Anti-infective therapy in special patient populations based on therapeutic drug monitoring

Corti, Natascia

Klinik für Klinische Pharmakologie und Toxikologie

(Direktor: Prof. Dr. med. G.A. Kullak-Ublick)

Kumulative Habilitationsschrift

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1. Publications

1.1 Five selected Publications representing the "kumulative Habilitationsschrift"

1. Preiswerk B, Rudiger A, Fehr J, **Corti N**. Experience with daptomycin daily dosing in ICU patients undergoing continuous renal replacement therapy. Infection. 2013 Apr;41(2):553-7
2. **Corti N**, Rudiger A, Chiesa A, Marti I, Jetter A, Rentsch K, Müller D, Béchir M, Maggiorini M. Pharmacokinetics of daily daptomycin in critically ill patients undergoing continuous renal replacement therapy. Chemotherapy. 2013;59(2):143-51
3. Reiber C, Senn O, Müller D, Kullak-Ublick G.A. **Corti N**. Therapeutic Drug Monitoring of Daptomycin: a Retrospective Monocentric Analysis. Ther drug monitoring (accepted for publication)
4. Curkovic I, Lüthi B, Franzen D, Ceschi A, Rudiger A, **Corti N**. Trimethoprim/Sulfamethoxazole pharmacokinetics in two patients undergoing continuous venovenous hemodiafiltration. Ann Pharmacother. 2010 Oct;44(10):1669-72
5. Meloni M*, **Corti N***, Müller D, Henning L, Weber R, Fehr J. Cure of tuberculosis despite concentrations of antituberculosis drugs below published reference ranges: A retrospective analysis. *Accepted for publication by Swiss Medical Weekly*.

1.2. Three publications of high scientific value, not discussed in the "kumulative Habilitationsschrift"

1. Pfister P*, **Corti N***, Hobbie S, Bruell C, Zarivach R, Yonath A, Böttger EC. 23S rRNA base pair 2057-2611 determines ketolide susceptibility and fitness cost of the macrolide resistance mutation 2058A-->G. Proc Natl Acad Sci U S A. 2005 Apr 5;102(14):5180-5
2. Serra AL, Braun SC, Starke A, Savoca R, Hersberger M, Russmann S, **Corti N**, Wüthrich RP. Pharmacokinetics and pharmacodynamics of cinacalcet in patients with hyperparathyroidism after renal transplantation. Am J Transplant. 2008 Apr;8(4):803-10.
3. **Corti N**, Heck A, Rentsch K, Zingg W, Jetter A, Stieger B, Pauli-Magnus C. Effect of ritonavir on the pharmacokinetics of the benzimidazoles albendazole and mebendazole: an interaction study in healthy volunteers. Eur J Clin Pharmacol. 2009

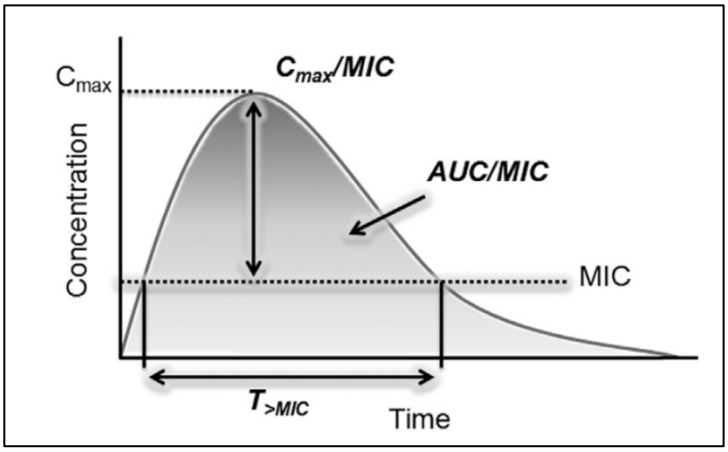
*denotes equal contribution of the authors

