Dosing software to optimize antimicrobial therapy based on TDM

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Scope of the lecture:

The most often applied TDM strategy when a patient given an aminoglycoside, is to sample at the end of an infusion and just before the next one. However, there are major limitations with such an approach: (i) no intervention in the choice of the starting dose; (ii) loss of time while waiting for the presumed steady-state; (iii) the necessity of respecting strict sampling times to interpret concentrations and (iv) nothing more than vague recommendations for a decrease or increase in the dose. In this context, strategies where aminoglycosides dosing is preceded and immediately followed by individualized PK-PD monitoring are more powerful.
In this talk, the speaker demonstrates the feasibility of integrating a PK software dedicated to aminoglycosides monitoring and illustrates the added-value of such a system to improve patient care.

Learning objectives:

1. To better understand the PK/PD relationships of aminoglycosides
2. To know the different PK tools available for the dose adjustment of these drugs
3. To understand the benefits of an effective connexion of PK tools at the clinical interface

Extended abstract:

Aminoglycosides are a typical candidate to discuss the feasibility, the utility and the obligation of using modelling for individual dose adjustments based on PK/PD modelling. First, the so-called “targets of concentrations” are defined. Thus, according to findings about aminoglycosides PK-PD relationships, it is consensually recognized that administration should aim to obtain (i) the highest peaks to maximise concentration-dependent killing, post-antibiotic effect and to prevent adaptive resistances, also (ii) the “drug free” periods

within the administration interval to avoid drug accumulation linked to the well-known nephrotoxicity and ototoxicity.

In this context, strategies where aminoglycosides dosing are preceded and immediately followed by individualized pharmacokinetic monitoring are powerful. They can ensure that both the Cmax/MIC targets are achieved early in therapy and that the "safe" trough concentrations are kept after several infusions. However, even though the added-value of a PK-based dose adjustment strategy might be obvious, numerous questions remain concerning the organization of such a service. Numerous PK or PK/PD software applications are available and have been used, but not all of them have been developed with the aim of being easily used for a routine activity. Among others, MW/PHARM or extensions of the USC*PACK clinical PC programs belong to the category of the ready-to-use tools especially dedicated to clinical use to guide and adjust therapy: they allow estimation of pharmacokinetic parameters on the basis of medication history, can take into account a varying status of the patient with respect, for instance, to body weight and kidney function, optionally using a Bayesian procedure, and include curve-fitting facilities. Using such programs, one can define desired target goals (Cmax, Cmin, length of infusion…). The option to run such a program off the shelf may be sufficient to start the activity, but using structural models of the program, one can also enter and store parameter values derived from one's own populations.

Ideally, a local study should be designed where a few patients are extensively sampled. Based on this database, tests have to be performed to evaluate the performances of the program. If the results are not satisfactory then, mean clearance, volume of distribution, the covariates influencing them have to be calculated and implemented into the program. Aminoglycosides represent the most favourable case to start out with, to build experience in developing PK models and MAP-BEs. Indeed, we are talking about drugs usually described by the simplest models, with CL/F and/or Vc/F variability that can be explained by simple covariates such as bodyweight or serum creatinine.

A lack of indubitable clinical-based evidence is often put forward as an argument when not confident in applying any kind of "PK dose adjustment". When focusing on antibiotic therapy, the objective end-points that have to be explored to evaluate the added-value of a "PK dose adjustment" strategy are: decreased durations of treatment, shortened lengths of hospitalization or reduced institutional expenditure. Some interesting results showing higher

antibiotic efficacy, shorter hospitalization, and reduced incidence of nephrotoxicity when practising a so-called PK dose adjustment have been reported. For example, a well-designed prospective concentration-controlled study was performed in 232 inpatients from four different hospitals .

To evaluate the impact on the dose adjustments of aminoglycosides when performed using Bayesian estimators, a local studies performed at the Limoges University Hospital (France). They roughly aimed at answering the following questions: When using MAP-BEs, do we propose any change in the dosage when a dose adjustment is requested? Do the clinicians respect our proposals? What are the predictive performances of the employed MAP-BEs? For this, a retrospective study over one year of activity was performed in patients given gentamicin and for which multiple dose adjustments were done by the Pharmacokinetic Unit. Briefly, in 134 hospitalized patients, when performing a first dose adjustment, an increase in the dose was proposed in about half of them, although more than 2/3's had been prescribed a dose around the consensually recommended 3mg/kg. At the next visit, the prescribed doses remained those previously recommended by the PK unit in more than 3/4's of the patients, which illustrated a good adherence by the clinicians. To estimate the predictive performance of the Bayesian estimation, patients with no significant change in their renal function (ie, creatinine clearance remaining stable) who came for a second dose adjustment and had been prescribed the dose proposed on their first visit were analyzed. Predictive performance of the MAP-BE was considered good if the dose did not need to be changed again, which was the situation in almost 80% of the cases.

Looking at the practice in the Limoges Hospital: Bayesian forecasting is usually based on a peak level after the first dose is administered, followed by a second level 6-12 hours later. This service is available 6 days/week, and gives the pharmacologists access to all patient data (by electronic patient files) in addition to measured levels. In this 2000-bed hospital, about 1500 dose adjustments of aminoglycosides are performed per year (giving a written advised dosing strategy in the EPF) by an expert system combining both in-house, NPEM and NONMEM programs (https://pharmaco.chu-limoges.fr; accessed September 2017).

References:

Proost JH, Meijer DK. MW/Pharm, an integrated software package for drug dosage regimen calculation and therapeutic drug monitoring.Comput Biol Med. 1992 May;22(3):155-63.

Destache CJ, Meyer SK, Rowley KM. Does accepting pharmacokinetic recommendations impact hospitalization? A cost-benefit analysis. Ther Drug Monit. 1990 Sep;12(5):427-33.

Burton ME, Ash CL, Hill DP Jr, Handy T, Shepherd MD, Vasko MR. A controlled trial of the cost benefit of computerized bayesian aminoglycoside administration. Clin Pharmacol Ther. 1991 Jun;49(6):685-94.

van Lent-Evers NA, Mathôt RA, Geus WP, van Hout BA, Vinks AA. Impact of goal-oriented and model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: a cost-effectiveness analysis.Ther Drug Monit. 1999 Feb;21(1):63-73.

Bartal C, Danon A, Schlaeffer F, Reisenberg K, Alkan M, Smoliakov R, Sidi A, Almog Y. Pharmacokinetic dosing of aminoglycosides: a controlled trial.Am J Med. 2003 Feb 15;114(3):194-8.