The Journal of Clinical Pharmacology
2017, 00(0) 1–8

DOI: 10.1002/jcph.852

Facilitate Treatment Adjustment After Overdosing: Another Step Toward 21st-Century Medicine

Gilbert Koch, PhD[1], Johannes Schropp, PhD[2], and Marc Pfister, MD[1]

Abstract

Overdosing occurs frequently because of prescription errors in neonates, infants, children, adolescents, and adults. Currently there is no quantitative approach that can be used by clinicians to adjust dosing so that toxic drug concentrations can be brought back to levels observed with safe and efficacious therapeutic doses. We present a mathematical solution that offers the time between last overdosing and next therapeutic dose to achieve therapeutic drug concentrations as soon as possible. To facilitate applications of this solution in clinical practice, a minimal amount of information has to be provided, and no simulations are necessary to compute the optimal waiting time. For educational purposes, we provide access to an online decision support tool for overdosing situations (**T**ime to next **Do**se **C**alculator) that (1) computes the waiting time after accidental overdosing in patients with normal elimination and (2) computes the waiting time and adjusted reference dosing for patients with abnormal elimination. This user-friendly online tool will help clinicians to quickly adjust a dosing schedule in overdosing situations to mitigate risk for negative clinical consequences.

Keywords

overdosing, dose adjustment, therapeutic dose, prescribing errors, pharmacokinetics

Prescribing errors frequently occur in adults[1–3] and pediatric patients. A 6-week study in 5 UK hospitals reported a prescribing error of 13.2% in pediatric inpatients, in whom errors in drug preparation are most common.[4] Once or repeated overdosing is an essential outcome of prescribing errors and a potentially fatal clinical situation in both, in- and outpatient settings, often leading to negative short- and long-term damage. Neonates and infants are at increased risk of overdosing because drug clearance is dramatically changing due to maturation processes during the first week of life, and daily dose adjustments are required based on individual patient characteristics. One of the critical questions after overdosing is to understand the time it will take for the drug concentration to return to the target range associated with correct therapeutic dosing. This is particularly important in clinical situations in which the next correct reference dose has to be administered at the right time to ensure safe and efficacious treatment, for example, antibiotics to treat life-threatening infection or immunosuppressive agents to preserve the transplanted organ. Quite a few drugs including antibiotics such as aminoglycosides[5] or glycopeptides[6] have a narrow therapeutic window between insufficient efficacy and increased toxicity. For example, high concentrations of aminoglycosides are associated with ototoxicity[7] and nephrotoxicity[8] in neonates, whereas low drug concentrations can result in unfavorable clinical outcomes and increase the risk of drug resistance.[9,10]

For these reasons, it is clinically relevant to have a quantitative approach that helps clinicians to adjust dosing strategy after overdosing so that drug concentration returns to a safe therapeutic range within the shortest possible time. In this work, we introduce a generally valid mathematical solution to calculate the optimal time for next therapeutic dose, called the waiting time, after an overdosing period, so that drug concentration returns to concentrations observed with correct therapeutic dosing.

We consider 2 clinically relevant overdosing cases:

1. Accidental incorrect administration of doses higher than the recommended reference doses to

[1]Paediatric Pharmacology and Pharmacometric, University of Basel, Children's Hospital, Basel, Switzerland
[2]Department of Mathematics and Statistics, University of Konstanz, Konstanz, Germany

Submitted for publication 31 May 2016; accepted 8 November 2016.

Corresponding Author:
Gilbert Koch, PhD, Paediatric Pharmacology and Pharmacometric, University of Basel, Children's Hospital, Spitalstrasse 33, 4056 Basel, Switzerland
Email: gilbert.koch@ukbb.ch

patients with normal ("typical") drug elimination.
2. Administration of recommended reference doses that require adjustment because of abnormal, reduced elimination, for example, as a result of impaired kidney function.

We propose a mathematical solution to assess the appropriate waiting time to next therapeutic dose in such overdosing events. The solution is based on pharmacokinetic models, which have been well established for decades,[11] and allows quantification of drug absorption, distribution, metabolism, and elimination. Our mathematical solution is illustrated by 2 case studies with amikacin and vancomycin. For educational purposes we developed an online decision support tool for overdosing, named the **T**ime to next **Do**se **C**alculator (TDOC), based on our mathematical solution.

