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van Zanten, A.R.H.

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Summary, general conclusions and future perspectives

CHAPTER 1

Infectious complications in critically ill patients are frequently encountered. Early diagnosis and institution of adequate therapeutic interventions are essential to provide best chances for a favourable outcome.

The aim of the present thesis was to evaluate several aspects of infectious complications in the critically ill. Firstly, clinical aspects are addressed, secondly pharmacological issues are studied and finally economic aspects of antibiotic treatment of infectious complications in the critically ill were investigated.

CHAPTER 2

Ciprofloxacin, a broad-spectrum antibacterial drug from the class of fluoroquinolones, is used in a wide range of infections in critically patients. A new method to quantify the total (unbound+protein-bound) ciprofloxacin concentrations in human serum is presented based on rapid liquid-liquid extraction, followed by reversed-phase liquid chromatography and UV detection at 280 nm.

The mean accuracy and precision were all within specifications. Metabolites and frequently used co-medications showed minimal interference. Sample storage conditions suitable for routine determination of serum ciprofloxacin concentrations for daily therapeutic drug monitoring at different temperatures (-80°C - +4°C) and storage (48 hours – 6 months) showed acceptable sample stability.

CHAPTER 3

In the case of fluoroquinolones the killing of bacteria is determined by the 'area-under-the-curve' (AUC), which can be obtained by mathematical integration of the serum concentration-time curve (surface area) and the peak concentration (C_{\max}).

The ratio of the AUC to the MIC of the causative micro-organism (AUC/MIC) is a good predictor of treatment efficacy. For ciprofloxacin various studies have suggested that an AUC/MIC-ratio of 125 is required for optimum clinical effects. Few data are available regarding the use of fluoroquinolones in critically ill patients. Therefore, we prospectively studied the pharmacokinetics of ciprofloxacin in 32 critically ill (age:68.7±17.4; SOFA-scores:7.3±3.4) patients. The measured drug levels were correlated to MIC values of pathogens commonly found in our ICU population. We studied ciprofloxacin pharmacokinetics after administration of 400 mg *bid* intravenously. This regimen lead to inadequate AUC/MIC and C_{\max} /MIC-ratios in many cases. Effective killing concentrations were only achieved in pathogens with MIC<0.25 mg/l. Female gender, CVVH, creatinin, and SOFA_{renal} points predicted higher AUC. Cumulative SOFA-scores were most predictive of high AUC's.

CHAPTER 4

In contrast to other categories of antibiotics such as quinolones and aminoglycosides, beta-lactam antibiotics do not have a significant 'post-antibiotic effect'. Based on this knowledge of the pharmacokinetics and pharmacodynamics of beta-lactam antibiotics, continuous infusion of these drugs is usually recommended as the most effective form of treatment. There is a close relationship between treatment efficacy and the duration of time that serum concentrations of the antibiotic exceed the minimal inhibitory concentration (MIC) for the causative micro-organism. According to the literature bacterial killing rates by beta-lactam antibiotics are largely determined by the percentage of time – at least 60-70% of the dosing interval – that antibiotic concentrations are 4-5 x MIC, while bacterial resistance is related to the time during which antibiotic concentrations are lower than MIC.

Very few studies have been performed to address the pharmacokinetics of continuous versus intermittent administration of cephalosporins in ICU patients. Various factors may combine in this category of patients that could significantly alter pharmacokinetics, such as impaired renal- and liver function, altered volume of distribution, use of numerous co-medications, etc. The effectiveness of antibiotic treatment and the prevention of antibiotic resistance may be even more important in the critical care setting than elsewhere, making effective dosing an issue of paramount importance.

Therefore, we performed a prospective randomised study to compare the pharmacokinetics of cefotaxime after continuous or intermittent administration in 44 consecutive ICU patients with respiratory infections (n=24; cefotaxime 2 grams/24 hrs, loading dose 1g vs. n=20; cefotaxime; 1 gram *tid*). Patients were well matched. We found that although C_{\max} , C_{mean} and AUC were higher during intermittent administration due to the higher daily dose, C_{\min} was significantly lower. During intermittent administration, these lower drug levels were significantly more frequently observed compared to

continuous infusion, in particular at the end of the dosing interval, potentially reducing the bactericidal effects. However, the relevant time of concentrations above 1.0 mg/l and 5.0 mg/l were similar in both groups, and exceeded thresholds of 60-70% time above MIC. We observed large (18-fold) individual variations in cefotaxime concentrations.

