CHAPTER 4.3 Therapeutic drug monitoring

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1 Introduction

Pharmacokinetic (PK) therapeutic drug monitoring (TDM) is defined as the measurement of drug concentrations in biological fluids to assess whether they correlate with the patients' clinical condition and whether the dosage or dosage intervals need to be changed. This is done to optimize the management of patients receiving drug therapy for the alleviation or prevention of disease [1]. Measurement of drug concentrations in whole blood, plasma or serum is the most obvious method [2].

PK TDM is the most commonly used form of drug monitoring in paediatric solid organ transplantation and stands for a concentration–time relationship. Within a dosing-interval one has to distinguish certain PK parameters (Figure 1), such as C_{max} (maximum concentration), T_{max} (time to maximum concentration) and C_0 (trough [predose] concentration). The area under the concentration–time curve (AUC) can be calculated by using the linear trapezoidal rule and reflects the total body drug exposure [3].

TDM is essential to optimise immunosuppressive therapy in paediatric kidney transplant patients. The main immunosuppressive agents, tacrolimus, cyclosporin A, mycophenolic acid (MPA), and everolimus have narrow therapeutic windows and significant variability in pharmacokinetics, especially when used together or with other drugs. TDM helps to achieve a good balance between efficacy and toxicity in this narrow therapeutic window (Figure 2). Drug-drug interactions (DDIs) between these agents and with other drugs can significantly affect their efficacy and safety, thereby affecting patient outcomes. This chapter provides an overview of TDM for these key immunosuppressants.

For the timing of TDM in children after kidney transplantation (KTx), see Chapter 4.2. In general, TDM is recommended early after initiation of therapy to rule out the possibility that a non-response is due to under-exposure. TDM may

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Figure 1 Pharmacokinetic parameters during a dosing interval. C_{max} maximum concentration, Tmax time to maximum drug concentration, C_o trough (predose) concentration

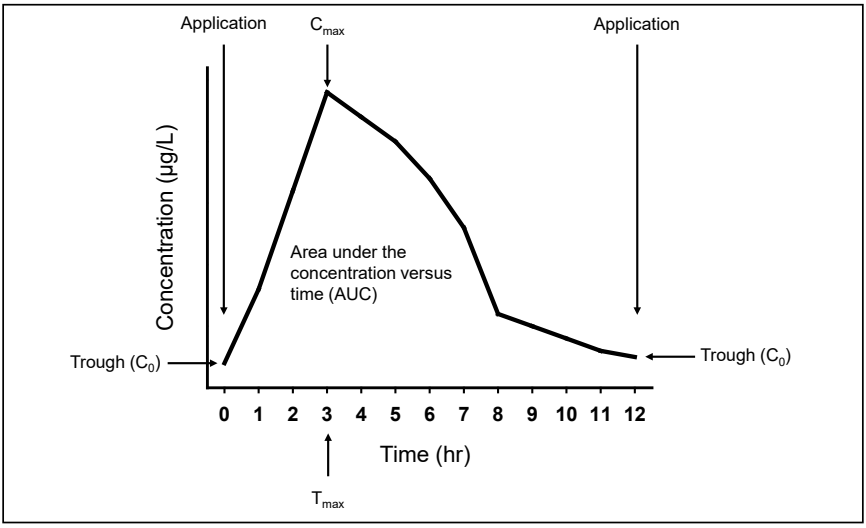
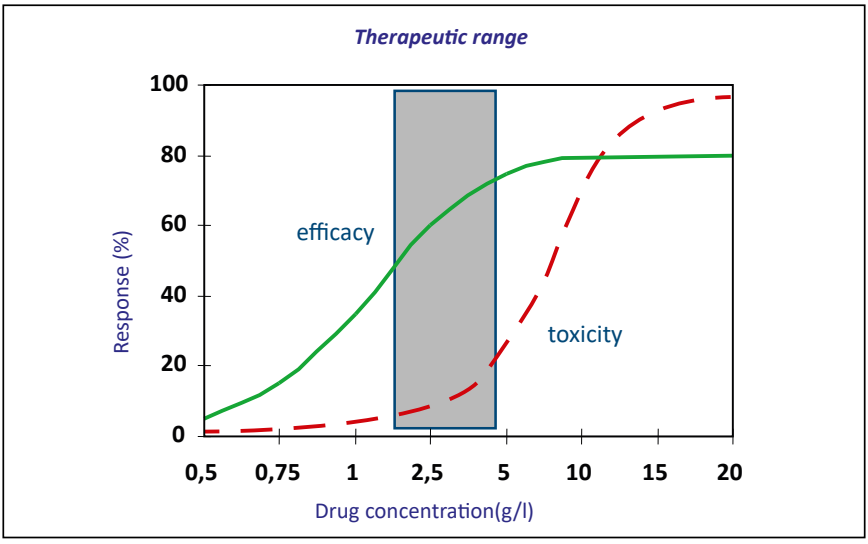


Figure 2 Balance between efficacy and toxicity showing the narrow therapeutic range. [Courtesy (and in honor of) V.W. Armstrong (†), Göttingen, Germany]



be useful in the setting of potential drug-related adverse events to verify an exposure that is well above the target range, which would allow dose reduction without the risk of loss of efficacy. TDM may also be useful after a change in therapy, especially with drugs that interact with the metabolism of the drug itself. In maintenance therapy, regular TDM at defined intervals can detect individual changes in the absorption and metabolism and thus facilitate dose adjustment.

