Drug Dosing Adjustments in Patients Undergoing Continuous or Intermittent Renal Replacement Therapy

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Contents

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1 Introduction

Intermittent haemodialysis is the renal replacement therapy (RRT) of choice in patients with chronic kidney failure. Acute kidney injury (AKI) requiring continuous RRT (CRRT) occurs in about 5% of ICU patients. Underdosing as well as overdosing of drugs may have serious consequences. Drug dosing in these patients should therefore use an individualised approach to ensure desired concentrations are achieved to enable effective therapy and to minimise drug toxicity.

2 Continuous haemofiltration and continuous/intermittent renal replacement therapy

Continuous haemofiltration and haemodialysis remove solutes including drugs from patients by different mechanisms. Haemodialysis uses the principle of diffusion across a semi-permeable membrane to clear solutes from blood. Haemofiltration on the other hand uses convection, which is solute movement down a pressure gradient across the RRT filter (high pressure on patient's side), results rapid clearance of small and large molecules (>2,000 Da). As opposed to older methods of RRT the size of the solute molecule is of only minor significance in modern renal replacement therapies. Even molecules that are considered large for drugs, such as *vancomycin* (~1500 Da), are eliminated efficiently via haemofiltration and to a lesser extent by haemodialysis in the presence of high-flux filters.

In case of continuous venovenous haemodialysis (CVVHD) diffusion enables free (non-plasma protein bound) solute molecules to pass through the membrane resulting in a solute concentration in the dialysate is approximately the same as the free drug concentration in plasma. Therefore, doubling the dialysate flow rate can result in a doubling of the amount of eliminated solute. In the case of intermittent haemodialysis the much larger volumes of dialysate even in the presence of lower drug concentrations in the dialysate will results in high overall solute clearance.

In the case of continuous venovenous haemofiltration (CVVH) drug clearance can be underpredicted. Where a combined modality such as continuous venovenous haemodiafiltration (CVVHDF) is used, solute clearances can be even greater than in CVVH which typically has greater solute clearances than CVVHD.

For all types of RRT, the free drug (or solute) will be cleared across the filter meaning that highly protein bound drugs appear to have less drug clearance occurring than for drugs with low protein binding. Further, the longer the duration of RRT the greater the opportunity for drug clearance resulting in larger daily drug clearances where the same RRT intensity is used. Where RRT intensity is increased, for example, blood flow rate through the filter or ultrafiltration flow rate is increased, increased solute clearance can also be expected. It is the combination of RRT type (haemodialysis, haemofiltration, haemodiafiltration), duration (continuous or intermittent) and intensity that will define the total daily RRT drug clearance.

3 What drug dosage is suitable for every individual patient?

The following questions are to be answered and the predefined values for the parameters should be adapted before adjusting a drug dosage:

1. *Is currently maximal effectiveness essential, accepting a higher risk of undesired adverse reactions (e.g. antimicrobial therapy of sepsis would typically be suggested for therapy that ensures maximal effectiveness)?* In these cases a maximum dose should be used and calculated doses should be rounded up.
2. *Is it possible to start with low doses and monitor for therapeutic effects?* In these cases a minimum dose should be used and calculated doses should be rounded off.

3. *Which dialysis method will be used, what dialysate flow and/or ultrafiltration flow rates will be used?* Blood flow and ultrafiltration flow rate as well as the duration of RRT are significant factors in determining likely drug cleararance during RRT.
4. *What is the current level of endogenous renal function (creatinine clearance)?*
5. *What other factors are present that may alter the patient's dosing requirements?*

If the drug is not included in the database:

1. *What non-renally eliminated drug amount in normal renal function is assumed?* (Q_0- value: 100 % = 1.0) Q_0 is the fraction of the bioavailable dose that is eliminated extrarenally. [Dettli L. The kidney in pre-clinical and clinical pharmacokinetics. Jpn J Clin Pharmacol Ther 15:241-254]
2. *What is the percentage plasma protein binding of the drug in this type of patient* (100% = 1.0)?
3. *What is the volume of distribution* (Vd [l/kg])?
4. *What is the half life [h] in the presence of normal renal function is assumed*?

Expert reviews and product information leaflets of drugs do not, or only sparsely, contain data regarding dosage during CRRT. Advice for dosing in the context of impaired renal function and intermittent dialysis is more common. Dosing on basis of guidelines (e.g. the "Ulmer Liste", "Freiburger Liste", see further literature below) is required for clinical practice in the context of few alternative options. These guidelines are useful, but intrinsically flawed because they are unable to account for the variations in dialysate flow rate, blood flow rate, duration of dialysis, or residual renal function that may be present in patients and some drugs may not be listed because there are no relevant studies.

The common guideline of basing drug dosing during CRRT on a creatinine clearance (CreaCl) of 30ml/min, when no other data is available may be flawed for many drugs. Likewise the generalisation that only dose adjustment during RRT is only required for drugs, which are primarily excreted through the kidneys, is incorrect. With these challenges, published formulas for calculation of doses have been proposed but these are not widely used because they are difficult to integrate in the routine clinical practice because of their complexity. To address these daily clinical problems, the algorithm we have developed accounts for all relevant factors and consistently recommends a rational and optimized dosage. The aim of these doses that we suggest for personalized patient therapy is to achieve plasma concentrations that are equivalent to those achieved with equivalent doses in patients with normal renal function. Another noteworthy advantage of this tool is the ability to calculate dosages for drugs not included in the database.

