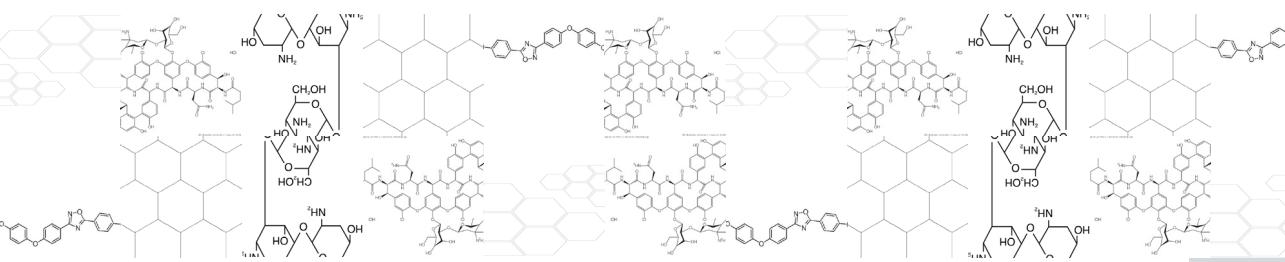
Strategies for optimization of Aminoglycoside and Vancomycin therapies : a Pharmacokinetic approach

Chapter 4

Summary, clinical implications and future perspectives



In this thesis we have investigated pharmacokinetically based strategies for optimization of aminoglycoside and vancomycin therapies. The current chapter will summarize and discuss the results of our studies investigating aminoglycoside and vancomycin pharmacokinetics in the studied patient populations with infections.

Once daily and extended interval dosing of aminoglycosides

As once daily dosing of aminoglycosides has gained popularity worldwide, more data are available on once daily dosing regimens in various clinically infected populations. In the study described in Chapter 2.1 we focused on adult cystic fibrosis (CF) patients. CF patients are frequently exposed to high doses of once daily dosed (ODD) tobramycin with relatively long treatment course duration in case of pulmonary exacerbations (1). The tobramycin dosages range from 10 to 15 mg/kg once daily in this population. Based on harmacokinetic/pharmacodynamic (PK/PD) considerations a high dose per kg bodyweight is a consequence of the relatively large volume of distribution and high clearance in comparison to other clinically infected populations treated with aminoglycosides (2). Current once daily high tobramycin dosing protocols in pediatric and adult CF patient populations result in high peak and low trough concentrations ensuring efficacy and limiting the risk of toxicity, respectively (3). In Chapter 2.1 the influence of the time of administration on the PK of tobramycin in adult CF patients was investigated. This study was designed to test the assumption that dosing in the evening results in a lower clearance and an increased area under the concentration-time curve (AUC) of aminoglycosides due to the circadian rhythm of renal function. In close collaboration, the effect of the circadian rhythm on tobramycin PK was studied in pediatric CF patients by investigators at the University of Nottingham, UK. Results from the latter studies indicate no clinically relevant effect of the administration time on tobramycin PK in CF patients. In Chapter 2.2 we performed a retrospective cohort study that investigated the effect of the time of administration of aminoglycosides in general ward patients and in intensive care unit (ICU) patients. In these clinically infected populations also no effects of the time of administration could be detected on the PK of aminoglycosides. Furthermore, the incidence of nephrotoxicity was not affected by the time of administration in the general ward population. We suggest that the lack of an effect of the time of administration on

aminoglycoside PK in CF patients, general ward patients and ICU patients is caused by a distortion of the 'normal' circadian rhythm in these clinically infected patients. Previous reports have demonstrated that changes in immunological status affect the circadian rhythm, e.g. sepsis will abrogate the normal melatonin secretion over the day (4-6). The presence of a 'normal' circadian rhythm is influenced by distortion of immunological homeostasis. In fact, based on our observations we hypothesize that intravenous antibiotic agents will rarely show a diurnal pattern since they are prescribed to patients with serious suspected or proven infections.

In Chapter 2.3 we investigated the PK and nephrotoxicity of ODD gentamicin and ODD tobramycin in a large retrospective cohort of infected general ward patients. The most important finding of this study was a fifty percent lower incidence of nephrotoxicity in patients treated with tobramycin compared to those treated with gentamicin. To our knowledge no previous studies have compared the clinical toxicity of two or more ODD aminoglycosides. Importantly, this study offers a pharmacological explanation for the difference in nephrotoxicity between gentamicin and tobramycin, since the PK analysis showed that gentamicin clearance was lower than tobramycin clearance. As a consequence, gentamicin exposure in terms of daily AUC was higher compared to tobramycin exposure. Mechanistically, our findings can be explained by the higher renal accumulation of gentamicin versus tobramycin inducing renal injury (7). Finally, a multivariate analysis showed that the AUC of the first administration was a strong predictor of the incidence of nephrotoxicity indicating 'early therapeutic drug monitoring (TDM)' using limited AUC sampling can be of additive value identifying those patients at risk and therefore is of clinical relevance.