2. Background to the presented work

2.1. Parameters describing efficacy of anti-infective agents

The individual dose response relationship of an anti-infective agent is the sum of a complex interaction of several factors. It is determined by the characteristic pharmacodynamic profile of an antimicrobial which is based in one part on the minimal inhibitory concentration (MIC) [1]. MIC is the most commonly used pharmacodynamic parameter to describe efficacy of an antibiotic towards a bacterial strain and is determined as the lowest antimicrobial concentration that inhibits growth of microorganisms in vitro. Defined by the relationship between optimal antimicrobial drug exposure pattern versus MIC, mainly two pharmacodynamic indices have been used to determine optimal dosing strategy [2]. For anti-infectives with a so called time-dependent effect, maximum efficacy can be reached by keeping antimicrobial serum concentration above MIC for a sufficient time period within the dosing interval (T>MIC). This is the case for beta-lactam antibiotics such as carbapenems or penicillins. For anti-infectives with a concentration-dependent effect such as daptomycin or aminoglycosides, magnitude of drug exposure in relation to MIC defines maximum efficacy. Peak plasma concentration (Cmax) and area under the curve (AUC) are pharmacokinetic (PK) variables that describe maximum drug exposure best. These variables are put in relation to MIC (Cmax/MIC and,or AUC24h/MIC) to determine optimal ratio. In concentration –dependent antibiotics higher doses and consecutively higher plasma concentrations of anti-infectives correlate with a better bactericidal effect.

Fig. PK/PD indices associated with the efficacy of the antibiotics



Ref: Asín-Prieto et al. J Infect Chemotherapy 2105

Individual pharmacokinetics of a drug i.e. absorption, distribution, metabolism and elimination define drug exposure in plasma and finally at target site. Organ function and severity of disease can influence pharmacokinetics of a drug leading to high inter-and intra-individual variability with the risk of suboptimal or excessive antimicrobial plasma concentration. Inadequate drug exposure not only bears the risk of therapeutic failure but also compromises outcome by selection of resistant strains[3]. Regular determination of drug plasma concentration i.e. therapeutic drug monitoring (TDM) during anti-infective treatment is a well-established tool to guide anti-infective dosing for antibiotics such as vancomycin or

aminoglycosides. For newer antibiotics like daptomycin and some older reemerging antibiotics like colistin routine TDM has not yet been established although knowledge on optimal drug exposure can be estimated based on animal data. To overcome PK variability and to find optimal dosing requirement, an individualized antibiotic dosing strategy has been advocated based on determination of antimicrobial plasma drug concentrations[4].

2.2. Anti-infective dosing in critically ill patients and in patients with acute renal failure undergoing continuous replacement therapy

Severe sepsis and septic shock are frequent reasons for administration of antimicrobials on intensive care units (ICU). Septic shock has a mortality as high as 80%, therefore administration of adequate antibiotic doses already in the first hours but also in the course of treatment is important to improve survival[5]. However, optimal antibiotic dosing is a challenge in critically ill patients. This is in part due to altered and variable drug pharmacokinetics which makes it difficult to apply dosing recommendations derived from healthy volunteers. Capillary leak in septic patients leads to an increase in volume of distribution, hypoalbuminemia increases free drug fraction, changes in intestinal motility and administration of enteral feeding can affect drug absorption[6] and rapid changes in organ function can increase or decrease drug clearance [4, 7].