The goal was to develop a user-friendly, instant solution that requires a minimal amount of information and computes an appropriate time to the next therapeutic dose without the need for performing simulations. In the first case, the recommended reference dosing, the half-life of the drug and the actual overdosing, that is, the doses higher than the recommended reference, have to be provided, and the waiting time is calculated without any therapeutic drug monitoring. In the second case, unadjusted reference dosing, that is, the recommended reference dose that is not adjusted to reduced drug elimination, the typical half-life of subjects with normal elimination, the desired therapeutic concentration, and a single measured drug concentration after multiple dosing (ie, drug concentration close to steady state) are required to calculate the waiting time for abnormal elimination. Moreover, with this information the correct adjusted reference dosing is obtained to continue with safe and efficacious dosing. For both cases we present real clinical incidents.

Mathematical modeling as part of quantitative clinical pharmacology is frequently used in drug research and development. The presented work bridges the gap between application of such methods and clinical practice, supporting clinicians who care for safe and efficacious use of drugs in neonates, infants, children, adolescents, and adults.

Methods

A patient with a correctly prescribed and administered dosing regimen of a drug can be considered a stable system, and overdosing is an external influence that might catapult the patient into a life-threatening situation. In general, 2 components are necessary to govern a perturbed system: (1) a mathematical model to describe the dynamics of the system, and (2) a method to control the system during perturbation. Translated to a patient with overdosing, these 2 steps are: (1) apply pharmacokinetic modeling to describe the drug clearance of the patient, and (2) develop a mathematical solution to calculate an appropriate waiting time and dosing strategy based on such a model to return the patient to therapeutic dosing.

The human body can be viewed as a unit, and homogenous distribution of the drug throughout the body is assumed. This so-called 1-compartment pharmacokinetic model adequately describes the concentration profiles over time for most drugs used in clinical practice[12] and was therefore applied in our mathematical solution. The waiting time after accidental overdosing until the blood concentration of a drug returns to the target range with therapeutic dosing is then calculated by solving a mathematical equation. This equation relates the drug concentration over time after overdosing, with the therapeutic target range characterized by the steady-state concentration obtained from the correct reference dosing.

For a patient with normal drug elimination, the waiting time until the next therapeutic dose depends on the reference dosing and the half-life of the administered drug. Here the half-life can be used to incorporate patient characteristics such as immature renal elimination in neonates and infants. Concentration measurements from therapeutic drug monitoring are not necessary. For patients with reduced drug elimination, the steady-state concentration obtained from reference dosing in subjects with normal elimination has to be adjusted by the difference of the desired correct therapeutic range and the actual observed steady-state concentration.

In this section, we present the necessary basic mathematical formalism and calculations but outsource details of the derivations to the Appendix. In step 1, we introduce the linear 1-compartment model. In the second step, we calculate the elimination rate for patients with normal and abnormal elimination. In the last step, we present a general valid method to define the waiting time and derive an explicit formula for the waiting time for the 1-compartment model with intravenous bolus administration.

For educational purposes, we developed an online decision support tool for accidental overdosing, the **T**ime to next **Do**se **C**alculator, based on our mathematical solution. In Figure 1 a conceptual plot of the input/output and functioning of the calculator is shown. The calculator is publicly and freely available for educational purposes at http://dosecorrection.mashframe.com.