In Chapter 2.4 we prospectively evaluated a gentamicin dosing regimen which is used in newborns with suspected or proven neonatal sepsis. This study showed that a dosing regimen of 5 mg/kg every 36h resulted in therapeutic exposure of over 90% of included subjects. It is important to note that this study was not performed in a neonatal intensive care unit (NICU) but in a level 2 special care nursery population. In accordance with previous reports (8), we found a strong relationship between the volume of distribution (L/kg) of gentamicin with bodyweight in our population, with a larger bodyweight-corrected volume of distribution in preterm infants due to differences in body composition. Gentamicin half-life decreased with lower gestational age, which has also been reported by others (9). A combination of low weight-corrected

volume of distributions with short half-lives will translate in concentration-vs-time-curves with high peak concentrations and steep slopes. Vice versa, in low-birth-weight premature newborns peak concentrations and half-lives were lower and longer, respectively. Interestingly, the AUC was not related to gestational age or body weight, meaning that using the proposed dosing regimen in low birth-weight more premature newborns on average had the same gentamicin exposure compared to older neonates with higher bodyweights.

Continuous infusion of vancomycin

In Chapter 3.1 we performed a review of the literature comparing the inter-patient exposure variability in clinically infected patients on continuous or intermittent infusion of vancomycin. This review showed that continuous infusion conferred a fifty percent lower inter-patient variability of vancomycin concentrations compared to intermittent infusion. This interesting finding based on the review of in total 34 published reports led to the design of a retrospective cohort study in an ICU population (Chapter 3.2). In this study we confirmed the hypothesis that the inter-patient variability in vancomycin exposure was significantly lower for continuously dosed versus the intermittently dosed critically ill patients. Furthermore, 'plateau' concentrations in continuous dosing showed a stronger correlation with estimated AUCs compared to trough concentrations during intermittent dosing. Two conveyable causes can largely explain the reported results in Chapter 3.1 and 3.2. First, since 'trough sample timing' can have a major influence on the measured vancomycin concentrations, an intermittent dosing regimen monitored by trough concentration is inherently prone to higher variability in comparison to continuous infusion and 'plateau' concentration monitoring (10). Second, when trough concentrations are monitored in case of intermittent dosing the variability of the AUC is not only affected by the vancomycin clearance, but also by the volume of distribution (Chapter 3.1 and 3.2). Patients with a relatively high volume of distribution will need higher intermittent dosages to maintain trough concentrations within the therapeutic range resulting in a large 'delta' between peak and trough concentrations and therefore in high AUCs, especially in once or twice daily dosing regimens. In Chapter 3.3 a simple method was presented to clinically implement a vancomycin continuous dosing nomogram based on historical within-population data obtained from

intermittently dosed patients. This chapter offers tools for clinicians considering a switch from intermittent to continuous dosing of vancomycin. Although not intended for use in other clinically infected populations the developed dosing nomogram was in accordance with the only other prospectively validated dosing algorithm (11).

Implications for clinical practice

In chapters 2.1 and 2.2 we showed that the time of administration did not affect the clearance or exposure in terms of AUC in CF patients, general ward patients and ICU patients. Hence, swifting administration times to the morning period is not recommended and 24 hour intervals should be maintained unless therapeutic drug monitoring results indicate that the dosing interval needs to be extended (12). Furthermore, since early initiation of antibiotic treatment is paramount to improve outcomes, the first administration of an aminoglycoside should take place as soon as possible after the diagnosis (13).
Although our findings deserve to be confirmed, results from Chapter 2.3 show a higher nephrotoxic potential of ODD gentamicin over ODD tobramycin in clinically infected patients treated for at least 3 days which may lead to the revision of (inter)national and local treatment protocols. In patients who are at high risk of developing nephrotoxicity and/or are likely to be treated over a longer period, tobramycin should be preferred over gentamicin. In fact, European cystic fibrosis treatment guidelines already advocate to choose tobramycin over gentamicin for this reason (14, 15). The same concerns with regard to cumulative toxicity apply to other highly exposed populations, e.g. patients treated for endocarditis. In order to optimize treatment with aminoglycosides ‘early’ AUC monitoring in addition to ‘trough levels’ should be implemented in daily routine, since our data suggest the AUC of the first administration is a strong predictor of nephrotoxicity.
The added value to the present literature of our study results presented in Chapter 2.4 on gentamicin dosing in neonates lies in the specific neonatal population investigated. Current dosing regimens in neonates are largely based on data obtained from neonates admitted to a NICU (9, 16, 17), while the number of neonates exposed to gentamicin is likely to be higher in level 2 special care nurseries. Albeit our data deserve to be prospectively confirmed in a second independent cohort of neonates admitted to a level 2 special care nursery, our findings show that a more uniform dosing protocol of 5 mg/kg per 36 hours can be implemented in level 2 unit compared to more complex dosing protocols proposed in neonates admitted to a level 3 intensive care unit (16, 18, 19). As described in Chapter 3.1 vancomycin continuous dosing

