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Pharmacokinetics of antifungal drugs in severely ill patients

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CHAPTER 7

Discussion

The main objective of this thesis was to improve the understanding of the pharmacokinetics of antifungal agents in severely ill patients. In addition the application of therapeutic drug monitoring was evaluated in order to eventually improve the outcome of antifungal treatment. In this chapter the results of the studies performed are discussed and perspectives for future research are provided.

ANIDULAFUNGIN

For pharmacokinetic studies it is essential to be able to measure concentrations of the drugs of interest. Therefore a validated method was developed to measure anidulafungin and also caspofungin concentrations in plasma (1). It is convenient if all drugs from the same class can be determined with the same method of analysis. Unfortunately it appeared not feasible to include also micafungin, the third echinocandin. The signal of anidulafungin and caspofungin were better when operating in the positive mode whereas the signal of micafungin was better in the negative mode. In addition, we would like to have been able to determine the free fraction because of the high protein binding of the echinocandins. Unfortunately, the simple method, using ultrafiltration, is not suitable for the echinocandins because of the adhesion to the ultrafiltration caps. For the separation of the free fraction time-consuming micro-dialysis methods are needed. Besides the difficulties in separating the free fraction, the concentrations of the free fraction would be below the limit of quantification of our method. Therefore, the only possibility at this moment is, to assume that the free fraction of anidulafungin is 1%. Perhaps in the near future complementary procedures may be of help to solve this problem (2).

The pharmacokinetics of anidulafungin were studied in critically ill patients who are rarely the population of interest in studies, although conceivably, anidulafungin treatment can be very important for these patients. A lower anidulafungin exposure was observed in the critically ill patients in our hospital (3). Assessing treatment outcome is challenging in critically ill patients with complex pathology, as final outcome is confounded by many factors not easily captured in studies with limited sample size. The clinical relevance of a lower exposure was therefore investigated based on the area under the concentration-time curve from 0 to 24 h (AUC_{0-24})/MIC ratio. The observed lower anidulafungin exposure in our patients may not be clinically relevant as all AUC_{0-24}/MIC ratios appeared above the target value based

on European Committee on Antimicrobial Susceptibility Testing (EUCAST) data (4). The caveat is that this was based on an estimated free fraction of 1%, not on a measured free fraction. The free fraction of anidulafungin in critically ill patients could be higher since a low plasma protein concentration is typical for those patients. This can possibly result in a free, unbound fraction of the exposure (*f*AUC) that could be comparable with the *f*AUC of the general patient population.

The observed variability in anidulafungin exposure was partly explained by total body water volumes and total bilirubin concentrations (3). No correlation could be established between anidulafungin exposure and disease severity scores or plasma protein concentrations (3). A correlation between exposure and disease severity was expected based on an increased clearance in more severely ill patients (5). Although disease severity scores were never developed or validated to explain pharmacokinetic variability, they were tentatively used to successfully explain pharmacokinetic variability of other drugs (6-9). A positive correlation between exposure and plasma protein concentrations was expected based on the high protein binding of anidulafungin (10) and the results from a study with caspofungin (11). In case of hypoalbuminaemia the apparent total volume of distribution and clearance of a drug are likely to increase, which would translate into a lower exposure (12). Again, measuring the free fraction of anidulafungin would be preferred but this was unfortunately not possible.

Currently there are limited data available on the distribution, metabolism, and elimination of anidulafungin, which makes it difficult to determine which pathophysiological changes in critically ill patients influence anidulafungin pharmacokinetics. From a clinical point of view, it would be helpful to identify patients at risk for a low and/or inadequate exposure beforehand. Future studies should therefore include a more heterogeneous population, i.e. not only critically ill patients, with larger variations in plasma protein and bilirubin concentrations, in order to be able to detect possible differences.

The data from the study in critically ill patients (3) were subsequently used to investigate if limited-sampling strategies were feasible (13). The anidulafungin exposure can be estimated accurately using a single sample drawn 12 h after the start of the infusion, by using linear regression or a population pharmacokinetic

model, in critically ill patients and in healthy volunteers. By using a limited-sampling strategy, a single blood sample can be drawn instead of a full concentration-time curve to assess the AUC, which is convenient for future research and in specific clinical situations. While developing the pharmacokinetic model in MW\Pharm for limited sampling the importance of including additional data other than the data of the concentration-time curve was noticed. The additional data ensured a more accurate estimation of the elimination half-life. When using only the data from the concentration-time curve, which shows a slow terminal elimination, the elimination half-life was overestimated to such an extent that it contradicted the observed relatively constant anidulafungin trough concentrations.