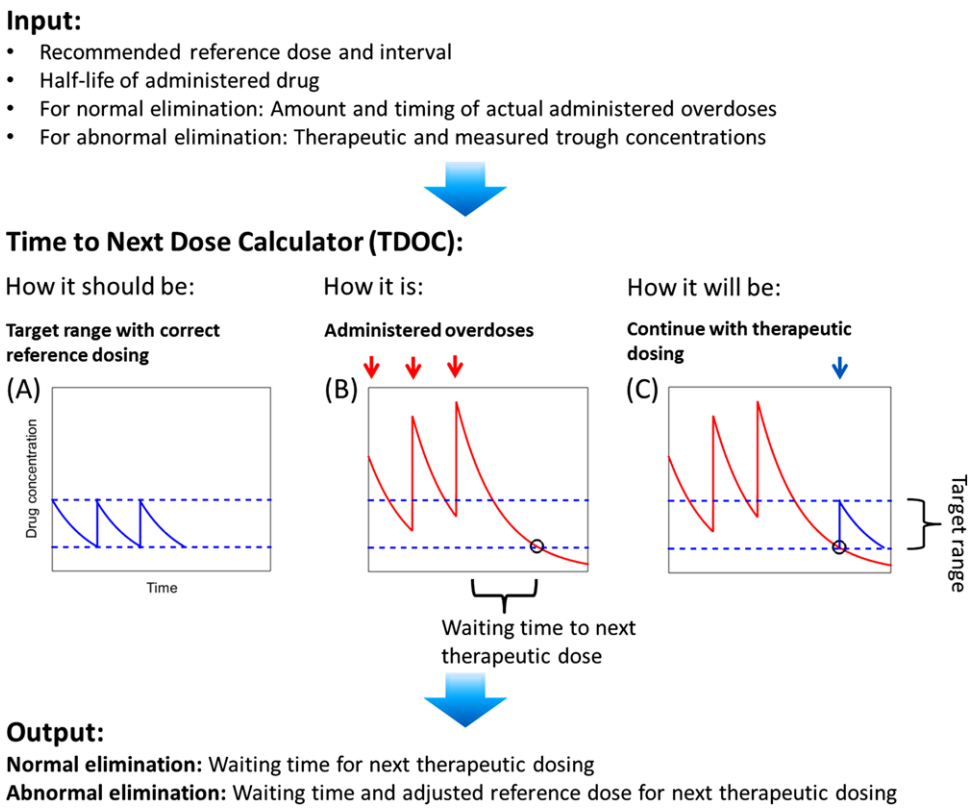

Figure 1. The conceptual plot shows the necessary steps to compute the waiting time for the next therapeutic dose to achieve drug concentrations within target range (dashed blue lines). As input, the recommended reference dosing and the half-life of the drug have to be provided. In addition, for normal elimination the administered overdosing and for abnormal elimination the desired and measured trough concentrations are necessary. (A) Target range and steady state of the therapeutic drug concentration (solid blue line). (B) Plot of hypothetical 3 times overdose (red solid line), and return of the drug concentration to the lower bound of the desired target range is marked (black circle). The waiting time is the difference between the last overdose and the lower bound of the target range. The output is the waiting time for the next therapeutic dose and also the adjusted reference dose in case of abnormal elimination. Hence, after the waiting time, safe and efficacious dosing is continued (C).

Definition of Drug Concentration, the Linear 1-Compartment Model, and the Steady-State Concentration

Drug concentration over time, $C(t)$, is the ratio of drug amount, $A(t)$, and the volume of distribution, V, for the drug:

$$C(t) = \frac{A(t)}{V}.$$

Please note that V is only a scaling factor relating amount with concentration. We characterize the dynamic of $C(t)$ with a 1-compartment pharmacokinetic model reading in differential equation form

$$\frac{d}{dt}C(t) = \frac{In(t)}{V} - k_{el}C(t), \quad C(0) = 0$$

where k_{el} is the elimination rate. The route of administration for multiple intravenous boluses is

$$In(t) = \sum_{i=1}^{n} d_i \delta(t - t_i)$$

where n is the number of doses, d_i is the administered dose at time t_i for $i = 1, \ldots, n$, and δ is the Dirac delta impulse function. The explicit solution of the linear 1-compartment model reads

$$C(t) = \frac{1}{V} \int_0^t \exp(-k_{el}(t - \xi)) \sum_{i=1}^{n} d_i \delta(\xi - t_i)\, d\xi. \quad (1)$$

The concentration after last intravenous bolus administration, $t \geq t_n$, is

$$C_n(t) = \frac{\exp(-k_{el}t)}{V} Q_n \quad (2)$$

with

$$Q_n = \sum_{i=1}^{n} d_i \exp(k_{el}t_i). \quad (3)$$

The steady-state concentration is defined for a reference dose, d_{ref}, administered equidistantly every τ time

units:

$$C_{SS}(s) = \frac{d_{ref}}{V}\exp(-k_{el}s)\left(\frac{1}{1-\exp(-k_{el}\tau)}\right), \quad 0 \le s \le \tau. \tag{4}$$

