International Journal of Clinical Pharmacy (2019) 41:1121–1130
https://doi.org/10.1007/s11096-019-00886-4

COMMENTARY

Optimising antimicrobial therapy through the use of Bayesian dosing programs

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Received: 25 February 2019 / Accepted: 27 July 2019 / Published online: 7 August 2019

Abstract
The optimisation of antibiotic dosing therapy with therapeutic drug monitoring is widely recommended. The aim of therapeutic drug monitoring is to help the clinician to achieve target pharmacokinetic/pharmacodynamic parameters, maximising efficacy and minimising toxicity. Computerised programs, utilising the Bayesian estimation procedures, are able to achieve target concentrations in a greater percentage of patients earlier in the course of therapy compared to linear regression analysis and population methods. This article summarises various methods for dose optimisation of antibiotics with a focus on Bayesian programs.

Keywords Antibiotics · Bayesian statistics · Pharmacodynamics · Pharmacokinetics · Software

Introduction

Optimisation of antibiotic exposure is highly likely to lead to improved patient outcomes [1]. Research has also demonstrated that obtaining target pharmacokinetic and pharmacodynamic indices early during the antibiotic course of therapy has been associated with an improved patient response and reduced mortality for two commonly used antibiotics namely vancomycin and aminoglycosides [2, 3].

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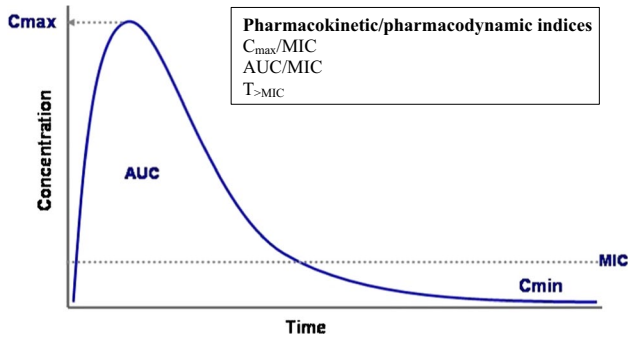
Pharmacokinetic and pharmacodynamic parameters

Key measurements of an antibiotic's concentration are typically expressed as pharmacokinetic parameters which includes the following: maximum concentration (C_{max}), minimum concentration (C_{min}) and Area Under the Curve (AUC) (Fig. 1) [4]. In contrast, pharmacodynamic parameters relates to the interaction of the antibiotic and its ability to kill or inhibit the target pathogen in the body. The pharmacokinetic and pharmacodynamics parameters can be combined in a quantitative relationship. For example, a pharmacokinetic parameter such as AUC and a microbiological parameter such as minimum inhibitory concentration (MIC). This is termed as a pharmacokinetic/pharmacodynamic index and is expressed as AUC/MIC [5].

The class of antibiotics correlates with which pharmacokinetic/pharmacodynamic indices predict the optimal outcome for antibiotic therapy (Table 1) [6]. Roberts et al. have identified pharmacokinetic/pharmacodynamic target values for a number of classes of antibiotics based on animal and human pharmacodynamic studies [1].

In this paper, we provide an evidence-based narrative review of the various methods for dose optimisation of antibiotics. We include the benefits, limitations, and challenges of different methodologies. We also describe a number of Bayesian programs that were identified via various search strategies: PubMed search for original and review articles



C_{max} - maximum concentration
C_{min} - minimum concentration
AUC - Area under the curve
MIC - minimum inhibitory concentration (of the organism the antibiotic is targeting) - pharmacodynamic parameter

Fig. 1 Pharmacokinetic parameters

from 2004 to 2019 as well as personal communication with clinicians. Programs identified via any of these methods had to meet the following criteria to be evaluated: Bayesian approach, currently available for clinical use and include population models for antibiotics. Programs that were not actively supported by the developer were excluded (i.e. programs not being actively updated and supported). The researchers who evaluated these programs (clinical pharmacist and infectious diseases physician) have extensive experience in pharmacokinetics and pharmacodynamics.