Acute renal failure (ARF) affects approximately 35% of ICU patients and continuous renal replacement therapy (CRRT) such as continuous veno-venous hemodialysis or continuous veno-venous hemo(dia)filtration is often required[8]. For a large number of antimicrobials that are predominantly eliminated by the kidneys dose adaptation is necessary in patients with compromised renal function and also in patients undergoing renal replacement therapy[9]. Dosing recommendations are usually based on specific studies investigating PK in patients with different degrees of chronic renal failure with or without intermittent hemodialysis (IHD)[10]. IHD is performed twice or three times per week over 3-4 hours and drug removal is limited to hemodialysis sessions. In contrast CRRT provides constant solute and daily drug removal over 24 hours which goes along with a more effective drug clearance and requires higher daily doses compared to IHD[11]. Therefore dosing recommendations derived from IHD studies cannot be applied to patients undergoing CRRT. Although studies investigating anti-infective pharmacokinetics in patients undergoing CRRT have increasingly been published in recent years[12, 13], PK data and dosing recommendations for most of newer and older reemerging anti-infectives were lacking until recently. Consequently antimicrobial dosing is often inadequate or even under dosed in this vulnerable patient population with complicated infections. Therefore knowledge about the optimal dose in CRRT is crucial[14].

2.3. Daptomycin in critically ill patients undergoing continuous renal replacement therapy

Daptomycin is the first lipopeptide antibiotic and exhibits a rapid concentration-dependent bactericidal action against Gram-positive organisms including methicillin-resistant Staphylococcus aureus or

vancomycin-resistant Enterococcus spp.[15]. Based on animal data, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) suggests a mean AUC24h/MIC target of 438 of total drug for bacteriostatic effect against susceptible *S.aureus* strains (MIC <0.5mg/l) and for a bactericidal effect even a mean AUC24h/MIC target of 1061 is recommended[16, 17].This exposure translates in a minimal plasma AUC24h of 400mg*h/l for a bactericidal effect. As Enterococci exhibit a higher daptomycin MIC even higher daptomycin plasma concentrations are probably needed. Although routinely determination of daptomycin plasma concentrations for therapy monitoring has not yet been established, analytical method for daptomycin measurement has been established at our institution since 2009 and is increasingly being used. Daptomycin is highly protein bound (90–96%) and is mainly eliminated by the kidneys with a mean renal clearance of 10ml/min. About 30% is presumably metabolized in the kidneys and excreted as metabolites and only 5% is excreted in the feces[18] . In *S. aureus* bloodstream infections, including those in patients with right sided endocarditis caused by methicillin-resistant and methicillin-susceptible strains, the labeled dose is 6 mg/kg every 24 h. As accumulation occurs in patients with renal failure, the dosing interval is prolonged to 48 h in patients with severe renal insufficiency (creatinine clearance <30 ml/min) or intermittent hemodialysis (IHD) [19]. However, official daptomycin dosing recommendations for patients undergoing CRRT are currently not available[19]. This results in differing dosing regimens in CRRT patients with risk of underdosing especially in cases where the dosing regimen for patients with severe renal failure i.e. q48h is applied. On one hand the high plasma protein binding (90–96 %) of daptomycin suggests that the drug may not be extensively removed by CRRT. However, the first PK study that was conducted in a CRRT model with bovine plasma enriched with daptomycin using filtration rates of 35 ml/kg/h or higher, showed that daptomycin CRRT clearance was comparable or even higher than clearance in patients with normal renal function (7–10 ml/min)[20]. Optimal daptomycin in critically ill patients undergoing CRRT has been a matter of debate. Some authors advocate a dose of 8mg/kg once every 48 hours [21, 22] in order to reach sufficiently high peak concentrations and to avoid high daptomycin trough concentrations and accumulation. Others found very low plasma concentration at doses of 4mg/kg every 24h and recommend a higher dose administered once daily to ensure efficacy [23]. Based on the findings of the model study we postulated that a daptomycin dose reduction or a prolongation of the dosing interval is not necessary in patient undergoing CRRT. We conducted two studies to investigate daptomycin pharmacokinetics and dosing in CRRT.