Using Eq. (4), the minimal and maximal values of the steady-state concentration for an intravenous bolus then read

$$C_{SS}^{min} = C_{SS}(\tau) = \frac{d_{ref}}{V}\ P \quad and$$

$$C_{SS}^{max} = C_{SS}(0)\ = \frac{d_{ref}}{V}\ (1+P) \tag{5}$$

with

$$P\ = \frac{\exp(-k_{el}\tau)}{1-\exp(-k_{el}\tau)}. \tag{6}$$

Elimination Rate for Normal and Abnormal Elimination

For patients with normal drug elimination, the elimination rate, k_{el}^{norm}, is calculated directly from the half-life, $T_{1/2}$, by

$$k_{el}^{norm} = \frac{\ln(2)}{T_{1/2}}. \tag{7}$$

The elimination rate for patients with an abnormal elimination is based on the normal elimination rate, k_{el}^{norm}, together with a multiplicative factor, α, describing the difference between the desired therapeutic range and the actual measured concentration and reads

$$k_{el}^{ab} = k_{el}^{norm} + \frac{1}{\tau}\ln\left(\frac{1+(\alpha-1)\exp\left(-k_{el}^{norm}\tau\right)}{\alpha}\right). \tag{8}$$

The adjusted reference dose for patients with abnormal elimination becomes

$$d_{ref}^{ab} = \frac{d_{ref}}{\alpha}. \tag{9}$$

Explicit Solving of the Equation Defining the Optimal Waiting Time

In general, the optimal waiting time, t_{wait}, is defined by the equation

$$C^* = C_n(t_{wait} + t_n) \tag{10}$$

where

$$C^* = \frac{d_{ref}}{V}\ P \tag{11}$$

is the target drug concentration to be achieved, in our case the minimal steady-state concentration. Solving Eq. (10) for the 1-compartment model with intravenous bolus provides the waiting time

$$t_{wait} = \frac{1}{k_{el}}\ln\left(\frac{Q_n}{d_{ref}P}\right) - t_n. \tag{12}$$

This formula is implemented in the TDOC. Please note that the waiting time is independent of the volume of distribution. For patients with normal elimination, k_{el} is set to k_{el}^{norm}. For patients with abnormal elimination, k_{el} is set to k_{el}^{ab} and d_{ref} becomes the adjusted dose, d_{ref}^{ab}.

Results

In this section we present 2 applications: case study I, with overdosing as a result of a prescription error (accidental overdosing), and case study II, with overdosing as a result of reduced drug elimination.

Case Study I — Accidental 10-Fold Amikacin Overdose in a Preterm Male 1-Day-Old

Amikacin is employed to treat bacterial infections and listed by the World Health Organization as one of the most important medications needed in a basic health system. Amikacin is administered intravenously and intramuscularly and eliminated primarily by the kidneys. High amikacin concentrations cannot only be ototoxic but also nephrotoxic[13] and as such lead to increased drug concentration by reducing renal drug elimination. In our case study, a 1-day-old preterm male neonate (gestational age, 29 weeks) with a weight of 1 kg experienced an overdosing event on his first day of life, receiving an intravenous amikacin dose 10 times higher than the weight-adjusted reference dose[14] of 8.4 mg (7.5 mg/kg/d). To account for age, the half-life of amikacin was set to 10–14 hours.[15] Given these inputs, the mathematical solution computed a waiting time of 54–63 hours, that is, at least 2 days to achieve safe and efficacious therapeutic concentrations with the next reference dose. Hence, the waiting time is estimated to be approximately 5 times the half-life. In Figure 2, amikacin concentration, the measured drug concentration, target range, and waiting time are shown for this neonatal patient.

Case Study II — Adjustment of Vancomycin Dosing in Male Infant Because of Elevated Drug Concentration as a Result of Impaired Kidney Function

Vancomycin is an antibiotic to treat serious life-threatening infections and is also listed by the World Health Organization as one of the most important medications. A 10-week-old male infant receiving weight-based reference dosing of 3 × 50-mg intravenous