Therapeutic drug monitoring

The aim of Therapeutic Drug Monitoring (TDM) is to assist the clinician to achieve target pharmacodynamic parameters, maximising efficacy and minimising toxicity. TDM was traditionally used to minimise toxicities for drugs with a narrow therapeutic index. It is increasingly used to optimise dosing in addition to preventing toxicity. TDM relies on the accurate and timely measurement of serum antibiotic concentrations and the availability of a defined therapeutic range for the antibiotic. Doses can then be adjusted to meet predefined pharmacokinetic and/or pharmacodynamic criteria utilising methodologies such as nomograms and algorithms which are described below [1].

Peak and trough monitoring

Although there are several methodologies available for dose optimisation, some centers use TDM in the simplest concept by monitoring the measurement of "peak" and "trough" concentrations. Empiric dosage adjustments are then made with ratio estimations without utilising methodologies such as nomograms and algorithms. There are number of limitations associated with this strategy. Peak concentrations have limited utility and only correlate with efficacy in 'concentration dependent' antibiotics. Trough concentrations only indicate when a subsequent dose should be administered and not the dose adjustment required for the patient. In addition, if an undetectable concentration is identified i.e. < 0.5 mg/L the clinician does not know at what time the concentration fell below the limit of detection, thus there is no useful information to inform modification to the dosing regimen [7].

These empiric adjustments result in a "trial and error period" with different dosage regimens until optimal serum concentrations are achieved [7]. This approach potentially results in incorrect dosage adjustments, prolonged periods to obtain targeted concentrations and unnecessary health care cost mainly related to the extra serum concentrations required to achieve the optimal dose [2].

Methods of dose individualisation

Several nomograms and algorithms have been developed to individualise pharmacokinetic monitoring for antibiotics. Three major methods of dose individualisation commonly used to target specific pharmacokinetic parameters are: [1] linear regression analysis (one compartment model) [2], population methods and [3] Bayesian estimation procedures [8].

Linear regression analysis

The first method used to fit serum concentrations to individual patient models was the Sawchuk–Zaske method using linear regression analysis [9]. The ALADDIN (Aminoglycoside Levels and Daily Dose Indicator) is also another

Table 1 Pharmacokinetic/pharmacodynamic indices correlating with efficacy

Classification	Target pharmacokinetic/pharmacodynamic indices	Antibiotics
Time-dependent	$T_{>MIC}$	β-lactams, carbapenems
Concentration-dependent	Cmax/MIC AUC/MIC	aminoglycosides
Concentration-dependent with time-dependence	AUC/MIC	glycopeptides; quinolones daptomycin colistin

example of this method. These methods use an a posteriori drug dosing calculation where the patient's pharmacokinetic parameters are calculated from at least two measured serum concentrations and assume a one compartment model [2]. These methods require specific patient information such as dose, concentration, time of concentration and dose, duration of infusion in order to accurately interpret the pharmacokinetic results (AUC, C_{max}, C_{min}, Cl and Vd). Based on the pharmacokinetic results the programs then determine the most appropriate dose and dosing interval adjustments for the patient. They also require additional resources such as access to computers at the point of patient care.

Although these methods are simple they do have a number of limitations: they only utilise serum concentration data around the dosing interval where the concentrations were obtained and therefore there is a loss of continuity of data [2]. The lack of population data, and hence the necessity to have two concentrations presents a limitation in some settings, such as paediatrics where it is often difficult to obtain blood samples.

Population methods

A population method, alternatively called an a priori dosing method, determines antibiotic dosage based on population pharmacokinetic parameters, without using the patient's individual pharmacokinetic results [2]. Nomograms such as the Hartford Nomogram [10] and the Begg Nomogram [11], use estimates of pharmacokinetic parameters such as volume of distribution in order to estimate dosage recommendations. The nomograms have proved popular as they are easy to interpret, require no specialised pharmacokinetic knowledge for the interpretation of the results and limited use of resources (personnel and/or computers). In addition, the patient information required to interpret the nomogram is also minimal such as dose, time of dose and concentration.