CHAPTER 5

In a randomized controlled prospective non-blinded study in 93 consecutive hospitalized patients requiring antibiotics for acute exacerbations of COPD (47 patients; cefotaxime (2 grams/24 hrs, loading dose 1g) vs. 46 patients; cefotaxime (1 gram *tid* intermittently), we evaluated serum drug levels, antibiotic susceptibility before and after treatment, and clinical efficacy. Similar pathogens were found in both groups, mostly *H. influenzae*, *S. pneumoniae* and *M. catharralis*. Average MIC values were similar in both groups before and after treatment. Clinical cure was achieved in 93% of cases in both groups. In microbiologically evaluable patients criteria such as 70% of treatment time with antibiotic concentrations \geq MIC and/or \geq 5xMIC were significantly better for continuous administration. Samples with suboptimal antibiotic concentrations were not found during continuous infusion vs. 65% of patients during intermittent administration. Continuous administration of cefotaxime is at least equally effective from a pharmacodynamic and microbiological perspective, may be more cost-effective, and offers the same clinical efficacy, even using a 1 gram lower daily dose.

CHAPTER 6

Costs are one of the factors determining physicians' choice of medication to treat patients in specific situations. However, usually only the drug acquisition costs are taken into account, whereas other factors such as the use of disposable materials, the drug preparation time and the staff workload are insufficiently taken into consideration. We therefore decided to assess true overall costs of intravenous antibiotic administration by performing an activity-based costing approach.

To assess the costs associated with drug preparation and administration we performed an observational time and motion study in two ICUs. For comparison, we also performed this analysis in a general internal medicine ward. In total, 103 routine acts of preparing and administering IV antibiotics were studied. The basis of a time and motion study is the measurement, through direct observation by the investigators and the research nurses involved in the study, of staff members performing specific tasks in a process that is subdivided into various components.

Four different methods of drug administration were used: continuous administration by volumetric pump, continuous administration by syringe pump, administration by 'unaided' infusion bag, and administration by direct IV injection. The average times

required for each of these procedures, including preparation and administration of the drug, were $4:49 \pm 2:37$, $4:56 \pm 2:03$, $5:51 \pm 3:33$ and $9:21 \pm 2:16$ min, respectively. When the costs for expended staff time and materials (not including drug costs) were calculated this resulted in average costs of € 5.65, € 7.28, € 5.36 and € 3.83, respectively, for administration of each dose of antibiotics. These costs represent between 11% and 53% of the total daily costs of antibiotic therapy. Compared with the acquisition costs, these indirect costs ranged from 13% to 113%. Not included in this comparison is the time required for insertion of an IV catheter, which was found to be $10:15 \pm 6:31$ min with an average calculated cost of € 9.17.

Use of IV antibiotics is associated with considerable workload and additional costs that can exceed the acquisition costs of the medications themselves. We concluded that the total costs of IV antibiotic administration are formed not only by the costs of the drugs themselves, but also, to a substantial degree, by the time expended by medical and nursing staff, costs of disposable materials and overhead costs.

CHAPTER 7

Sinusitis is a well recognised complication in critically ill patients. It has been linked to both nasotracheal and orotracheal intubation. We studied the incidence of sinusitis in 351 patients with fever of unknown origin in the intensive care unit with the aim of establishing a protocol that would be applicable in everyday clinical practice. Therefore, sinus X-rays (SXR) were performed in 198 patients with fever for which an initial screening (physical examination, microbiological cultures and chest X-ray) revealed no obvious cause. All patients were followed with a rigorous protocol, including antral drainage in all patients with abnormal or equivocal results on their SXR. 129 had obvious or equivocal abnormalities. Sinus drainage revealed purulent material and positive cultures (predominantly *Pseudomonas* and *Klebsiella* species) in 84 patients. Final diagnosis for the cause of fever in all 351 patients based on X-ray results, microbiological cultures, and clinical response to sinus drainage indicated sinusitis as the sole cause of fever in 57 (16.2%) and as contributing factor in 48 (13.8%) patients with FUO. This will underestimate the actual incidence because SXR and drainage were not performed in all patients.