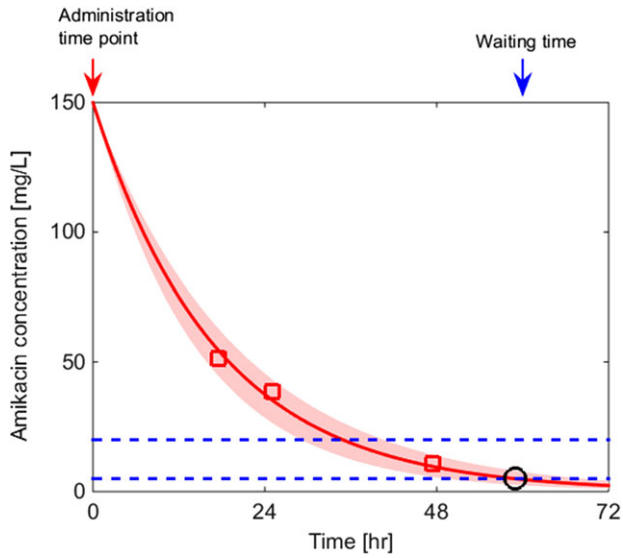

Figure 2. Amikacin concentrations for half-lives from 10 to 14 hours (shaded red area), measured drug concentrations (red squares), and target range (dashed blue lines) are shown. Indicated is the waiting time (black circle) of 59 hours for a half-life of 12 hours after amikacin concentration (solid red line) returned to the lower bound of the target range.

bolus every day for 7 days[16] (38 mg/kg/d) suffered an undetected kidney impairment. A measurement of the trough level on day 7 (steady-state condition) showed a 3.5 times (multiplicative factor α in Eqs. (8)–(9)) higher concentration as the recommended level of 15 mg/L.[17] Normal half-life for infants is reported[18] to be 5 hours. Using Eqs. (7)–(8) the abnormal half-life of vancomycin in this patient is $T_{1/2}^{ab} = 12$ hours, resulting in a waiting time of 30 hours. From Eq. (9), the adjusted dose becomes 14 mg 3 times a day. The action from the clinician was to first administer a single dose of 50 mg on day 8 and a single dose of 25 mg on day 9. Continuation with a dose of 25 mg per day would lead to a subtherapeutic vancomycin concentration in this patient. In Figure 3, vancomycin concentration, measured drug concentrations, target range, the dose adjustment from the clinician, and the continuation of treatment based on our mathematical solution after the waiting time are shown.

Discussion

What are current clinical behaviors after overdosing due to a prescription error? One approach is to simply estimate the waiting time by multiplying the drug half-life by a factor 3 to 5.[19] Although this rule of thumb is based on a linear 1-compartment model, obviously, it is only an empirical guidance and may not be appropriate for multiple dosing with accumulation behavior. Further, this rule assumes knowledge about the individual half-life of the patient and a concentration measurement from therapeutic drug monitoring. Another approach is to skip 1 or 2 administrations or reduce the next doses based on some personal experience. This approach needs repeated drug monitoring to return the concentration after several "guessed" dosing adjustment attempts to the target range.

In contrast to these empirical trial-and-error approaches, our mathematical solution leverages pharmacokinetic principles[20] and control theory[21,22] and provides an accurate assessment of time to the next safe and efficacious dose, not only after a single overdose but also after multiple consecutive overdoses with potentially life-threatening drug accumulation. Our solution was applied to 2 fundamentally different

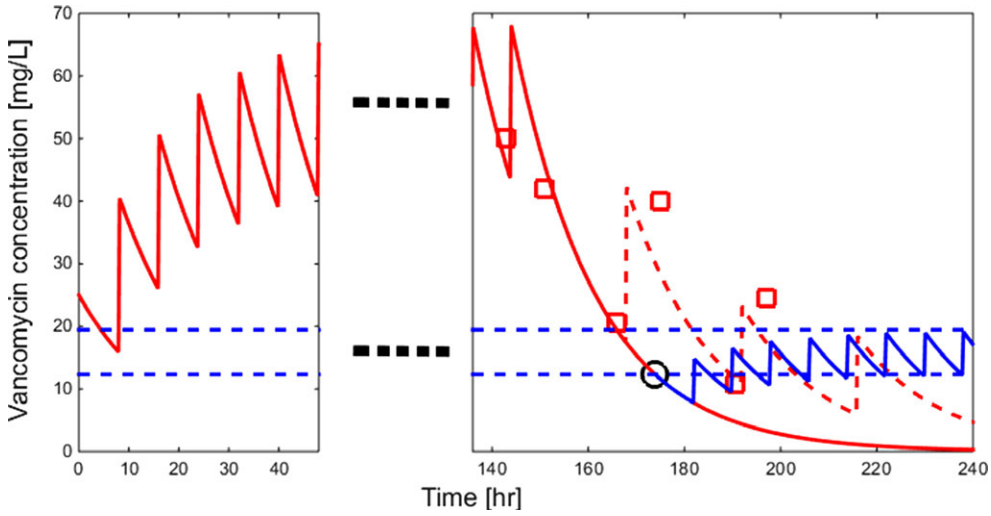

Figure 3. Vancomycin concentrations (solid red line), measured drug concentrations (red squares), and target range (dashed blue lines) are shown. Indicated is the waiting time (black circle) of 30 hours after vancomycin concentration returned to the lower bound of the target range. The dose adjustment from the clinician (dashed red line) and from our mathematical solution after the waiting time (solid blue line) is shown.