Although nomograms have been widely used, it is important to ensure that the individual patient matches the population for which the nomogram has been developed. In addition all nomograms assume stability of pharmacokinetic parameters, such as creatinine clearance, which may not occur in a sick patient. There are a number of limitations associated with nomograms such as they are only available for a limited number of antibiotics at pre-defined doses. In addition, the Hartford Nomogram has not been validated in patients that may have altered kinetic parameters i.e. burns, pregnant patients, ascites, dialysis [10]. In addition, several studies have found a lack of agreement in dose recommendations made by the population-nomogram methods [12, 13]. Unfortunately the patients' pharmacokinetic parameters were not described in these studies. Due to these limitations nomograms are no longer being recommended by published guidelines [14, 15].

Bayesian estimation procedures

The Bayesian approach offers the advantage that it makes optimal use of all information contained in the population model (a priori) combined with the most current pharmacokinetic information from the patient (a posteriori) to develop the patient's most precise regimen [2, 8]. Numerous programs exist which apply different approaches to calculating individualised antibiotic doses for patients. Importantly, not all programs contain all relevant antibiotics, although the developers of most programs state that additional pharmacokinetic models for antibiotics can be included in these programs on request or by the user. To ensure robust bedside antibiotic dosing is possible, many of these programs have, or are developing electronic medical record interfaces and smart phone applications which can be used at the patient's bedside [16]. Examples of programs designed for clinical use are described in Table 2. Other programs have been designed for research use only and are beyond the scope of this paper [17, 18].

One of the advantages of utilising a Bayesian program is that pharmacokinetic and pharmacodynamic parameters for the patient can be calculated utilising a single measurable concentration. In addition, some of the Bayesian programs can calculate the optimal time to obtain a serum concentration for a patient and antibiotic thus minimising the number of serum concentrations that are required.

Patient individualisation dosing strategies utilising Bayesian strategies have demonstrated that a greater percentage of patients will achieve the targeted concentration as compared to patients who receive a fixed dose strategy [19, 20]. Bayesian programs have been shown to improve patient care by minimising drug toxicity and maximising drug efficacy. They have also demonstrated a reduction in the number of blood samples required to calculate the optimal dose and provide flexibility around sample times [21, 22]. Individualised, Bayesian modelling of medications is especially beneficial to patients for whom there are limited dosing guidelines, such as children and patients with altered physiologic function [23].

The predictions made by different Bayesian programs are generally similar, however, at times there can be substantial differences between programs for some individual patients. These differences can be attributed to the underlying pharmacokinetic distribution assumptions made in the model and should always warrant further evaluation [24]. This highlights the importance that these programs should be utilised by health care practitioners with a sound clinical knowledge and judgement who also have specialized skills in pharmacokinetics and pharmacodynamics.

Table 2 Comparison of Bayesian programs

	Best dose	DoseMeRx	Rxkinetics	ID ODS	TDMx	MWPharm++	PrecisePK
Pharmacokinetics							
Method	Bayesian non-parametric approach	Bayesian parametric approach	Antibiotic Kinetics: Bayesian parametric approach APK: Bayesian plus population analysis tool	Bayesian parametric approach and Monte Carlo Simulation	Bayesian parametric approach	Bayesian parametric approach	Bayesian parametric approach
Pharmacokinetic parameter & PK/PD indices used to calculate subsequent doses	AUC Cmax Cmin	AUC Cmax Cmin $\%T_{>MIC}$ Cmax:MIC AUC:MIC	AUC Cmax Cmin $\%T_{>MIC}$ Cmax:MIC AUC:MIC	AUC Cmax Cmin $\%T_{>MIC}$ Cmax:MIC AUC:MIC	AUC Cmax Cmin $\%T_{>MIC}$ Cmax:MIC AUC:MIC	AUC Cmax Cmin Caverage	AUC Cmax Cmin $\%T_{>MIC}$ Cmax:MIC AUC:MIC
Output from program	Doses, predicted concentrations at any level and pharmacokinetic parameter estimates	Doses and pharmacokinetic parameter estimates	Doses and pharmacokinetic parameter estimates	Doses, pharmacokinetic parameter estimates and PTAs	Doses, pharmacokinetic parameter estimates and PTAs D-optimal design theory ('Optimise sampling' module)	Doses and pharmacokinetic parameter estimates	Doses and pharmacokinetic parameter estimates
Special population groups	renal impairment dialysis different ethnic groups ICU	paediatrics neonates cystic fibrosis ICU obese dialysis	paediatrics renal impairment cystic fibrosis burns	burns ICU	cystic fibrosis Neonates	ICU	paediatrics neonates pregnant burns ICU obese dialysis

