology difficult to use at the bedside. This can be overcome by utilizing new and future decision support tools to automate the Bayesian adaptive control process without the involvement of clinical pharmacologists. However, this may present another possible barrier because the generated dosing recommendations are potentially boundless. An assay error or incorrectly recorded drug dosing or timing of sample could result in the algorithm recommending a harmful or ineffective dosing plan. The clinician must be aware of this and warning messages could be built into the system to alert care providers to doses that are outside of an accepted range. Thus, this technology has the potential to reduce the risk of medication errors. Also, the best use of Bayesian analysis requires real time measurement of medication concentrations but not all facilities are equipped to perform this function. DBS samples have the advantage that they could be mailed overnight to regional centers for LC-MS/MS analysis and results returned by electronic mail so dosing adjustments can be undertaken. This still requires the clinician to have access to a decision support system integrated into the electronic health record. Web-based platforms offer a solution that can make this possible for optimizing dosing. Furthermore, using plasma as the source for drug levels may not reflect the drug exposure at the receptor site. Medications need to be studied individually to test this assumption. Assay variability can also complicate results and this difference needs to be solved. Finally, perhaps the most significant barrier is the lack of information concerning exposure-response relationships for many drugs used in the NICU. The model assumes a known target concentration exists but often this is not the case[59]. The development of PD biomarkers to assess desired outcomes and side effects must be

undertaken to better guide dosing[62]. Using Bayesian analysis to decrease some of the PK variability by controlling drug exposure will aid in these PD studies.

Conclusion

Precision dosing is possible in neonates through model-informed Bayesian analysis methods that take advantage of PK/PD models, bedside pharmacologic testing, and electronic decision support tools. The application of this learn-confirm and apply approach allows neonates to fully realize the benefits of PK/PD model-based individualized dosing. It may seem axiomatic that this approach will improve outcomes but hypothesis-driven research is warranted in order to move this science forward.

In conclusion, despite rapidly changing physiology and incomplete knowledge of developmental pharmacology and pharmacogenomics in neonates, improved efficacy and better safety can be realized through PK/PD modeling and Bayesian analysis. It is further anticipated that the Precision Medicine Initiative that aims to capitalize on advances in genome biology, next-generation sequencing and digital health coupled with ongoing PK/PD studies will complement the gains that have been realized through BPCA and PREA legislations that mandate or encourage inclusion of infants in drug clinical studies.

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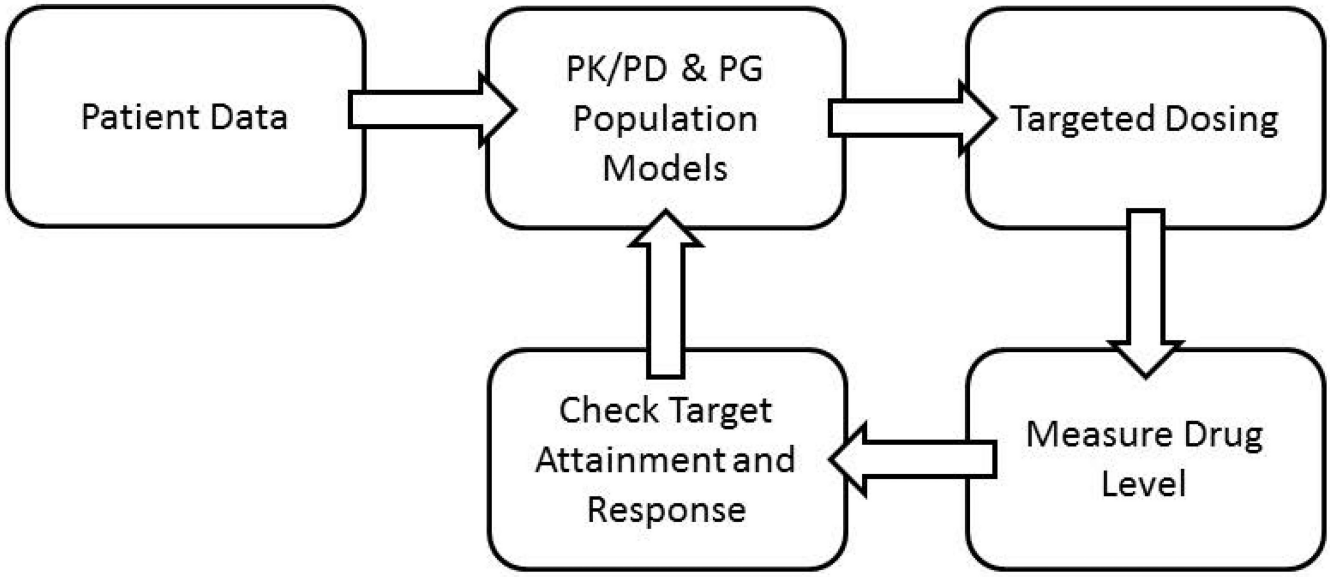

Fig. 1.

