Clinical toxicology

PROMOTION OF AN APPLIED PHARMACOKINETIC SOFTWARE, NAMED PHARMONITOR, DEVELOPED TO OPTIMIZE INDIVIDUAL DOSAGE REGIMEN THROUGH A NATIONAL QUALITY CONTROL PROGRAM

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Key words: software, therapeutic drug monitoring, pharmacokinetics, aminoglycosides

ABSTRACT

To improve the practice of therapeutic drug monitoring, the Belgian Health Authorities have decided to support the development of an upgraded version of a pharmacokinetic program, so-called PharMonitor 1.0.0. Based on the Sawchuk-Zaske method, this software is a valuable and user-friendly tool for individually adjusting dosage regimens of aminoglycosides. It allows maximal speed, flexibility, reliability and optimal traceability. Moreover, the software is easily customized according to the user's selection (language, concentration units, drug target ranges, creatinine clearance, ...). Reports can be generated in PDF format after appropriate validation. The software can be connected to most laboratory information systems. Additional applications should be developed on PharMonitor 1.0.0. (other classes of drugs, Bayesian approach, ...). Once freely distributed to all Belgian laboratories, this software is expected to reduce the variability observed through external quality assessment schemes (EQAS), in the interpretation of drug concentrations.

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INTRODUCTION

For many years, selecting the appropriate drug has been the cornerstone of the therapeutic strategy. However, over the last decade, there is evidence that determining the correct dosage regimen (i.e. dose and interval of administration) is at least of the same importance in maximizing successful outcome (1-4). The concept of personalized medicine is becoming a reality, through therapeutic drug monitoring (TDM), applied pharmacokinetics (PK), pharmacogenetics, etc...

To design an optimal dosage regimen, the knowledge of data such as route, dose, rate and interval of administration, and the accurate estimation of the drug PK behavior need first to be considered when

performing TDM. While care units usually have to face logistic difficulties in providing accurate drug dosage information (e.g. sampling times, dose amount or changes in dose), it is challenging for laboratories to provide correct interpretation of drug concentrations with consistent dosage recommendations based on PK calculations. In Belgium, results from the external quality assessment scheme (EQAS) organised by the Belgian Health Authorities confirm the lack of consistency in the drug dosage interpretation among laboratories, even though inter-laboratory and inter-method assessment displays good performances in the analytical results (coefficient of variation < 10 %). These data strongly suggest the need for a promotion of a PK-based dosing method dedicated to the TDM of aminoglycosides, serving as primary class of drugs tested.

To improve the practice of TDM, the Scientific Institute of Public Health (Institut Scientifique de Santé Publique-Wetenschappelijk Instituut Volksgezondheid or ISP-WIV) decided to support the development of an improved version of a PK software, so-called PharMonitor (5). The ultimate objective is to freely distribute such software to all Belgian laboratories involved in TDM, and to provide assistance to clinical biologists in the interpretation of analytical and clinical data (e.g. dose, interval of administration, sampling times, serum drug levels, kidney function, ...), and in designing optimal dosage regimen of drugs. Progress in dosage interpretation reached with such tool could be further assessed through EQAS (quality controls including case reports) used as efficiency indicators.

MATERIAL AND METHODS

Computational method

Due to the wide interindividual variability in the aminoglycoside PK, various PK-based dosing methods have been reported over the last 25 years to individualize their dosage regimen (6). Among these methods, the non-Bayesian least-square approach has the distinctive advantage to not require knowledge of the PK parameter distribution in the population (6, 7). Initially described by Sawchuk and Zaske (8, 9), this method was shown to be robust; it has been widely used and validated in various populations, including patients with extreme PK parameter values (8, 10-12). In addition, the minimal number of required time points makes this approach easy to implement in clinical practice; at least two blood samples have to be drawn during the elimination phase to reliably assess the drug PK.