Table 2 (continued)

	Best dose	DoseMeRx	Rxkinetics	ID ODS	TDMx	MWPharm++	PrecisePK
Antibiotics	gentamicin: adult tobramycin: adult amikacin: adult vancomycin: adult, paediatric, neonate voriconazole: adult, paediatric meropenem: adult piperacillin/tazobactam: adult cefepime: paediatric	amikacin: adult, paediatric gentamicin: adult, paediatric, neonate tobramycin: adult, paediatric vancomycin: adult, paediatric, neonate meropenem: adult linezolid: adult piperacillin: adult teicoplanin: adult	vancomycin: adult, paediatric gentamicin: adult, paediatric tobramycin: adult, paediatric	listed antibiotics below only available for adults: vancomycin, gentamicin, tobramycin, amikacin, ciprofloxacin, daptomycin, cefepime, ceftazidime meropenem, piperacillin/tazobactam flucloxacilllin telavancin, doripenem amoxicillin and clavulanic acid, acid, levofloxacin, polymixin, tigecycline	meropenem: adult piperacillin: adult amikacin: adult tobramycin: paediatric gentamicin: adult, paediatric, neonate vancomycin: adult	vancomycin, gentamicin, tobramycin, amikacin, ciprofloxacin, cephalosporins, colisitin, ampicillin, benzylpenicillin, meropenem, and piperacillin	vancomycin: adult, paediatric gentamicin: adult, paediatric amikacin: adult, paediatric tobramycin: adult, paediatric ciprofloxacin: adult levofloxacin: adult ofloxacin: adult
Add population antibiotic model interface	Yes	Developers to add additional models	Yes	Yes	Modification of some existing pharmacokinetic models Developers to add additional models	Yes	No
Models							
A priori regimen	Yes	Yes	Yes	Yes	Yes	Yes	Yes
First dose handled	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Non-steady-state situation	Yes	Yes	Yes	Yes	Yes	Yes	Yes
General characteristics							
Usability	Training required	User friendly	User friendly	User friendly	User friendly	Training Required	Training Required
Network capability (Web, server or terminal based)	Terminal R package Web based	Web based, cloud-hosted	Yes	Terminal, Web based, mobile	Web based	Terminal and server	Terminal Web based

Table 2 (continued)

	Best dose	DoseMeRx	Rxkinetics	ID ODS	TDMx	MWPharm++	PrecisePK
Compatibility	Windows (terminal/web/R), Mac (web/R), Linux (web/R), iOS (web), Android (web)	Mac, Windows, Linux, Android, iOS	Windows, Android, iOSs	Windows, Android, iOS (app.id-ods.org)	Mac, Windows, Linux, Android, iOS (big screen required for mobile devices)	Windows	Mac, Windows
Interfacing	No	Yes, full API exists and a SMART-on-FHIR integration is available (validated within Cerner and Epic). Custom integrations can also be performed.	Limited	Yes (capability is available)	No	Yes, with Mirth™ Connect technology (cross platform HL7 interface engine)	Yes, using FHIR integration
Storage patient records/database for subsequent retrieval	Yes, on local files (no real database)	Cloud-based in the same geographical region as the client. Patient data is encrypted both at rest and in transmission. HIPAA complaint	Yes (desktop only)	Yes in-app and on server	No	Yes	Yes, on local files or cloud-based. HIPAA complaint, encrypted Amazon Web Services servers
Report generation	Yes, customizable	Yes, customizable	Yes, customizable	No	No	Yes, customizable	Yes, customizable
Manual available	Yes	Yes	Yes	Yes	Yes	Yes + video links	Yes
Validation							
Clinical validation studies	Yes [26, 27]	Yes [28]	validation by developers (not published)	Yes [20, 29]	Yes [30]	Yes [17]	Yes [18]
Descriptive characteristics							
Cost as supplied by developer as of April 2019	Terminal version is free Web and R version by arrangement	Web-based platform access fee = USD$ 25 per year per bed plus drug model (trial version available)	dependent on application: Antibiotic Kinetics (USD$ 25 to $125) & APK (USD$ 75 to USD$ 390) (trial version available)	Web-based, Android, iOS versions are free	Current version is free	€ 10 850,00 (institution license—5 users), € 2500 single license, € 800 annual maintenance and support fee	Individual: USD $99/month—per device (non-commercial use) Institution: USD $595/month—20 devices Institution+: USD $795/month—100 devices Enterprise: USD $995/month—unlimited devices (trial version available)
IT support	Yes	Yes 24 h IT support	Yes	Yes	No	Yes	Yes