2.4. Therapeutic drug monitoring in anti-tuberculosis treatment

TB treatment is a major challenge for patients, physicians and health care systems. First line antibucerculosis drugs such as isoniazid, rifampicin, pyrazinamide and ethambutol are administered over the first 2 month in pulmonary TB. Isoniazid and rifampicin are then continued over 4 month[24] . A well-conducted six month TB treatment is effective: cure rates of >95% can be achieved in pulmonary TB under directly observed therapy (DOT) [25-27]. Several factors complicate TB treatment. Case series [28, 29] and non-controlled clinical studies [30-34] indicate that comorbidities such as HIV infection and chronic diarrhoea might increase the risk of poor absorption of antituberculosis drugs (ATD). In vitro

data show a clear concentration-dependent effect on Mycobacterium tuberculosis for all first-line ATD drugs[35, 36], consequently higher drug concentrations levels should correlate with antituberculosis efficacy and low levels with therapeutic failure. In this context treatment guidance through therapeutic drug monitoring (TDM) has been advocated by some authors[37, 38]. However reference ranges for ATD plasma concentrations published so far are based on PK studies in healthy volunteers or Tbc-patients and represent peak drug concentrations usually reached under standard dosing conditions[39 40]. Moreover these ranges do not take into consideration a possible synergistic effect of ATD. So far there is no clear evidence that ATD serum concentrations below these reference ranges are associated with treatment failure.

Mostly retrospective data support that slow response to treatment, prolonged infectiousness, emergence of drug resistance and higher rates of relapse or treatment failures in Tbc- infected patients might be related to low serum concentrations [32, 34, 38, 41-46]. However two clinical studies that have investigated ATD concentrations in relation to reference ranges and clinical outcome prospectively found an association of reduced efficacy only with low pyrazinamide plasma levels[42, 47]. Due to the heterogeneity of study design these results are difficult to interpret, therefore additional clinical data are needed to define ideal sampling time and true therapeutic range of ATD.

3. Discussion of the selected publications

3.1. Experience with Daptomycin Daily Dosing in ICU Patients Undergoing Continuous Renal Replacement Therapy

In a first pilot study, we retrospectively compared daptomycin plasma peak and trough concentrations that were measured routinely between May 2008 and December 2010 in 7 critically ill patients with and in 4 patients without CRRT exposed to a once-daily daptomycin regimen. Patient characteristics and microbiological data, including minimum inhibitory concentrations (MICs), if available, were additionally collected from the patient charts. In CRRT patients, daptomycin plasma concentrations were in the range of those patients with normal or mildly impaired renal function. No drug accumulation was detected in CRRT patients with once-daily daptomycin dosing. Peak and trough plasma concentrations showed a high intra- and inter-patient variability in both groups. No correlation was found with dose per kg body weight or the CRRT effluent flow rate. When doses of 4 mg/kg were used, Cmax was in the lower range of values measured in healthy volunteers at the equivalent dose and at daptomycin doses of 6 mg/kg they were substantially lower compared to equivalent doses in healthy volunteers[48, 49]. Microbiological eradication was successful in 8 of 11 patients. Two of three patients with unsuccessful microbiological eradication and fatal outcome had an *Enterococcus faecium* infection.

In this study we found a first evidence for our assumption that a full daptomycin dose with a once daily administration could be adequate for patients with acute renal failure undergoing CRRT. Furthermore the data indicate that with the labelled dose of 6mg/kg for *S.aureus* bacteraemia could even lead to underdosing in individual cases especially in patients with an enterococcal infection. In view of the high variability of daptomycin exposure independent of dose and CRRT modality used, a routinely

measurement of daptomycin plasma concentrations to optimize daptomycin dosing might be warranted.