4 When should a suggested drug dosage adjustment be checked?

Drug doses should be adjusted for estimated endogenous levels of renal function not just during RRT, but also before beginning or ending RRT. This dose calculation tool can recommends doses for the same patient with and without the use of RRT. In 4-5 hours intermittent haemodialysis typically eliminates the same amount of drug, that is cleared by CRRT in a 24 hour period. In the presence of intermittent dialysis, the suggested dose is usually applied as an additional dose before, during, or after the treatment. The calculation can also provide useful guidance in the case of drug intoxication. In the case of acute overdoses it is possible to estimate the probability of success of dialysis as a therapy, by considering the drug amount excreted via the dialysate.

5 How should drug dosage be adapted?

The aim of many drug therapies is to maintain consistent serum concentrations over time. If dose reduction is necessary, this reduction can occur by keeping the same dosage interval while reducing the size of the administered dose. If limitations of the available formulation are present (e.g. tablets are not further divisible etc.), the dosage interval can be prolonged with the typical dose being maintained. In oral long-term therapies an interval of application of 12 or 24 hours is suggested. In rare cases where increased doses may be required, it is recommended that the dosing interval be shorted and the dose maintained. In the case of intermittent dialysis and drug administration twice daily, it seems to be appropriate to apply one drug dose in the morning and one in the evening. If drug administration is only once daily, it is recommended to apply drugs 12 hours before dialysis (dialysis in the morning, application of the drug in the evening; dialysis in the afternoon or evening, application in the morning). With more regular dosing, at the time of dialysis, mean steady state serum concentrations are expected and the risk of an over- or underestimation of the amount of RRT clearance of drug is minimized. This will serve to prevent a decrease of serum concentrations below the therapeutic range. In some cases (e.g. concentration dependent antibiotics; see section 7 below) it is not appropriate to reduce the single dose and dosing intervals may need to be increased far beyond 24 hours (36 to 96 hours). In other cases where drug clearance occurs only by RRT, drug dosing only on RRT days may be appropriate. Where uncertainty exists, consultation with a pharmacokinetic specialist is strongly recommended.

6 When and how should the additional dose be applied when using intermittent dialysis?

For most drugs, the best method of administering additional doses in intermittent dialysis is by continuous infusion of the amount of drug estimated to be eliminated during the procedure. In this way the drug loss caused by dialysis is evenly compensated and the serum concentrations are not affected. In the case of high clearance dosage forms (i.v. bolus, oral administration) it may be appropriate to administer the first half of the dose at the beginning and the other half at the mid-point of the dialysis. The additional dose of slow release formulations may be applied at the beginning of the dialysis to prevent a drop of the serum concentration below the therapeutic range during dialysis. Alternatively, in many cases, the additional administration may be postponed (after the dialysis) or even may be dispensed with, especially if the dosing is only once a day and the calculated extra amount is relatively low.

7 The special case of *aminoglycosides*

In contrast to most drugs, in aminoglycoside therapy (*gentamicin*, *amikacin*, *tobramycin*, *netilmicin*) consistent serum concentrations are desired. High peak concentrations following administration and a complete clearance before the next administration is optimal. Therefore, the calculated daily dose is guided by the amount of drug is eliminated within 24 hours or by one-time dialysis. For patients where high doses are suggested (e.g. sepsis) complete clearance of the drug within 24 hours is not possible by either CRRT or intermittent dialysis. Target trough concentrations may be achieved 48 to 72 hours following administration, depending on the patient's renal function and frequency of daily dialysis. Dose adjustment on the basis of serum concentrations and pharmacokinetic consultation (TDM) is strongly recommended. For the treatment of endocarditis where low continual exposures are desired, even a single dose (e.g. *gentamicin* 1mg/kg) every 24 hours may be appropriate in CRRT. In intermittent dialysis administration of a single dose (e.g. *gentamicin* 1mg/kg) after every dialysis may be a good choice. Nevertheless, therapy should be guided by measured serum concentrations.

8 Limits of the algorithm

The chosen algorithm involves some risks and uncertainties. In particular, the following aspects are to be considered:

- Are there any contraindications, precautions or other restrictions?
- Is the patient's non-renal drug clearance equivalent to a normal patient, e.g., is there concomitant liver dysfunction or interaction with other drugs?
- Are there active metabolites, which in other circumstances have different pharmacokinetic characteristics (e.g. *midazolam*, *carbamazepine*, *morphine*)?
- Is there a possibility of irreversible adsorption of the drug to the filter?
- Is the indivual drug respond , even with plasma concentrations in target range, not adequate?
- Is a loading dose appropriate?
- Is it more reasonable to adjust the dose by varying the size of the drug dose (e.g. time dependent antibiotics) or by varying the interval at which it is administered (e.g. concentration dependent antibiotics)?
- Is almost complete drug elimination before the next dose required (e.g. *aminoglycosides*)?

Continuous clinical monitoring of the therapeutic outcomes of therapy and for possible adverse reactions is always required. If plasma concentration monitoring (i.e. TDM) is available, this should be used to increase the safety of therapy and may contribute to the optimisation of therapeutic outcomes. Therapeutic drug monitoring (TDM) is strongly recommended particularly for narrow therapeutic index drugs. An alternative simple, noninvasive method to quantify the amount of drug elimination by renal replacement therapy is the quantification of the amount of drug in haemofiltrate or dialysate. These concentrations may also be used to estimate the free, and thus pharmacologically active drug concentrations in plasma.
All in all, metabolism and renal clearance of drugs can show a very high inter- and intraindividual variation, especially in critically ill patients in the ICU. By using RRT, there is theoretically a defined, reproducible and controllable factor on drug elimination. By rational dosing of drugs in this situation a lower inter- and intra-patient variation of serum concentrations will occur resulting in more consistent therapeutic effectiveness and safety.

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