Table 2 (continued)

	Best dose	DoseMeRx	Rxkinetics	ID ODS	TDMx	MWPharm++	PrecisePK
Developer	Michael Neely, Roger Jelliffe, School of Medicine University of Southern California, U.S.A.	DoseMe	R. Tharp, School of pharmacy and Health Profession, Creighton University, USA	Andras Farkas, Gergely Daroczi	Prof. Sebastian G. Wicha, University of Hamburg, Germany, Dr Charlotte Kloft, Dr. Martin Kees, Alexander Solms, Iris Minichmayr, Institute of Pharmacy, Freie Universität Berlin, Berlin, Germany	D.K.F. Meijer et al. University of Groningen, The Netherlands (developer) Faculty of Medicine Charles University, Prague, Czech Republic	Healthware Inc.
Version reviewed	15.2	2.4.x	Rxkinetics for Windows 2.3.11	2.7.0	Beta version	1.6.7	19.04.03
Further information	www.lapk.org/software.php Partnering with InsightRx to incorporate BestDose into their platform	doseme-rx.com listed on the ARTG (#226237) CE-marked (NL-CA002-2014-32089)-permitting European use. U.S.A: MDDS and clinical decision support carve-outs of the 21st Century Cures Act (2016)	www.rxkinetics.com	www.optimum-dosing-strategies.org	www.tdmx.eu	www.mediware.cz	precisepk.com

ID-ODS individually designed optimum dosing strategies, *AUC* area under the curve, *Cmax* maximum concentration; *Cmin* minimum concentration, *ICU* intensive care unit, *IT* information technology, *PTA* probability of target attainment, *SMART* substitutable medical applications, reusable technologies on FIHIR (health information exchange standard); *ARTG* Australian Register of Therapeutic Goods, *MDDS* medical device data systems, *APK* adult and pediatric kinetics

How are doses calculated for an individual patient utilising a Bayesian program?

In Bayesian dose adaptation, the dose of the antibiotic is adjusted to ensure the individual patient's exposure meets pharmacokinetic/pharmacodynamic targets. Information about the specific patient (e.g., weight or creatinine clearance), serum drug concentrations, and a population pharmacokinetic model, from the relevant population, are included (Fig. 2). The population pharmacokinetic model contains a series of mathematical equations including parameter estimates and their distribution for clearance and Vd [16].

An initial dose can be calculated for a patient, for the most appropriate antibiotic for the patient's infection, utilising a Bayesian software package and the patient's data (e.g., weight and creatinine clearance) to increase the likelihood of achieving pharmacokinetic/pharmacodynamic targets early in the course of therapy. After the first or subsequent doses have been administered serum concentration(s) are then obtained to estimate the patient's individual pharmacokinetic parameters for the antibiotic. In addition, the MIC of the selected antibiotic to the pathogen can be sought from the microbiology laboratory. The software package combines the patient's observed data plus the population pharmacokinetic model to estimate the Bayesian posterior pharmacokinetic parameters for the individual. The appropriate dose that achieves the pharmacokinetic/pharmacodynamic targets required for a patient is calculated and used to make the necessary adjustments to the patient's regimen [16].