VORICONAZOLE

At this moment there are various data available for voriconazole; voriconazole pharmacokinetics display large inter- and intra-individual variability and there is evidence for the added value of therapeutic drug monitoring of voriconazole. In addition, a validated method for the analysis of voriconazole was already available (14). Therefore the focus for voriconazole was on the ability to explain more of the observed pharmacokinetic variability and on the application of therapeutic drug monitoring in daily practice in patients admitted to the intensive care.

Although the importance of voriconazole therapeutic drug monitoring seems accepted by clinicians and pharmacists, given that in most patients voriconazole concentrations were measured, the implementation requires improvement given the frequent premature sampling, incompleteness of data on clinical context and lack of follow up on recommendations. The effect of education of health care professionals is limited (15) and wanes with time (15, 16), especially in teaching hospitals due to frequent changes in staff. Nowadays there are opportunities to support effective therapeutic drug monitoring with clinical decision rules. However in our hospital there was not enough clinical information digitally available, at the moment the study was conducted, to design an efficient clinical decision rule. A multidisciplinary approach – for instance by means of antifungal stewardship – will probably be able to overcome problems encountered.

Inflammation, reflected by C-reactive protein (CRP) concentrations, is associated

with voriconazole trough concentrations(17). A limitation of this retrospective study was that only a part of the variability of voriconazole pharmacokinetics could be explained, partly because data on the polymorphisms of cytochrome P450 isoenzymes were not available and polymorphisms of cytochrome P450 2C19 contribute to the inter-individual variability of voriconazole pharmacokinetics (19). Further prospective research is therefore necessary that includes data on the polymorphisms of cytochrome P450 isoenzymes. It would be desirable to also gather data on the voriconazole n-oxide, interleukin 6, and interleukin 8 concentrations. Voriconazole n-oxide is the main metabolite of voriconazole (20) and the ratio of voriconazole and this metabolite could possibly change when the inflammatory status of the patient changes. Measuring pro-inflammatory cytokines, as interleukin 6 and 8, is preferable because the cytokines influence the cytochrome P450 isoenzymes (21). We used CRP concentrations as a marker for inflammatory status because concentrations of pro-inflammatory cytokines were not available due to the retrospective nature of this study. Cytokines stimulate the production of acute-phase proteins and especially CRP concentrations change rapidly when the inflammatory status of a patient changes (22).

When more prospective data are gathered regarding the influence of inflammation on voriconazole concentrations it could be possible to develop a dosing algorithm that may predict the voriconazole concentration based on patient characteristics and voriconazole dose and route of administration. So far it has been challenging to build a pharmacokinetic model for voriconazole. Using data from ICU patients, an attempt was made to build a model for voriconazole in critically ill patients in MW\Pharm. Unfortunately, these efforts have not yet resulted in an easy-to-use and validated model. Information on cytochrome P450 isoenzymes was lacking due to the retrospective nature and we were not aware of the possible influence of inflammation on voriconazole pharmacokinetic at that moment. Hope et al. succeeded in developing a pharmacokinetic model for voriconazole although even this model is not yet broadly applicable in daily practice, since only intravenously administered voriconazole was included in the model and it was only tested in patients without invasive fungal infection (23). Developing a model for daily practice is still challenging, since several factors contribute to the pharmacokinetic variability and we still do not know if we are currently able to explain all of the observed variability. Besides, for the development of a pharmacokinetic model for

voriconazole, software is required that is able to take into account all the factors that contribute considerably to the variability of voriconazole pharmacokinetics and is easy to use in daily practice.

In conclusion, the research performed contributed to the knowledge about the pharmacokinetics of antifungal agents in severely ill patients, but continued efforts are required for improvement. Management of invasive fungal infections can be improved by a multidisciplinary approach, in clinical practice as well as in research. For anidulafungin, clinical validation of AUC/MIC ratios and more insight in the pharmacokinetic variability between patients is necessary. Although many factors explaining the variability of voriconazole pharmacokinetics have been identified, it is not unconceivable that there are more factors that influence voriconazole pharmacokinetics. A dosing algorithm or pharmacokinetic model would be useful for clinical practice. