Louvain centre for Toxicology and Applied Pharmacology

Therapeutic drug monitoring:
A multidisciplinary approach to reach personalized medicine

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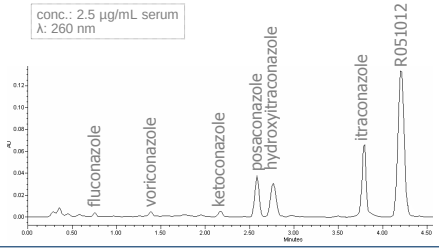
Analytics

FIG.1. UPLC-UV chromatogram of 6 antifungals



Since therapeutic drug monitoring (TDM) becomes an integral part of the patient management, our centre needs to remain at the cutting edge of analytical techniques developments, in terms of sensitivity, specificity and validation process (UPLC, LC-MSMS, etc…) for number of drugs:

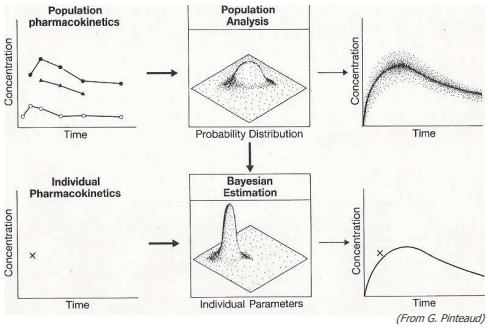
e.g. immunosuppressive agents, antibiotics, antifungals, cytotoxic drugs, in different biological matrices (serum, blood, tissues, lymphocytes, …).

Pharmacometrics

Pharmacometrics will quantify all parameters involved in PK-PD relationship. To achieve optimal, cost-effective and personalized TDM, the understanding of the drug pharmacokinetics (PK), pharmacogenetics (PG) and pharmacodynamics (PD) is mandatory. In our centre, population PK (popPK) and Bayesian modeling, along with optimal sampling strategy, are applied. While population approach enables to account for sources of interindividual variability, such as genetic factors, demographic data and pathophysiological parameters, optimal sampling strategy provides an efficient basis for future PK-PD investigations. Current therapeutic applications include immuno-suppressive agents in transplant patients and antibiotics in critically ill septic patients.

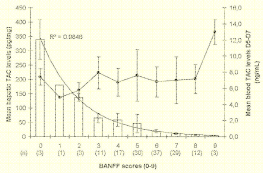
Some softwares used in our centre: JMP [statistics]; WinNonlin [PK]; NONMEM, PsN, Xpose4, WinBUGS [popPK]; PopED, WinPOPT [optimal design]

FIG.2. Population PK modeling with optimal sampling strategy for Bayesian estimation



(From G. Pinteaud)

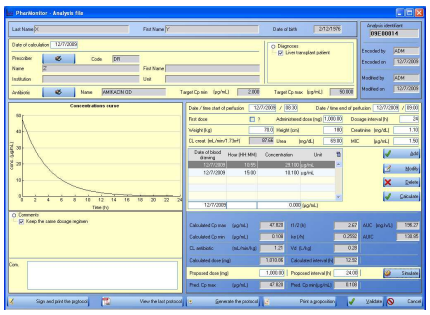
FIG.3. Relationship between tissue or blood tacrolimus conc. and rejection scores (BANFF)



Choice of the target biological matrix:
For some drugs, an improvement in the relation PK-PD may be reached by measuring or predicting drug concentrations in alternative target matrices such as tissues or lymphocytes.

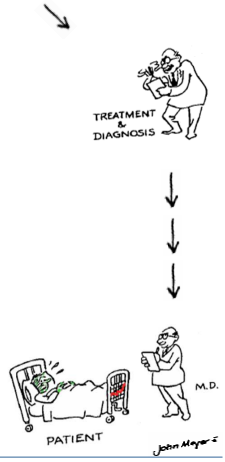
Expert software

FIG.4. Calculation sheet of PharMonitor 1.0.0.

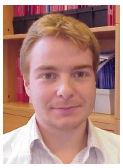


In order to improve the TDM practice, the Scientific Institute of Public Health in Belgium (ISP/WIV) supports the development of an upgraded version of a software, so-called PharMonitor. Based on the Sawchuk-Zaske method, the software is a valuable and user-friendly tool for individually adjusting dosage regimens of aminoglycosides. It is easily customized according to the user's selection (language, concentration units, drug target ranges, creatinine clearance, …) and can be connected to most laboratory information systems.

Further versions of PharMonitor should integrate new methodological and statistical tools, such as popPK with Bayesian approach. In addition, the software 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 popPK analysis has been performed. Moreover, rational dosage regimen for both concentration- and time-dependent antibiotics will be designed using the appropriate efficacy index.




Prof. P. Wallemacq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