The Sawchuk-Zaske method is based on a one-compartment model with first-order elimination. It provides a clinically useful framework for estimating the individual concentration-time curve with the resulting PK parameters (Equations 1-3):

$$t_{1/2} = \frac{\ln(2)}{k_e} \quad \text{(Equation 1)}$$

$$Vd = \frac{K}{k_e} \bullet \frac{(1 - e^{-k_e \bullet t_{inf}})}{(C_{max} - C_0 \bullet e^{-k_e \bullet t_{inf}})} \quad \text{(Equation 2)}$$

$$CL = Vd \bullet k_e \quad \text{(Equation 3)}$$

where $t_{1/2}$ is the elimination half-life (h), k_e is the elimination rate constant (h^{-1}), Vd is the volume of distribution (L), K is the infusion rate (mg/h), t_{inf} is the infusion duration (h), C_{max} is the maximal concentration extrapolated at the end of infusion (mg/L), C_0 is the minimal concentration obtained from the previous dosage regimen (mg/L), and CL is the total body clearance (L/h).

From these individual PK parameters, the approach allows the estimation of the dosage regimen which is required to obtain the target peak and trough concentrations (Equations 4 and 5):

$$\tau = \frac{-1}{k_e} \bullet \ln\left(\frac{C_{min\ target}}{C_{max\ target}}\right) + t_{inf} \quad \text{(Equation 4)}$$

$$Dose = t_{inf} \bullet C_{max\ target} \bullet Vd \bullet k_e \bullet \frac{(1 - e^{-k_e \bullet \tau})}{(1 - e^{-k_e \bullet t_{inf}})} \quad \text{(Equation 5)}$$

where τ is the interval of administration (h), $C_{min\ target}$ is the target minimal concentration (mg/L) and $C_{max\ target}$ is the target maximal concentration (mg/L); dose is expressed in mg.

A more practical and convenient dosage regimen (i.e. realistic and easier to apply in clinical practice) will be simulated using the Equations 6 and 7:

$$C_{max} = \frac{K_{desired}}{Vd \bullet k_e} \bullet \frac{(1 - e^{-k_e \bullet t_{inf}})}{(1 - e^{-k_e \bullet \tau_{desired}})} \quad \text{(Equation 6)}$$

$$C_{min} = C_{max} \bullet e^{-k_e \bullet (\tau_{desired} - t_{inf})} \quad \text{(Equation 7)}$$

where $K_{desired}$ and $\tau_{desired}$ are the desired infusion rate (mg/h) and interval of administration (h), respectively.

The Sawchuk-Zaske method allows designing optimal dosage regimen during any dosing interval taking into account the previous PK of the patient. In the

Equation 2, while C_0 will be equal to zero for a first drug administration, it will be equal, at steady state, to C_{min} of the current dosage regimen, obtained by extrapolation at the end of the interval of administration.

Hardware/software specifications

PharMonitor 1.0.0. has been written for a Windows environment; it is compatible for Windows 32 bits (98/NT/2000/XP/Vista). Minimal XGA (1024x768) resolution is recommended. The software has been developed in an "open" structure, in order to easily accommodate improvements and further developments.

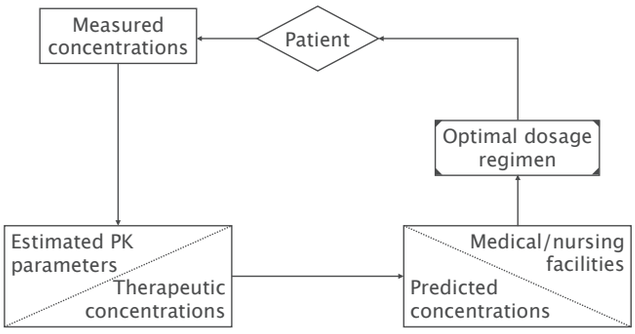

Figure 1. *Strategic approach of the PharMonitor software for individually adjusting the dosage regimen of aminoglycosides*

RESULTS

PharMonitor 1.0.0. is a PK software based on the Sawchuk-Zaske approach. It has been designed to estimate individual PK parameters and to predict the dosage regimen needed to reach the clinical target levels. It allows to users making quantitative recommendations with a maximal precision through quick dosage adjustments. Figure 1 displays the rationale behind the software. Minimum weighted squared regression is used to fit the data; the resulting line is used to graph the individual concentration-time curve.

Moreover, when encoding biometric and biochemical data, the creatinine clearance is automatically calculated based on the Cockcroft-Gault (13) or the simplified MDRD (14) equation, according to the user selection for adult patients, and based on the Schwartz equation (15), for children. The efficacy index AUIC (area under the inhibitory curve) is similarly computed, as far as the MIC (minimal inhibitory concentration) is provided (16).