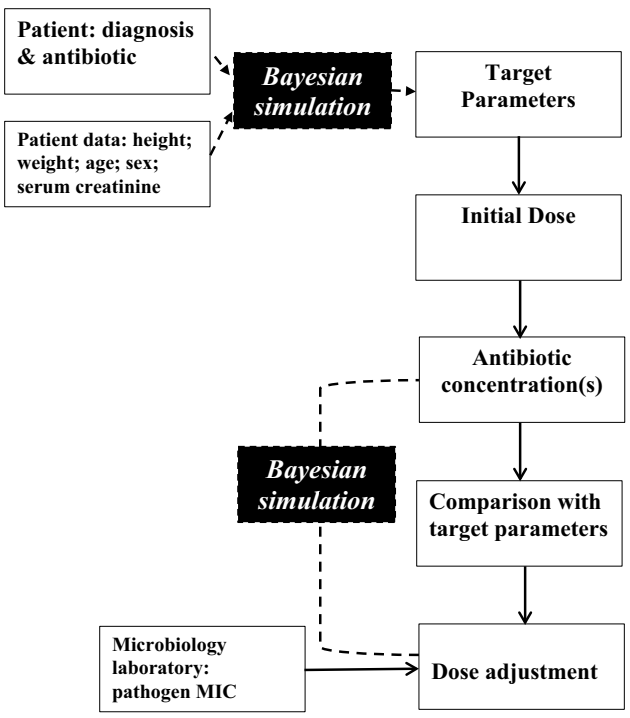


Fig. 2 Bayesian dose adaptation

Summary

The ideal method for monitoring antibiotics is one that predicts an accurate, clinically appropriate dose, requires minimal resources and is easy to use. The advantage of the nomograms are that they require only one serum concentration, are easy to interpret and require no specialised pharmacokinetic knowledge. Nevertheless, concerns have been raised about their reliability given the large interpatient variability in antibiotic pharmacokinetics and are no longer recommended by published guidelines. The linear regression methods, i.e. Sawchuk–Zaske and ALADDIN, require two serum concentrations after an antibiotic dose and do not utilise population data to assist in calculating the patients pharmacokinetic/pharmacodynamic indices. Utilising population data the Bayesian estimation procedures can calculate doses based on one serum concentration. They are currently the closest to an ideal solution for clinical use which can achieve a greater percentage of patients attaining target concentrations as compared to other methodologies [9, 20].

It is important to remember that the Bayesian estimation procedures are decision support programs and are not diagnostic tools. They allow the end user the flexibility to choose appropriate target parameters to tailor the recommendations to a patient. Therefore, they require skilled personnel, usually clinical pharmacists and or clinical pharmacologists, with an understanding of pharmacokinetics and pharmacodynamics to use and interpret the information. Additionally, it should be stressed the software is only as good as the data entered—if the time of administration of the drug or specimen collection is inaccurate, then erroneous results may occur.

Bayesian programs estimating antimicrobial AUC have been available for over 30 years, however, adoption of these programs into the clinical setting has been variable despite being recommend by published guidelines [14, 15, 25]. When implementing a Bayesian program a change in clinical practice may be required. It is important to select a program that supports the specific patient population being treated. Because of this one program may not be able to meet all the health service requirements and the limitations of the program should be carefully assessed before being adopted into clinical practice. It is also important to note that implementation may require a significant financial investment for health services. This may include the potential cost of purchasing the software, employment of clinicians who are experts in pharmacokinetics and pharmacodynamics and the support required for Information Technology. Although some programs might be available at no initial cost they may

not necessarily provide customer support, implementation and integration requirements for sites. Hence, it is important to consider the overall cost of implementation rather than the isolated purchase cost of the program.

In conclusion, Bayesian estimation procedures are decision support programs and should be used wherever feasible to optimise patient care in conjunction with pharmacokinetics and pharmacodynamics and clinical expertise. We encourage clinicians to carefully consider the benefits, limitations, and challenges of different methodologies of dose optimisation prior to implementation of a Bayesian program.

Acknowledgements The authors would like to express their sincere gratitude to the developers of the reviewed programs, for providing us with access to the required software and offering feedback on our analysis of the individual programs.

Funding No funding was received.

Conflicts of interest The authors declare that they have no conflict of interest.

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