real-case overdosing situations. In the first case study, an accidental 10 times single overdose occurred in a patient with normal elimination behavior. To calculate the waiting time for the next safe and efficacious dose, we emphasize that no therapeutic drug monitoring is needed, and only the reference dosing, the half-life, and the actual overdoses are necessary. In the second case study, a patient with undetected kidney impairment was treated with a reference dose for subjects with normal drug elimination. With knowledge about the desired therapeutic target drug concentration and a single measured trough concentration after multiple dosing, our mathematical solution allows computation of the individual half-life corresponding to the abnormal elimination behavior, the waiting time, and the correct adjusted reference dose to continue with safe and efficacious dosing after the waiting time.

The presented solution to calculate an appropriate waiting time after overdosing can be applied to any drugs that follow the dynamics of a linear 1-compartment model. For drugs with more complex pharmacokinetic behavior, our method can be adjusted to any other pharmacokinetic model, such as models with more compartments, physiologically based models with several compartments to describe different organs, models with nonlinear elimination behavior to describe saturation effects, or even target-mediated drug disposition models based on drug-receptor binding kinetics.

For educational purposes, a freely and publicly online support decision tool, the TDOC, was developed for accidental overdosing in patients with normal elimination and overdosing because of an unadjusted reference dose in patients with reduced drug elimination, for example, because of impaired kidney function. Note that the current version of the online calculator needs a half-life of drug only to calculate time to next dose, whereas more complex models may require additional data inputs from physicians, which in turn can make such online tools less user friendly in clinical practice. In addition, the TDOC can be applied to drugs administered with a short infusion and orally administered drugs with fast absorption.

The presented work represents a "bench-to-bed translation," leveraging mathematical modeling as part of quantitative clinical pharmacology[23] to facilitate implementation of personalized medicine in clinical practice.[9] Our calculator supports clinicians with a quantitative clinical pharmacology component who care for optimizing treatment adjustment in neonates, infants, children, adolescents, and adults after any accidental overdosing, taking into account both amount and timing of overdoses.

The clinical relevance of the TDOC was highlighted based on 2 common overdosing situations. The TDOC can be used for educational purposes, allowing clinicians to simulate and investigate all kinds of different overdosing scenarios and to gain further understanding of the dynamics of drug exposure after overdosing events. After appropriate validation with additional clinical data, the TDOC also has the potential to become a clinical decision support tool.

Of course, dose adjustments in overdosing situations are complex, as multiple factors need to be considered. As such, our calculator is not a medical device, as it provides quantitative clinical pharmacology inputs clinicians may or may not consider when they adjust treatment strategies in case of overdosing. The developed **T**ime to next **Do**se **C**alculator, TDOC, serves as an example of a "human-in-the-loop" process in which treatment options are calculated based on a computer model assisting caregivers, who make the final clinical decisions.

Acknowledgments

We thank Dr. Sachin Sanduja and Paul Jewell from Rudraya Corporation, New Jersey, for developing and implementing the website of the **T**ime to next **Do**se **C**alculator.