Developed in a familiar spreadsheet environment, as displayed in Figure 2, PharMonitor 1.0.0. has the advantage to be a user-friendly tool for the analyses. Because the software has to be used in routine clinics, it has been conceived to ensure:

- maximal speed: estimation of the individual PK parameters and the optimal dosage regimen takes < 5 minutes;
- flexibility: data may be easily added, deleted or recalled at any stage of an analysis;
- optimal traceability: all PK analyses and results are referenced with the user identification and the date of encoding and/or modification.

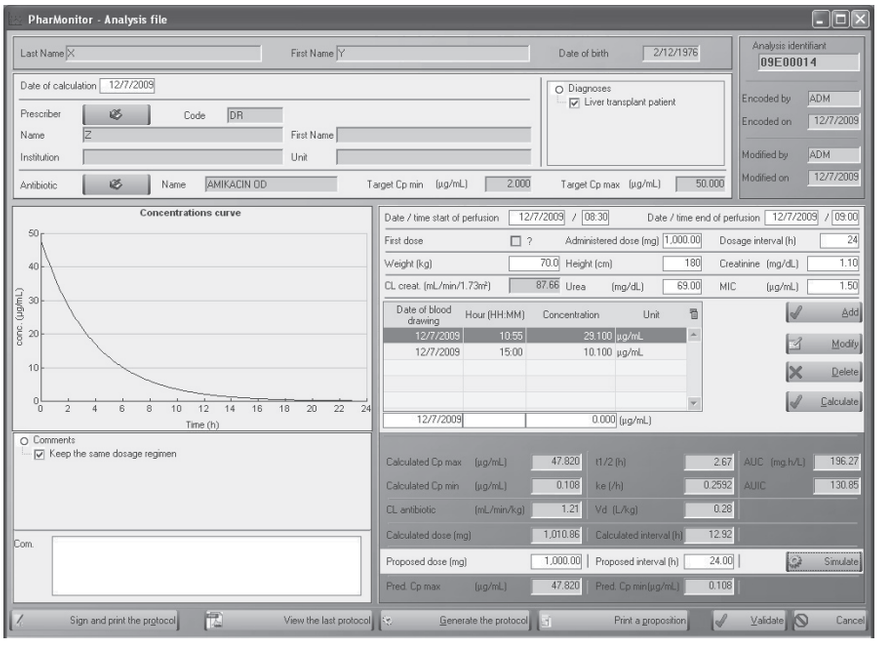

Figure 2.
Print screen from the calculation sheet of PharMonitor 1.0.0., indicating:

(a) patient and treatment information (age, body weight, size, kidney function, name of drug, ...), actual dosage regimen (dose, interval of administration), times of blood drawing and respective drug concentrations;
(b) pharmacokinetic (PK) computation, concentration versus time PK profile, creatinine clearance and area under the inhibitory curve (AUIC);
(c) dosing recommendations with predicted concentrations

- customization according to the laboratory standards: units (mg/dL, mg/L, g/L or µmol/L), language (English, French or Dutch), target drug concentrations (peak or trough concentrations), personalized report including the logo of the laboratory, the numerical identification codes for patients or analyses,...

In addition, interpretation of results and dosage advices can be provided at the end of the PK analysis. A report in PDF format will be generated once the protocol has been validated by the clinical biologist. The report actually includes information about the current treatment of the patient, the analytical and PK results, and the dosage regimen recommendations. Because the software can be connected to the most laboratory information systems (LIS), reports can be electronically sent to the requesting clinicians as rapidly as possible.

Technical facilities as complete printing report, online help and warning messages are also available.

DISCUSSION

PharMonitor 1.0.0. is an upgraded PK software providing a reliable and practical approach in optimizing the dosage regimen of drugs such as aminoglycosides. It has been designed to assist clinical biologists in the drug dosage adjustment and to help them for decision-making, taking into account the current clinical constraints of efficacy and toxicity. Use of such software should ensure therefore a safer, more rationale and cost-effective use of drugs. Also, once freely distributed by the ISP-WIV to all Belgian laboratories, one could expect an improvement in the consensus or agreement reached among laboratories, for the antibiotic dosing interpretation. An example of high discrepancy in the concentration interpretation could be illustrated by the simple definition of the peak concentration. The term "peak concentration" is frequently cited in the literature, but rarely clearly defined. It could correspond (i) to the extrapolated value obtained at the end of the infusion time (T_0) from a one-compartment model, (ii) to the true concentration obtained at T_0, or extrapolated from a two-compartment model, or (iii) to the current blood sampling value (i.e. corresponding to a standard blood drawing for instance 1 h after the end of infusion). All values may be dramatically different, causing some possible misinterpretation. An other example of misinterpretation could result from variable and unusual blood sampling times, possibly due to the unavailability of the nursing staff at a particular moment. The interpretation of concentrations corresponding to "unusual" timing can only be reached through the use of a PK model, allowing a wider flexibility to the nursing staff, provided they mention the exact blood sampling times.