Schematic diagram of PK/PD modeling with Bayesian adaptive support tools using fluconazole as an example in a two week old infant born at 24 weeks gestation. Patient data (gestational age of 24 weeks, post-natal age of 2 weeks, and not on ECMO) are incorporated into the PK/PD model to target drug exposure based on the exposure-response relationship. When drug plasma level is outside the target range or clinical response is suboptimal, the drug concentration is input into the model to further refine the dosing regimen. This can be repeated if the desired outcome is not reached or the patient's clinical status changes

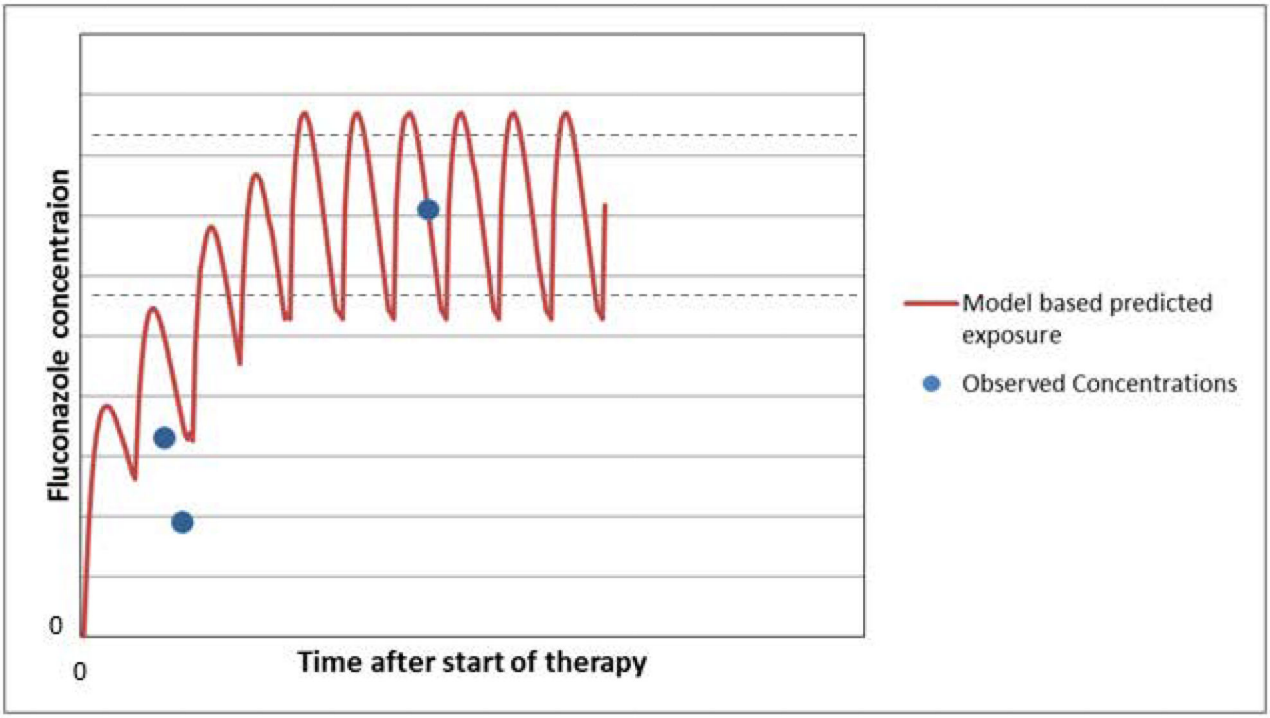

Fig. 2.

