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Development of a Smart Phone application prototype to individualize antibiotic dosing in critically ill patients based on the results of population pharmacokinetic models and Monte Carlo simulations

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ABSTRACT/REVISED

Objectives: Currently available smartphone technology can help facilitate mobile computing at the point of care. The objective of this study was to develop the prototype of an application for mobile devices that will provide individual dosing recommendations based on Probabilities of Target Attainment (PTA) for several antibiotics. Here the example of meropenem (MER) is presented.
Methods: Population pharmacokinetic (popPK) model for MER in critically ill patients is used to estimate PTAs for 5000 virtual patients per simulation. The model and conditions are coded into Rapporter, the template based on-line application for the R software environment for statistical computing and graphics. PTAs for short, extended, and continuous infusion regimens for the target ƒT>MIC of 40% for MICs up to 32 µg/ml in serum are established assuming 2 to 15% protein binding and lognormal distribution for all pharmacokinetic parameters.
Results: An easy to use, single html page is produced that is compatible with modern browsers used on mobile devices. The user provides patient demographic and laboratory information via this user friendly interface in conventional units, which is then passed through the template of conditions in Rapporter. After the computation of PTAs for the candidate dosing strategy the background information with supporting evidence, estimated pharmacokinetic parameters, summary of patient demographic information, and the chart for PTAs at doubling MIC distributions will be displayed in a standard pdf format. PTAs of > 90% are conveniently highlighted at each MIC and the explanation of the results in a concise manner is provided.
Conclusions: The development of this cross-platform application provides the foundations for a multi-model based, point of care clinical decision support tool on mobile devices for clinicians interested in optimizing antimicrobial therapy. This system can be used to improve antibiotic dosing practices at the bedside via the utilization of modern principles of antimicrobial pharmacodynamics, popPK model based approach and Monte Carlo simulation.

INTRODUCTION

In the past several years, adaptation of the use of mobile devices by health care professionals has become increasingly more common[2]. Tablets, iPad®s and smartphones are relatively new technologies that combine mobile telecommunications and data processing in a devices that can facilitate mobile computing at the point of care. The availability of these devices enable clinicians to have access to several other technologies at the point of care, including electronic medical records, hospital information systems, and clinical decision support systems. This recently observed increased adoption of mobile devices by health care professionals demonstrates the invaluable opportunity for improved communications at the point of care anywhere at any time. Based on a recent systematic review of the literature, the majority of applications for health care professionals focus on the diagnosis of diseases, followed by medical calculators and drug reference resources[3]. Drug reference resources generally provide information on the pharmacology, dosing, dosage form, drug interactions and the contraindications associated with the use of the agents. The Hopkins Antibiotic Guide and the Sanford Guide both have been available for many years now, with sections focusing on the dosing of antibiotics[4,5]. Neither of these two popular resources provide drug dosing information based on the results of high quality popPK models. Other software products such as RightDose® and MW/PHARM® capable of incorporating popPK models and covariate relationship into patient specific dosing recommendations are not available for mobile platforms. They also do not provide the opportunity to evaluate different dosage regimens for probabilities of target attainment based on Monte Carlo simulation. As mobile devices become more and more popular, transition of the free-standing software to a web – based application is likely inevitable. Virtually all available devices have the option to view websites, with some having significantly better aesthetic appearance compared to others[6]. In this experiment, we report on the development of a multi-platform, web-based clinical application equipped to provide optimum antibiotic dosing information via the use of population pharmacokinetic models and Bayesian adaptive feedback or Monte Carlo simulation for critically ill patients at the point of care.