References

1. Dean Franklin B, Vincent C, Schachter M, Barber N. The incidence of prescribing errors in hospital inpatients: an overview of the research methods. *Drug Saf.* 2005;28(10):891–900.
2. Lewis PJ, Dornan T, Taylor D, Tully MP, Wass V, Ashcroft DM. Prevalence, incidence and nature of prescribing errors in hospital inpatients: a systematic review. *Drug Saf*. 2009;32(5):379–389.
3. Tully MP. Prescribing errors in hospital practice. *Br J Clin Pharmacol.* 2012;74(4):668–675.
4. Ghaleb MA, Barber N, Franklin BD, Wong IC. The incidence and nature of prescribing and medication administration errors in paediatric inpatients. *Arch Dis Child.* 2010;95(2):113–118.
5. Mingeot-Leclercq MP, Glupczynski Y, Tulkens PM. Aminoglycosides: activity and resistance. *Antimicrob Agents Chemother*. 1999;43(4):727–737.
6. Tan H, Guo H, Wang S, Kong Q, Li W, Zeng W. Chemistry and biology of glycopeptides with antibiotic activity. *Protein Pept Lett*. 2014;21(10):1031–1047.
7. Selimoglu E. Aminoglycoside-induced ototoxicity. *Curr Pharm Des.* 2007;13(1):119–126.
8. Mingeot-Leclercq MP, Tulkens PM. Aminoglycosides: nephrotoxicity. *Antimicrob Agents Chemother*. 1999;43(5):1003–1012.
9. Wilbaux M, Fuchs A, Samardzic J, et al. Pharmacometric approaches to personalize use of primarily renally eliminated antibiotics in preterm and term neonates. *J Clin Pharmacol*. 2016;56(8):909–935.
10. Ritz N, Bielicki J, Pfister M, van den Anker J. Therapeutic drug monitoring for anti-infective agents in pediatrics: the way forward. *Pediatr Infect Dis J.* 2016;35(5):570–572.
11. Wagner JG. History of pharmacokinetics. *Pharmacol Ther.* 1981;12(3):537–562.
12. Dhillon S, Kostrzewski A. *Clinical Pharmacokinetics*. Pharmaceutical Press; 2006.
13. Langhendries JP, Battisti O, Bertrand JM, et al. Once-a-day administration of amikacin in neonates: assessment of

nephrotoxicity and ototoxicity. *Dev Pharmacol Ther.*1993;20(3-4):220–230.
14. Kenyon CF, Knoppert DC, Lee SK, Vandenberghe HM, Chance GW. Amikacin pharmacokinetics and suggested dosage modifications for the preterm infant. *Antimicrob Agents Chemother*. 1990;34(2):265–268.
15. Pacifici GM. Clinical pharmacokinetics of aminoglycosides in the neonate: a review. *Eur J Clin Pharmacol*. 2009;65(4):419–427.
16. Broome L, So TY. An evaluation of initial vancomycin dosing in infants, children, and adolescents. *Int J Pediatr.* 2011;2011:470364.
17. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. *Clin Infect Dis.* 2011;52(3):e18–e55.
18. Asbury WH, Darsey EH, Rose WB, Murphy JE, Buffington DE, Capers CC. Vancomycin pharmacokinetics in neonates and infants: a retrospective evaluation. *Ann Pharmacother*. 1993;27(4):490–496.
19. Downie G, Mackenzie J, Williams A. *Pharmacology and Medicines Management for Nurses*. Churchill Livingstone; 2003.
20. Gabrielsson J, Weiner D. *Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications*. 4th ed. Taylor & Francis; 2007.
21. Sontag ED. *Mathematical Control Theory: Deterministic Finite Dimensional Systems*. New York: Springer; 2013.
22. Schropp J. One-step and multistep procedures for constrained minimization problems. *IMA J Numerical Analysis*. 2000;20:135–152.
23. Powell JR, Gobburu JV. Pharmacometrics at FDA: evolution and impact on decisions. *Clin Pharmacol Ther*. 2007;82(1):97–102.

Appendix

Explicit solution of the 1-compartment model after last dosing

Solving the integral in Eq. (1) gives

$$C_n(t) = \frac{1}{V}\sum_{i=1}^{n} d_i \exp\left(-k_{el}\left(t - t_i\right)\right) \tag{A1}$$

$$= \frac{\exp\left(-k_{el}t\right)}{V}\sum_{i=1}^{n} d_i \exp\left(k_{el}t_i\right). \tag{A2}$$

Steady-state concentration for intravenous bolus administration

For the steady-state condition we have an equal reference dose, $d^{ref} = d_i$, and an equidistant dosing interval, $\tau = t_{i+1} - t_i$, for $i = 1, \ldots, n-1$. From Eq. (A1) we obtain

$$C_n\left(t\right) = \frac{d^{ref}}{V}\sum_{i=1}^{n} \exp\left(-k_{el}\left(t - t_i\right)\right) \;\; for\; t \geq t_n. \tag{A3}$$