CHAPTER 8

The administration of antibiotics should be carefully targeted at the proven or suspected causative pathogen(s), using a strategy that takes pharmacokinetics and pharmacodynamics for the applied antibiotic into consideration to increase efficacy and reduce the risk of antimicrobial resistance. In addition, in times of tight budgets and increased workload, economic aspects of drug therapies should also be taken into account.

In critically ill patients host defence factors play an important role, as many ICU patients should be regarded as having (temporarily) diminished immune functions, due to factors such as downregulation of immune function following severe infections, administration of drugs such as corticosteroids, underlying chronic diseases, impairment or interruption of local defence systems (e.g. endotracheal intubation and mechanical ventilation) and various other factors.

First, in this overview the question was addressed whether adequacy of antibiotics matters in ICU patients. From the literature, evidence was provided that the administration of the right antibiotics in the treatment of both community-acquired and nosocomial infections in critically ill patients appears to be a major determinant of outcome. In addition, although adequate treatment may have been instituted, outcome is also determined by the pathogens involved and other factors such as the severity of illness.

Second, the timing of antibiotic administration was addressed. Available data suggest that not just the appropriateness of antibiotic treatment but also the speed of initiation of this treatment is a major determinant for outcome in critically ill patients. Earlier initiation of therapy may significantly improve outcome; conversely, a prolonged delay may lead to marked reductions in favourable outcome.

To decrease the risk of inappropriate choice of antibiotics several measures may be considered: the use of antibiotic practice guidelines, consulting an infectious disease specialist or microbiologist, and implementing more rapid methods of microbiological identification. Furthermore, intensivists should be familiar with the pathogens most frequently involved in community-acquired and nosocomial infections encountered in their ICU. Initiation of (empirical) antibiotic treatment based on this knowledge as well as individual patient characteristics will increase the likelihood of initiating the right therapy. In many cases this will require initial treatment with broad-spectrum antibiotics, which can be changed when the culture results are known.

When treating patients with antibiotics also pharmacokinetic and pharmacodynamic aspects should be taken into consideration. From the pharmacokinetic perspective, dose adjustments may be necessary in case of reduced or increased drug elimination.

The pharmacodynamic interaction between antibiotic and pathogen differs between various classes of antibiotics. The bactericidal activity of the different classes of antibiotics can be either time or concentration dependent or both. If time dependent killing is the major determinant of microbiological cure, more frequent dosing or continuous administration should be considered (e.g. continuous infusion of beta-lactam antibiotics). In concentration dependent killing once-daily administration may be optimal to increase efficacy and reduce toxicity (e.g. aminoglycoside administration). If both mechanisms play a role, as in dose dependent-killing, increasing the dose may be

necessary to improve the AUC/MIC ratio (e.g. ciprofloxacin administration). Due to large variations in drug levels found in ICU patients after administration of the same dose, therapeutic drug monitoring probably should be used more frequently for efficacy reasons and not only, as is common, for reasons of preventing toxicity.

Considering costs, the total costs and not only drug acquisition costs should be taken into account. Total administration costs may vary among different antibiotics. Continuous infusion may be a strategy to reduce staff workload as well as costs. Increased workload has been associated with adverse outcome, increased complication rates, increased length of stay, and even with higher mortality.

In conclusion, individual treatment strategies combining patient characteristics, bacterial susceptibility, knowledge of pharmacokinetics/pharmacodynamics and therapeutic drug monitoring of antibiotics may help improve microbiological and clinical outcome and decrease the risk antimicrobial drug resistance in critically ill patients. If also administration costs are combined with the previous aspects, rational use of antibiotics in the ICU will result, likely promoting optimum efficacy for the lowest costs.

CHAPTER 9

Critical care organisational aspects are briefly mentioned to provide contextual information on the setting in which many ICU patients in the Netherlands are treated for infectious complications during their stay in the intensive care.

GENERAL CONCLUSIONS

Physicians treating critically ill patients should be aware of the high risk of sinusitis and take appropriate preventive measures, including the removal of nasogastric tubes in patients requiring long-term mechanical ventilation. Routine investigation of fever of unknown origin should include computed tomography scan, SXR or sinus ultrasonography, and if necessary antral drainage.