METHODS

Monte Carlo simulation and the pharmacodynamic target

- 5000 trial Monte Carlo simulation (R software environment for statistical computing via Rapporter).[1,7]
  - Elimination rate constant estimates from the central compartment are based on using the explanatory variable of CrCl and the inter individual variability (IIV) identified in the model.
  - Volume of the central compartment is estimated as a function of the actual or adjusted body weight and the IIV identified in the model.
  - Inter-compartmental transfer rate constants are simulated using the mean and standard deviation values identified in the model.
  - All pharmacokinetic parameter estimates are assumed to follow lognormal distribution, with protein binding set at 2 to 15%.
  - Two compartment model with constant intravenous input and first order output is used to estimate concentration – time profiles for each simulated patient at the increments of 1/48th of the dosing interval and after the fourth dose.
  - PK/PD Index of the ƒT>MIC of 40% is utilized as the goal of evaluation to establish the PTA by calculating the percentage of patients likely to achieve the pharmacodynamic endpoint at each MIC.

Technology overview

- Using any of the popular devices and browsers [1] all parameters passed to Optimum Dosing Strategies (ODS) website [2] are seamlessly transmitted to Rapporter servers over a secure channel for evaluation.
- The channel is backed up by a content delivery network [3] that is also speeding up connection as well as making it possible to provide high availability for ODS users.
- The cluster of webservers [4] process the queries and read the required models and programs to memory from the distributed system of databases [5] to be passed along to the R [6] workers.
- The computations are run in a secured and stateless R environment so that no sensitive information would be stored for future R sessions. The statistical tasks will use any of the numerous, user contributed packages found on CRAN, and the templates can call even OpenBUGS [7] as a Bayesian interface.
- The results are returned in Pandoc's markdown format [8] that could be transformed to any popular document format – along with the generated plots in the analysis.

Figure 1. Graphical overview of the technology used to generate the reports

RESULTS

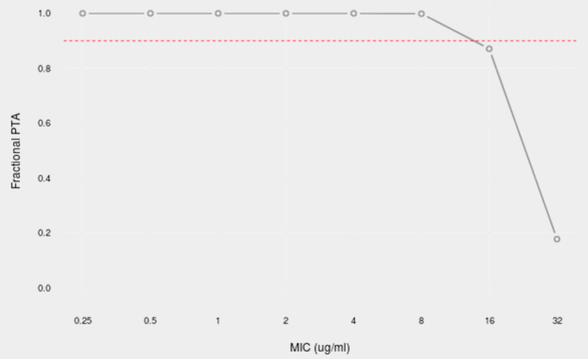

Figure 2. Graphical output for Probabilities of Target Attainment

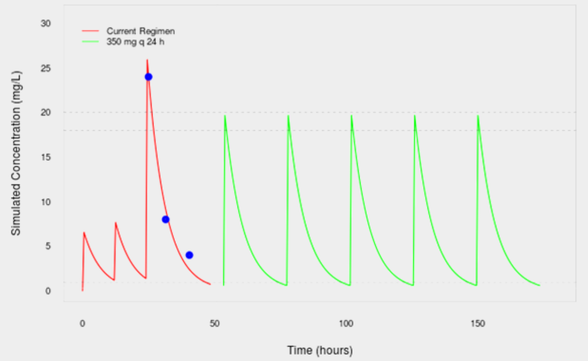

Figure 3. Graphical output for a revised dosing regimen via Bayesian adaptive feedback

CONCLUSION

- The development of this cross-platform application provides the foundations for a multi-model based, point of care clinical decision support tool on mobile devices for clinicians interested in optimizing anti-infective therapy.
- This system can be used to improve antibiotic dosing practices at the bedside via the utilization of modern principles of antimicrobial pharmacodynamics, popPK model based approach and Monte Carlo simulation.
- Subsequent development and inclusion of several other antibiotics such as the aminoglycosides, cefepime, ceftazidime, ceftriaxone, ciprofloxacin, daptomycin, doripenem, fluconazole, imipenem, levofloxacin, meropenem, piperacillin and tazobactam, tigecycline, and vancomycin led to the development of ID - ODS®, a web - based clinical decision support tool used to individualize antimicrobial therapy.

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