3.2. Pharmacokinetics of Daily Daptomycin in Critically Ill Patients Undergoing Continuous Renal Replacement Therapy

This prospective PK study in critically ill patients with acute renal failure undergoing CRRT was conducted with the aim to determine daptomycin PK, daptomycin clearance in dependence of the CRRT filter and effluent rate used and to formulate a dosing recommendation. Patients with an established first-line antibiotic treatment for proven or suspected Gram-positive infection were included and in addition 6mg/kg daptomycin i.v. was administered every 24h for study purposes over 5 days. Extensive pharmacokinetic blood sampling was performed on day 1, 3 and 5. We found that daptomycin removal in CRRT was comparable to daptomycin clearance in normal renal function and no drug accumulation occurred with the once- daily dosing. The mean AUC24h of 667.4 mg·h/l in these patients was in the range of AUC24h observed in healthy volunteers and translates into the AUC24h/MIC target of >1061 mg·h/l for a bactericidal action in *S.aureus* strain with a MIC<1mg/l[17]. However, in contrast to healthy volunteers a high variability of daptomycin exposure was observed with daptomycin AUC24h as low as 265 mg*h/l in individual cases. In case of *S.aureus* MIC >1mg/l or in enterococcal infections low daptomycin concentrations theoretically bear the risk of therapeutic failure. We further observed a strong correlation of AUC24h to peak and especially trough concentrations (R2=0.94, p <0.001) indicating that daptomycin trough concentration is a valuable parameter for therapeutic drug monitoring in critically ill patients undergoing CRRT.

In conclusion a once daily dosing of at least 6mg/kg seems adequate in the majority of ICU patients with renal failure undergoing CRRT. However, in certain patients higher daily doses might be required. In view of the high variability of daptomycin exposure in this patient population determination of daptomycin trough concentrations is an important tool to optimize daptomycin dose in dependence of individual PK parameters and specific MIC of infecting organism.

3.3. Therapeutic Drug Monitoring of Daptomycin: a Retrospective Monocentric Analysis

The efficacy of labelled daptomycin doses of 4mg/kg once daily in the treatment of complicated skin and soft tissue infections (cSSTI) and 6mg/kg for blood stream infections including those with right-sided endocarditis caused by methicillin-resistant *S.aureus* and methicillin-susceptible strains was proven in two pivotal trials [50, 51]. Daptomycin use and efficacy in other types of infection has mainly been investigated in retrospective studies[52, 53]. The available data indicates that doses up to 12mg/kg have been administered safely and have been recommended for severe and difficult to treat Gram-positive infections, such as bacteremia, infective endocarditis and osteomyelitis[54]. The focus in all these studies was to investigate specific dosing regimen and outcome. However daptomycin plasma concentrations were not determined therefore the knowledge about effective drug exposure in relation to efficacy and its interindividual variability is lacking.

Daptomycin plasma concentration measurement was established at the University Hospital of Zurich in January 2009 and has increasingly being used since then. The objective of this retrospective study was to describe variability of daptomycin plasma concentrations and to determine the main factors associated with excessive or low drug exposure. Patients with at least one determination of daptomycin plasma concentration in the period of 2009-2012 were eligible. A total of 332 daptomycin plasma concentrations were determined in 86 patients. We tested clinical and demographic data such as daptomycin dose and dose interval, weight, different categories of renal function or renal replacement therapy and their association with daptomycin exposure by a multilevel linear regression analysis. We found that only 28% ($P<0.005$) of Cmin variability and 8% ($P=0.08$) of Cmax variability was explained by the factors included in the analysis. These findings reveal that daptomycin plasma concentrations are often unpredictable and underline the usefulness of daptomycin therapeutic drug monitoring especially in critically ill patients.

