

Clinical Pharmacology and how to use successful drugs even better!

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In October 2015 we celebrated the 25th anniversary of the International Association for Therapeutic Drug Monitoring and Clinical Toxicology. During the congress of IATDMCT in Rotterdam (www.iatdmct2015.org) new developments in individualizing pharmacotherapy were presented. In the early days of IATDMCT the focus was largely on development of analytical techniques, but now there is a strong tendency to aim for clinical implementation of new methods and new dosing strategies. Studies on analytical validity are now followed by studies on clinical validity and on clinical utility. It is not enough to be able to measure compounds with sensitive and specific assays. We need to show the correlations between drug exposure and clinical outcomes, and we also need to show how clinical outcomes improve if our dosing strategies are based on these measurements.

It also was clear during the meeting that improvements in the care for our patients will not only come from the introduction of new drugs. There is still a lot of room for improvement by learning to use the drugs we already have in a better way. It is extremely important that we constantly ask ourselves why we do things in a certain way. Do accept that our current practice is not always based on solid evidence, but do realize that an important proportion of our daily decisions is based on copying the strategies of our peers or of our teachers.

In my work as a transplant nephrologist I see large numbers of patients on maintenance treatment with immunosuppressive drugs. Tacrolimus has become the most frequently used calcineurin inhibitor to prevent rejection

after solid organ transplantation. Considering the almost empty industry pipeline it is likely that tacrolimus will maintain its position as the main immunosuppressive drug for the next decade, and beyond. Current practice is to start tacrolimus on the day of transplantation in a standard dose, based on bodyweight and adjust the dose thereafter, with therapeutic drug monitoring (TDM). Pre-dose tacrolimus concentrations measured in whole blood are the norm.

For the initiation of tacrolimus treatment the CYP3A5 genotype can now be taken into account, and algorithms to individualize the starting dose have been developed. Reaching target levels after the transplant procedure is considered crucial, to prevent the occurrence of early acute rejection of the transplanted organ. Genotyping patients can now be done at low cost in a short period of time. CPIC guidelines already propose specific dosing recommendations related to different CYP3A5 genotypes (1). But, the authors were careful enough to mention that their recommendations are for patients for whom a CYP3A5 genotyping result is available already (1). The prospective clinical trials have not yet shown that CYP3A5 genotype guided dosing does improve clinical outcomes such as incidence of rejection, or renal function (2). Therefore genotyping patients with the aim to adjust the tacrolimus starting dose is not widely accepted.

After the transplantation there is an extensive monitoring of tacrolimus concentrations, and in general physicians and surgeons make their own decisions on how to adjust the dose. This rather intuitive dose adaptation approach

often does not take into account whether or not patients are in a steady state situation, and time-dependent changes in the pharmacokinetics are not taken into account. With computer software, dosing schemes can be optimized to achieve a selected target concentration for each patient based on their demographic and clinical characteristics and, if available, on previously measured drug concentrations (3). Størset et al showed that the proportion of tacrolimus concentrations per patient within the target range was significantly higher with computerized dosing than with conventional dosing. In this small randomized trial there was even a hint to improved clinical outcome (3). We can do better, and adjusting doses based on population pharmacokinetic models will assist the physician in achieving the best available care for each individual patient.

As mentioned already, the preferred matrix for measurement of tacrolimus is whole blood. However, whole blood is full of erythrocytes, and these cells are known to bind tacrolimus. Evidently erythrocytes do not contribute to the immunosuppressive effect of tacrolimus. It would make sense to measure tacrolimus concentrations at the site of its biologic activity. Isolating peripheral blood mononuclear cells (PBMCs), and measurement of the intracellular tacrolimus concentrations in these PBMCs may better represent the pharmacodynamic effect of this immunosuppressive drug (4). The polymorphically-expressed ATP-binding cassette (ABC) transporter proteins, in particular ABCB1 and ABCC2, are likely to play a role in the distribution of drugs in plasma and intracellular compartments (5). ABCB1 gene polymorphisms

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also appear to be related to the risk of developing calcineurin inhibitor-related nephrotoxicity. Studies are ongoing to evaluate the importance of gene polymorphisms in these transporter proteins. We are also exploring the relationship between intracellular and whole blood tacrolimus concentrations, the influence of gene polymorphisms on the ratio between the two, and on correlations with clinical outcome measures (5).

Trough level measurement is what is routinely done for TDM. Whether or not area-under-concentration-versus-time curves (AUC) would give a better assessment of drug exposure is unclear. In a busy transplant program AUC measurements may be logistically challenging. To facilitate blood sampling new techniques have been developed, including dried blood spots.

The dried blood spot method would allow patients to collect multiple samples over a 12-hour dosing interval. This is both convenient for the patient and for the outpatient clinic, where nursing staff would not be able to make AUCs for large numbers of patients simultaneously.

Finally, in patients on a stable tacrolimus dose sometimes fluctuations in tacrolimus concentrations are observed, while in other patients the tacrolimus exposure seems more stable. This intra-patient variability in tacrolimus exposure has been shown to predict poor outcome, and interventions to reduce this variability have been developed. Physicians should discuss adherence with patients in whom a high within-patient variability is observed (6). Several studies have shown that switching patients from a twice-

-daily to a once-daily tacrolimus formulation will reduce within-patient variability. This offers a relatively easy intervention, with potential high gain in graft survival.

The examples shown above illustrate that even for drugs that have run out of patent we should consider changing the ways we treat patients. Do not take old habits for granted. That we have always done it this way is a very poor rationale. New analytical methods, including mass-spectrometry, offer the possibility to measure drugs in matrices not considered feasible before. Bayesian dosing strategies can provide benefit to physicians who now apply the trial and error approach for TDM. And finally, dried blood spot assays will allow more extensive sampling strategies, that may benefit TDM as well.

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