We set $s + t_n = t$ for $s \in [0, \tau]$ and obtain with Eq. (A3)

$$\begin{aligned} C_n^{ref}\left(s\right) &= C_n \;\; \left(s + t_n\right) \\ &= \frac{d^{ref}}{V}\sum_{i=1}^{n} \exp\left(-k_{el}\left(s + t_n - t_i\right)\right) \\ &= \frac{d^{ref}}{V}\exp\left(-k_{el}s\right)\sum_{i=1}^{n} \exp\left(-k_{el}\left(n - i\right)\tau\right) \\ &= \frac{d^{ref}}{V}\exp\left(-k_{el}s\right)\sum_{i=0}^{n-1} \exp\left(-k_{el}\tau\right)^i \\ &= \frac{d^{ref}}{V}\exp\left(-k_{el}s\right)\left(\frac{1 - \exp\left(-k_{el}n\tau\right)}{1 - \exp\left(-k_{el}\tau\right)}\right). \end{aligned}$$

In the limit $n \to \infty$ we have

$$\begin{aligned} C_{SS}\left(s\right) &= \lim_{n\to\infty} C_n^{ref}\left(s\right) \\ &= \frac{d^{ref}}{V}\exp\left(-k_{el}s\right)\left(\frac{1}{1 - \exp\left(-k_{el}\tau\right)}\right), \\ &\quad 0 \leq s \leq \tau \end{aligned} \tag{A4}$$

and Eq. (4) is shown. Eq. (A4) describes the steady-state concentration profile during 1 arbitrary cycle.

Normal half-life

The half-life of the 1-compartment model with d objects at time $t = 0$ in compartment C reads

$$\frac{d}{dt}C(t) = -k_{el}^{norm}C\left(t\right), \quad C(0) = d \tag{A5}$$

where k_{el}^{norm} is the normal elimination rate. The explicit solution of Eq. (A5) is

$$C\left(t\right) = d\exp\left(-k_{el}^{norm}t\right) \tag{A6}$$

Inserting Eq. (A6) in the definition of the half-life $T_{1/2}$

$$C\left(T_{1/2}\right) = \frac{1}{2}C\left(0\right)$$

gives

$$\begin{aligned} \exp\left(-k_{el}^{norm}T_{1/2}\right) = \frac{1}{2} \;\; &\Leftrightarrow \;\; -k_{el}^{norm}\,T_{1/2} \\ = \ln\left(\frac{1}{2}\right) \;\; &\Leftrightarrow \;\; T_{1/2} = \frac{\ln\left(2\right)}{k_{el}^{norm}}\;. \end{aligned}$$

Hence, for a given half-life the elimination rate can be calculated by Eq. (7).

Abnormal half-life

The abnormal elimination rate k_{el}^{ab} is calculated from the difference of the measured and desired drug concentrations of the steady state. The difference is described by the factor α. Using Eq. (6) with $k_{el} = k_{el}^{norm}$ we set

$$P_{ab} = \alpha P \Leftrightarrow \frac{\exp\left(-k_{el}^{ab}\tau\right)}{1-\exp\left(-k_{el}^{ab}\tau\right)} = \frac{\alpha \exp\left(-k_{el}^{norm}\tau\right)}{1-\exp\left(-k_{el}^{norm}\tau\right)}. \quad \text{(A7)}$$

With $f(z) = \frac{z}{1-z}$, Eq. (A7) reads

$$f\left(\exp\left(-k_{el}^{ab}\tau\right)\right) = \alpha \cdot f\left(\exp\left(-k_{el}^{norm}\tau\right)\right)$$

and with $f^{-1}(z) = \frac{z}{1+z}$ we obtain

$$\exp\left(-k_{el}^{ab}\tau\right) = f^{-1}\left(\alpha \cdot f\left(\exp\left(-k_{el}^{norm}\tau\right)\right)\right) = \frac{\alpha \exp\left(-k_{el}^{norm}\tau\right)}{1+(\alpha-1)\exp\left(-k_{el}^{norm}\tau\right)}$$

Logarithmizing results in

$$-k_{el}^{ab}\tau = \ln(\alpha) - k_{el}^{norm}\tau - \ln\left(1+(\alpha-1)\exp(-k_{el}^{norm}\tau)\right)$$

and Eq. (8) is shown.

Calculation of the waiting time

Substituting Eqs. (2), (11) in Eq. (10)

$$\frac{d^{ref}}{V}P = \frac{\exp\left(-k_{el}\left(t_{wait}+t_n\right)\right)}{V} Q_n$$

$$\Leftrightarrow \ln\left(d^{ref}P\right) = \ln(Q_n) - k_{el}\left(t_{wait}+t_n\right)$$

results in Eq. (12).