3.4. Trimethoprim/Sulfamethoxazole pharmacokinetics in two patients undergoing continuous venovenous hemodiafiltration

Trimethoprim/sulfamethoxazole (TMP/SMX) is the drug of choice for the treatment of Pneumocystis jirovecii pneumonia (PJP) and for infections with the opportunistic bacillus *Stenotrophomonas maltophilia*. Both types of infection are found predominantly in immunocompromised patients and in patients with multiple comorbidities. Especially PJP-patients are most often hospitalized at the intensive care unit and in cases of severe disease acute renal failure can occur and CRRT is required. As TMP and SMX are excreted in part by the kidneys as unchanged drugs (50–70% and 10–30%, respectively), renal dysfunction leads to diminished elimination. Dose reduction and/or prolongation of dosing interval are therefore recommended in patients with renal failure[55, 56]. However, until this investigation was done no data or labelled dosing recommendations were available concerning TMP/SMX dosing in CRRT patients. We therefore determined pharmacokinetics and CRRT clearance in two anuric critically ill patients undergoing continuous veno-venous hemodiafiltration (CVVHDF) treated with intravenous TMP/SMX in order to derive a dosing recommendation. In both patients TMP/SMX dosage was reduced to 50% of the standard dose on starting CVVHDF. We found that both TMP and SMX were cleared to a significant degree by CVVHDF in our patients, with haemodialysis probably contributing to a greater extent to their elimination compared to hemofiltration alone. TMP-Cl_{CVVHDF} was in the lower range of the renal clearance reported for normal renal function and SMX Cl_{CVVHDF} even significantly exceeded normal renal clearance. TMP peak concentrations were in the lower range and SMX peak concentrations were one third of those described and recommended in the literature[57, 58]. We therefore concluded that in critically ill patients undergoing CVVHDF, TMP and SMX dose reduction is not required to ensure adequate exposure. Based on these findings dosing recommendations in house were revised and full dose TMP/SMX is now administered in CRRT patients at our institution. This publication has served as reference article concerning TMP/SMX dosing in CRRT during the last years. Our data has been supported meanwhile by a CRRT model study and a case report investigating PK in extended dialysis [59, 60].

3.5. Cure of tuberculosis despite concentrations of anti-tuberculosis drugs below published reference ranges: A retrospective analysis

Based on the fact that therapeutic reference ranges of anti-tuberculosis drug (ATD) are not defined, we retrospectively investigated the frequency of ATD concentrations below reference ranges in TB patients with therapeutic drug monitoring (TDM) during 2010 to 2012 at our institution. Clinical and microbiological outcome data were additionally evaluated. Maximum ATD concentration was estimated (eCmax) by assessing the highest value during a sampling period, in which about half of ATD concentrations were determined 2h after drug intake. eCmax was categorized into 3 groups: "within the reference range", "low" and "very low". In total we analysed drug concentrations from 175 serum samples collected from 17 patients. In all but one patient (94%), at least one eC_{max} value was below the reference range. Overall eCmax was below the reference range in 78% of INH, 90% of RMP, and 50% of RFB measurements and in 30% of PZA and EMB determinations. 57% and 50% of all INH and RIF levels were categorized as "very low". In 7 of 17 patients INH and RMP levels were concurrently low or very low. However, 16 of 17 (94%) patients completed therapy and were cured based on WHO guidelines. Our study underlines the need to validate whether the reference ranges published by Peloquin, and widely used ever since, represent reliable therapeutic target concentrations that correlate with the TB treatment outcome in the clinical setting. Our data suggest that the therapeutic ranges for INH and RMP might be below the suggested ranges especially when combination treatment is used. Based on these finding a large-scale prospective PK and outcome study has been set up and is now ongoing in Uganda with the aim to investigate the association between serum concentrations of ATD and tuberculosis treatment response in HIV-TB-co-infected individuals (clinicaltrials.gov - NCT01782950).

4. Value of presented work

With the results of the discussed studies we were able to suggest an optimized dosing regimen of two antibiotics in critically ill patients with severe infections undergoing renal replacement therapy. This has major implications for the avoidance of under dosing with the risk of treatment failure in this susceptible patient population. We additionally for the first time present an approach for daptomycin drug monitoring in patients undergoing CRRT by demonstrating a clear correlation between trough levels and drug exposure. Furthermore, we provided insights into the validity of reference ranges of anti-tuberculosis drugs which offers rational for further investigations.

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