2 Mycophenolic Acid (mycophenolate mofetil [MMF, CellCept©], mycophenolate sodium [EC-MPS, Myfortic©])

Mycophenolic acid (MPA) is the pharmacologically active moiety of MMF or EC-MPS formulations. Monitoring MPA exposure is complex due to high intra- and inter-individual variability. MPA underexposure is a serious concern as it increases the risk of graft rejection. Several factors influence MPA levels in children, including age, weight, albumin levels, and kidney function. The risk of underexposure is particularly high in young children due to their more rapid clearance and variable absorption of MMF. The MPA exposure that leads to overexposure is not well defined. Side effects may be more likely to correlate with free MPA exposure, which is difficult to measure.

Relying on predose level monitoring alone for MPA is less reliable than for other immunosuppressive agents (see below), because the predose level does not necessarily correlate with total body drug exposure (AUC). Therefore, calculation of an estimated MPA-AUC (eMPA-AUC) using a limited sampling strategy (LSS) is important to ensure adequate immunosuppressive efficacy.

To avoid underexposure, the following measures are recommended: (i) regular TDM (see also Chapter 4.2); (ii) dose adjustments: MMF doses should be individually adjusted based on TDM results. If necessary, an increase in the MMF dose may be considered; (iii) avoidance of drug interactions: The concomitant use of drugs that affect the pharmacokinetics of MPA should be closely monitored.

Algorithms for calculating MPA-AUC

MPA-AUC is considered the gold standard for monitoring MPA exposure, as it provides a reliable estimate of the immunosuppressive effect. However, in clinical practice, full AUC determination, which requires multiple blood samples over time, is rarely performed in clinical practise. Instead, abbreviated algo-

rithms are used to estimate the AUC based on a limited number of samples (see also Chapter 4.2).

Common algorithms include:

i. Bayesian pharmacokinetic models: These models are based on population data and use a limited number of sampling points to estimate the full AUC. They take into account individual pharmacokinetic parameters to allow for more precise dose adjustments. However, these estimates are difficult to develop and use, because they require specialised PK modelling software.
ii. Linear algorithm: A simpler approach is to use a linear model, where the AUC is estimated based on two or three sampling points (see also Chapter 4.2). In the case of co-medication with cyclosporin A, a significant pharmacokinetic interaction with MPA must be considered: Cyclosporin A inhibits the multidrug resistance protein 2 (MRP-2), which is responsible for the excretion of MPA glucuronide (MPAG), an inactive metabolite of MPA, into the bile. Inhibition of this transporter reduces the conversion of MPAG back to MPA in the intestine, thereby reducing MPA reabsorption and, hence, MPA exposure. This DDI results in an overall decrease in MPA-AUC and C_{max} and an increase in T_{max}. Therefore, it is mandatory to use different LSSs and algorithms to estimate MPA-AUC with or without cyclosporin A co-administration (see also Chapter 4.2).
iii. Predose level-based AUC estimates: Due to enterohepatic recirculation, which causes a secondary peak in the plasma MPA concentration between 6 and 12 h after oral intake, the term predose level should be used instead of the term trough level. The predose level alone does not provide a reliable AUC estimate [4].

MPA can also be given mycophenolate sodium. Compared with MMF, EC-MPS has a delayed absorption and therefore has a different PK profile. An LSS for EC-MPS requires more concentration measurements, including later time points, than those for MMF (see also Chapter 4.2).

Key Drug-Drug Interactions

- Cyclosporin A: see above.
- Tacrolimus: Unlike cyclosporine, tacrolimus has a less pronounced effect on the pharmacokinetics of MPA. It does not significantly interfere with the enterohepatic recirculation of MPA. As a result, MPA exposure tends to be higher when used in combination with tacrolimus. However, careful moni-

toring of MPA levels is still required, especially in the early post-transplant period.
- Proton Pump Inhibitors (PPIs): PPIs such as omeprazole may reduce the bioavailability of mycophenolate mofetil by affecting gastric pH. This interaction can lead to lower MPA levels, however, these changes are regarded to be small and not likely to have clinically major effects.