protocols are rapidly gaining interest and are being implemented in clinical practice. Apart from some practical advantages over intermittent infusion, continuous infusion of vancomycin shows a more predictable exposure and thus the odds of an optimal target attainment as shown in Chapter 3.1 and 3.2 are better. In addition, continuous infusion of vancomycin might also be preferred since the drug preparation time, the staff workload and costs are reduced and it may also shorten hospital length of stay.(20, 21), (22) and has shown to be safe concerning stability (23). Of course, there are also potential disadvantages to continuous infusion. Sufficient numbers of volume controlled infusion pump systems have to be secured and compatibility with other simultaneously infused drugs can be an issue. Nevertheless, 'Y-site'-compatibility of vancomycin with many drugs has been demonstrated (24). Finally, based on our methodology described in Chapter 3.2 a 'tailored' dosing algorithm of vancomycin can be designed for clinically infected populations aiming to achieve a priori target exposure using historical within-population data, a PK model and PK software.

Suggestions for future studies

Toxicity studies in populations treated with 'traditional' dosing regimens of aminoglycosides or vancomycin have been performed in the past. However, limited data are available on the recommended dosing regimens from most recent guidelines with respect to clinical outcomes (25, 26). For example, the most recent treatment guidelines for the treatment of multi-resistant S. aureus (MRSA) of the Infectious Diseases Society of America (IDSA) promoting high exposure targets for vancomycin are sparsely supported by safety data (27). Moreover, most toxicity studies on aminoglycosides were performed in the multiple daily dosing era. Therefore, prospective studies investigating the toxicity of currently prescribed once daily or extended-interval dosed aminoglycosides in highly exposed populations e.g. patients suffering from endocarditis are warranted. Newly developed high dosing protocols of vancomycin for long-term MRSA treatment also raise questions about the risk/benefit ratio (28).
Furthermore, there is a need for pharmacokinetic studies investigating vancomycin exposure in patients on continuous infusion in detail during the first 24 hours of therapy (29-31). Therefore, we advocate future studies to address this issue first by incorporating intensive

PK monitoring during the first 24 hours to design proper PK models of continuous infusion of vancomycin and identify optimal sampling times for limited sampling strategies in clinically infected populations. Secondly, determinants for patients at risk of under- or overexposure may be identified. Next, we recommend the implementation of 'early TDM', which has recently also been suggested for intermittent dosing of vancomycin (32). The AUC24h and steady state concentation can be estimated accurately shortly after initiation of vancomycin from two serum samples drawn within 12 hours after initiation of therapy using a validated PK model and PK software. This 'early TDM' approach offers the opportunity to swiftly identify patients that are or will be significantly under- or overexposed and may thereby enable clinicians to improve patient outcomes. Finally, the ongong debate on the preferential mode of administration of vancomycin should be addressed by large multi-center investigations preferably of prospective randomized design.

Many experts believe that clinical usage of tobramycin and gentamicin will increase due to resistance to our current first line antibiotic armamentarium (33-36). This could result in selection pressure of first choice aminoglycosides on a global scale. Recently, the Swedish Reference Group for Antibiotics (SRGA) has carried out a risk-benefit analysis of aminoglycoside treatment based on clinical efficacy, antibacterial spectrum, and synergistic effect with beta-lactam antibiotics, endotoxin release, toxicity, and side effects. For instance, in cases of suspected infection caused by multidrug-resistant Enterobacteriaceae the SRGA nowadays promotes amikacin instead of gentamicin or tobramycin which is generally more active against extended-spectrum beta-lactamase (ESBL)-producing and quinolone-resistant Escherichia coli than other aminoglycosides (37).
Of interest, after the introduction of the SRGA guidelines the increase in Swedish orders of amikacin immediately lead to drug shortages in other EU countries. This is just one examples showing that antimicrobial agent shortages are of global concern and not limited to second or third world countries nowadays (38). It is a multifactorial problem and the current situation of antibiotic shortages is unfortunately more likely to aggravate than to disappear in the years to come.
With regard to the amikacin nephrotoxic and ototoxic potential, there is mechanistic and clinical evidence that the risk of developing nephrotoxicity is relatively low compared to the others within-class drugs (39, 40). Nevertheless, more studies on amikacin with current once daily

dosing regimens are needed. For similar reasons, netelmicin, a previously used aminoglycoside which is though to have a low nephrotoxic potential (40, 41), will regain interest. It is also worthwhile to mention plazomicin, a promising aminoglycoside, that has been tested in phase 3 studies (42). Plazomicin is designed to overcome tobramycin and gentamicin resistance. Human studies to date have not yet reported nephrotoxicity or ototoxicity, but lack of plazomicin ototoxicity has been reported in the guinea pig model for plazomicin (42). Given the reported increase in bacterial resistance to current antimicrobial agents, plazomicin may be considered a welcome addition to the antibacterial armamentarium pending positive results from large-scale clinical trials and other required clinical studies. In conclusion PK/PD studies of 'new' dosing regimens of 'older' aminoglycoside antibiotics are urgently needed, anticipating broad clinical use of these antimicrobal agents in patient populations with serious infections and a high drug exposure.