Ciprofloxacin is frequently used in the ICU setting. We recommend to use higher doses of ciprofloxacin (1200 mg daily) to ensure optimal bacterial killing and avoid antibiotic resistance, as bacteria in ICU patients frequently have higher MICs than 0.25 mg/l and drug levels are insufficient using 800 mg per day to be effective in pathogens with higher MICs. A new and rapid method to measure ciprofloxacin drug levels is available.

Both in COPD and ICU patients continuous cefotaxime infusion leads to adequate drug levels and time above threshold drug levels for more than 60-70% of the dosing interval compared to intermittent administration, although a one gram lower daily dose was used. In the COPD patients clinical and microbiological cure and resistance patterns of pathogens were similar, suggesting no negative effects on outcome or the development of resistance using continuous infusion.

Continuous infusion both reduces costs and workload. It may reduce time intervals below MIC and facilitate therapeutic drug monitoring. Based on these observations we recommend continuous administration of cefotaxime as the preferred mode of administration both in COPD as well as in ICU patients. We are confident that these results can also be achieved in other patients groups and with other antibiotics with time-dependent killing such as beta-lactam antibiotics.

The overall quality of care, outcome, and patient and family satisfaction in intensive care units may be linked to the workload and staffing levels. Budgetary restrictions may play an important role in the organisation of the ICU, and cost reduction is an important issue in intensive care medicine today since ICU costs account for up to 10% of overall hospital expenditure. Antibiotics are among the most frequently used drugs in intensive care patients, and thus account for a substantial proportion of drug expenditure in ICUs. When performing pharmacoeconomic evaluations of ICU expenditure, it is customary to consider only the direct price of purchasing these medications. To assess the total costs of intravenous drug therapy in the ICU setting, however, it is necessary to take into account the effect on the workload of nurses and medical staff as well as other health care workers, and to evaluate other costs associated with preparation, administration and monitoring of IV antibiotic therapy. Gaining insight into all the factors that contribute to the actual total overall costs of drug therapy may help increase awareness into what actually drives the costs of hospital services, and to identify opportunities for cost savings.

FUTURE PERSPECTIVES

Every thesis provides answers, but will probably generate more questions as well. From the perspective of infectious complications an important question to address is whether we will be able to more effectively prevent the occurrence of infectious complications. With respect to ventilator-associated pneumonia, the most frequently encountered infectious complication in ventilated patients, preventive measures such as the semirecumbent position, subglottic suction drainage, kinetic therapy and selective decontamination of the digestive tract may be considered.

With respect to the host factors, no major effective strategies to improve the immune function or local and systemic defence mechanisms in critically ill patients have come available yet. As more knowledge on the inflammatory response in critical illness emerges, negative effects on immune function and defence mechanisms may become more evident, potentially leading to effective therapeutic interventions in the future. With respect to antibiotics, clinical or microbiological failure and the emergence of resistance may, at least in part, be due to inadequate use of antibiotics, inadequate dosing and administration and unexpected variations in drug levels in standardised dosing regimens. In particular, critically ill patients are at risk for these aspects due to

complex pharmacokinetic influences and interactions, more frequently encountered resistant pathogens, and disturbed host defence factors. Therefore, more research on PK/PD of antibiotics in ICU patients could be performed. We cannot be confident that extrapolation of pharmacokinetic and pharmacodynamic data from less severely ill patients can also be used to treat ICU patients. More individualised strategies will lead to the need for more therapeutic drug monitoring. More rapid and reliable methods to measure antibiotic drug levels of a spectrum of commonly used antibiotics in ICU patients should come available. We know that adequacy, timing and dosing of antibiotics matter for the outcome of our patients. And we know that our armamentarium of antibiotics will not be growing very rapidly as the number of new antibiotics that will reach the market is limited and pathogens will become more resistant. Therefore, we should optimise our antibiotic treatment strategies and do more research in this field. This will help to avoid the situation that we can support any organ system and monitor organ functions with spectacular devices and not being able to treat the underlying infectious complication effectively.

The challenging aspect of this research area is to combine the knowledge of experts from areas such as microbiology, pharmacy, infectious diseases and critical care medicine. Intensivists are confident to treat patients in a multidisciplinary setting and must be able to infect others with enthusiasm for this important research area of critical care medicine. Although treating patients with antibiotics for infectious complications has a long track-record in medicine, the knowledge on effective and safe antibiotic treatment in the most seriously ill patients is still in its childhood.