3 Tacrolimus

Tacrolimus is a calcineurin inhibitor metabolized via the CYP3A4 and CYP3A5 pathways. In young children, tacrolimus clearance is faster due to higher enzyme activity compared to older children and adults. This results in lower tacrolimus blood levels at the same dosage. Therefore, this patient group often requires higher doses per kilogram of body weight to achieve therapeutic target levels (see also Chapter 7.2), resulting in a lower concentration-to-dose (C/D) ratio in smaller children [5]. TDM is crucial to regularly monitor trough levels, to avoid both underexposure, which increases the risk of rejection, and overexposure, which is associated with toxicity. Intrapatient variability of tacrolimus trough levels over time is associated with adverse graft outcomes and can help to assess potential underexposure [5].

Key Drug-Drug Interactions
- CYP3A4 Inhibitors/Inducers: Tacrolimus levels are highly susceptible to drugs that inhibit or induce CYP3A4. For instance:
  - CYP3A4 inhibitors such as ketoconazole, diltiazem, and macrolide antibiotics (e.g., erythromycin) increase tacrolimus levels, potentially leading to toxicity (e.g., nephrotoxicity, neurotoxicity).
  - CYP3A4 inducers like rifampin, carbamazepine, and phenytoin reduce tacrolimus levels, increasing the risk of graft rejection.
- Calcium Channel Blockers (CCBs): The CCBs diltiazem and verapamil increase tacrolimus concentrations by inhibiting its metabolism. These interactions require dose adjustments and close TDM to prevent toxicity.

Drug interactions, particularly with CYP3A4 modulators, necessitate frequent monitoring, especially when new medications are introduced or discontinued.

4 Cyclopsorine A (Sandimmun optoral©)

Cyclosporine A, a calcineurin inhibitor, inhibits T-cell activation by blocking the transcription of IL-2. Cyclosporine A has complex pharmacokinetics and numerous drug interactions, making TDM critical. Like tacrolimus cyclosporine A is metabolized via the CYP3A4 and CYP3A5 pathways and displays the same DDIs.

Key Drug-Drug Interactions

- Everolimus: Cyclosporine A can increase blood levels of mTOR inhibitors like everolimus by interacting with CYP3A4, the enzyme responsible for their metabolism. This can lead to increased risk of toxicity. TDM is essential to manage the delicate balance between effective immunosuppression and adverse effects when combining these drugs.
- Statins: Cyclosporine A also interacts with statins, which are increasingly used to manage post-transplant dyslipidemia in children (see also Chapter 11.5). It inhibits the metabolism of statins, potentially increasing the risk of myopathy and rhabdomyolysis. This interaction requires careful monitoring of statin doses and potential dose reductions.

Variations in drug absorption and metabolism, as well as interactions with medications like statins and mTOR inhibitors, require regular monitoring and dose adjustments.

5 Everolimus (Certican®)

Everolimus is a mammalian target of rapamycin (mTOR) inhibitor and is extensively metabolized by CYP3A4 in the gut and liver. Due to its narrow therapeutic index and significant pharmacokinetic variability, therapeutic drug monitoring (TDM) is essential to optimize dosing, reduce toxicity, and minimize the risk of graft rejection.

The PK of everolimus differs significantly between children and adults due to developmental differences in drug absorption, distribution, metabolism, and excretion. Infants and young children exhibit faster drug clearance and require higher doses to achieve therapeutic levels. Factors such as age, body weight, genetic polymorphisms in drug-metabolizing enzymes (e.g., CYP3A4 and

CYP3A5), and concurrent use of other medications can greatly influence blood levels of this mTOR inhibitor.

TDM for everolimus is usually based on trough levels, which are measured just before the next dose. Trough levels provide a reliable estimate of the drug's steady-state concentration and are easier to obtain in clinical practice compared to full pharmacokinetic profiles.

Key Drug-Drug Interactions

- Cyclosporine A: see above.
- Tacrolimus: Tacrolimus, being less of a CYP3A4 inhibitor than cyclosporin A, has a milder impact on everolimus levels. Nonetheless, the combination of tacrolimus and everolimus still requires careful monitoring due to the potential for nephrotoxicity and other side effects.
- CYP3A4 Inhibitors and Inducers: Similar to tacrolimus and cyclosporine A, everolimus levels are influenced by CYP3A4 inhibitors and inducers. Medications such as azole antifungals and macrolide antibiotics can increase everolimus concentrations, while rifampin and antiepileptic drugs can reduce its levels. Close TDM is essential when these agents are used concurrently with everolimus.

TDM should be performed regularly, especially when combined with other CYP3A4 substrates or inhibitors. Monitoring helps optimize immunosuppression while minimizing the risk of adverse events.

6 Conclusion

Therapeutic drug monitoring plays a critical role in managing immunosuppressive therapy in transplant patients, particularly when multiple agents with significant drug-drug interactions are used. Mycophenolic acid, cyclosporine A, tacrolimus, and everolimus all have narrow therapeutic windows and are subject to complex pharmacokinetic interactions. Effective TDM ensures appropriate drug exposure, minimizes toxicity, and reduces the risk of graft rejection, ultimately improving patient outcomes.

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