Based on the Sawchuk-Zaske method, PharMonitor 1.0.0. has the advantage to directly assess doses and intervals of administration which are compatible with the nursing or medical staff. In addition, it allows designing optimal dosage regimen for steady state patients from only two blood samples drawn at convenient times for the nursing personnel.(i.e. just before infusion and after the end of infusion in the post-distributive phase). The predictive performances of the software have previously been reported (5).

The main options of the software includes: (i) analysis of the drug PK from dosing and sampling history; (ii) determination of the optimal drug dosage regimen; (iii) advices for the future dosage regimen; (iv) determination of the kidney function; (v) generation of the report in a PDF format including results and recommendations. Moreover, PharMonitor 1.0.0. can be connected to the most LIS, so that the workflow can be streamlined and the validated protocols can be electronically sent to care units.

Further versions of PharMonitor should integrate new methodological and statistical tools. More complex PK models, such as Bayesian approach, will be integrated into the software, as well as the optimal sampling strategy based on the D-optimality theory (17). The rationale behind this strategy actually is to select the sampling times that will lead to model parameter estimates with the smallest possible joint confidence regions (18). Three-compartment models will not be considered, since one and two-compartment models both describe the most clinically relevant portion of the PK behavior of most drugs. In addition, the PharMonitor use will be extended to other classes of drugs, like immunosuppressive agents (i.e. mycophenolate acid, tacrolimus) and ß-lactams (e.g. piperacillin, ceftazidime, cefepime, meropenem) for which a full population PK analysis has been performed. Moreover, rational dosage regimen for both concentration- and time-dependent antibiotic will be designed using the appropriate efficacy index (Equations 8-10) (8, 16). While the ratio of maximal concentration to minimal inhibitory concentration (MIC) of the infecting pathogen (C_{max}/MIC) and AUIC are believed to better predict the therapeutic outcome for aminoglycosides, the percentage of the dosing interval with concentrations exceeding the MIC of the infecting pathogen (T [%]

>MIC) is considered to be the most relevant index indicating the β-lactam efficacy (1-4, 19-21).

$$\frac{C_{max}}{MIC} = \frac{Dose}{t_{inf} \bullet k_e \bullet Vd \bullet MIC} \bullet \left(\frac{1 - e^{-k_e \bullet t_{inf}}}{1 - e^{-k_e \bullet \tau}} \right) \quad \text{(Equation 8)}$$

$$T[\%] > MIC = \ln\left(\frac{Dose}{Vd \bullet MIC} \right) \bullet \frac{t_{1/2}}{0.693} \bullet \frac{100}{\tau} \quad \text{(Equation 9)}$$

$$\frac{UC_{24}}{MIC} = \frac{Dose}{Vd \bullet MIC} \bullet \frac{t_{1/2}}{0.693} \bullet \frac{24}{\tau} \quad \text{(Equation 10)}$$

The PharMonitor application could also serve as a platform to interpret other xenobiotics, such as ethanol in forensic or drug-driving areas of expertise, based on Belgian legislation recommendations.

In conclusion, PharMonitor 1.0.0. should be considered as a practical and valuable tool for individually adjusting dosage regimen of aminoglycosides. At our institution, clinical experience highlights the importance of a computer-assisted TDM in the optimization of the intra-hospital use of drugs. The software is supported by the Belgian Scientific Institute of Public Health, which provides freely distribution, training and technical support to all Belgian laboratories, in order to improve the TDM practice with consecutive impact in public health. Future challenge is to clearly establish therapeutic ranges to optimally standardize interpretation of drug therapies.

Acknowledgments: The development of PharMonitor 1.0.0 has been possible thanks to a grant from the ISP-WIV (Institut Scientifique de Santé Publique-Wetenschappelijk Instituut Volksgezondheid).

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