Using fluconazole treatment as an example in a two week infant born at 24 weeks gestation who is not on ECMO and has normal renal function the initial dosing regimen would suggest a loading dose of 25 mg/kg followed by a maintenance dose of 12 mg/kg every 12 hours. After fluconazole has been started a plasma drug level is obtained. Using the dosing information and drug level the 24 hour AUC can be calculated using the population PK model and compared to the goal (> 400 mg*hr/L). In this case the 24 hour AUC is too low. The decision support tool using Bayesian optimization then recommends a new dosing regimen so that the target AUC is obtained. The new dosing scheme with a higher maintenance dose every 12 hours after giving a one time loading dose is interrogated by obtaining another fluconazole level. The updated dosing regimen is subsequently simulated in the population PK model to determine the new 24 hour AUC. This time it is appropriate, thus the right dose has been determined for this patient

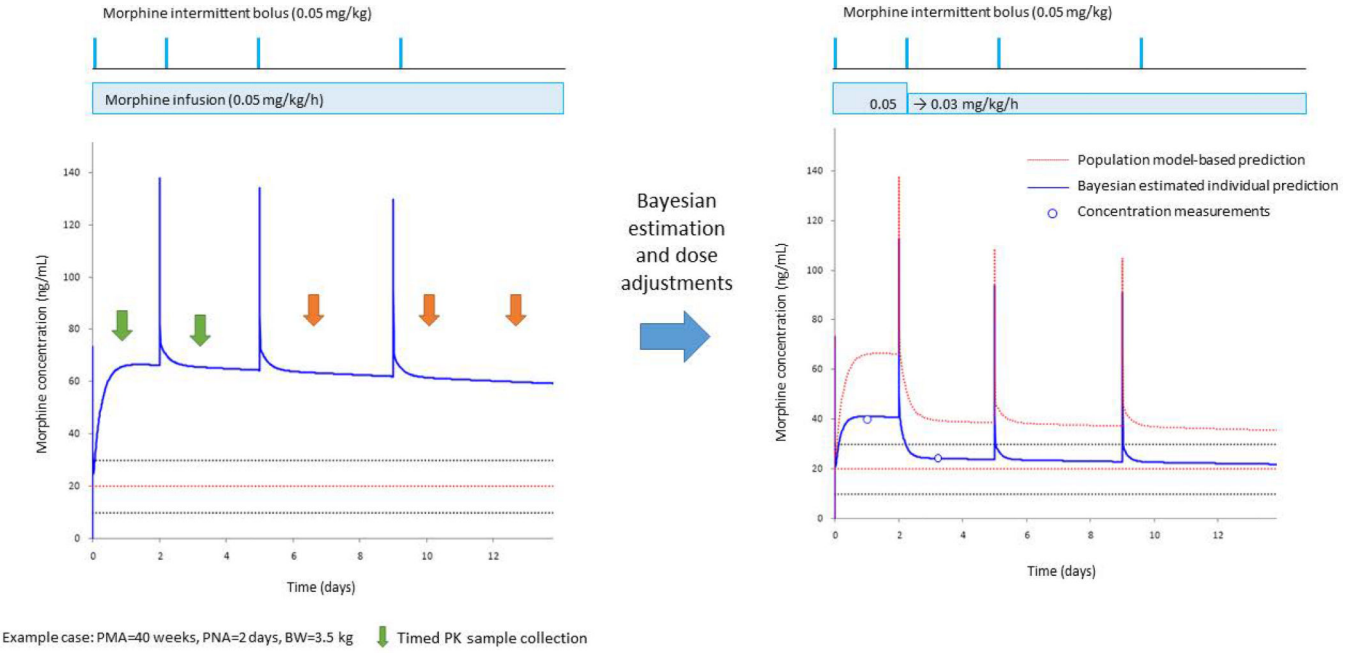

Fig. 3.

Bayesian estimation integrated within the electronic health record allows for precision dosing in neonates. The figure represents model-based PK simulations for a standard neonate (postmenstrual age: 40 weeks, postnatal age: 2 days and body weight: 3.5 kg) as an example. The left panel shows the population PK model-based morphine PK profile (solid blue line) for a standard morphine initial continuous infusion and “as needed” bolus doses. The Upper panel represents the morphine doses for intermittent bolus (horizontal lines) and continuous infusion (box). The dotted lines represent the potential target concentration range of 10–30 ng/mL (mean 20 ng/mL in red). Vertical arrows represent the time of PK sample collection by timed (green) or opportunistic sampling (orange). The right panel shows the adjusted dose and resulting individual PK profile based on the Bayesian estimation. The observed concentrations (open circles) were less than the expected concentration based on the population PK profile (dotted red line) suggesting this neonate had a higher clearance when compared to the average neonate. Therefore, the continuous infusion dose was decreased by 40% to target to the individual predicted concentration (blue line) fitted within the suggested target range (horizontal dotted lines). (Figure courtesy of Dr. Tomoyuki Mizuno, Cincinnati Children’s Hospital Medical Center)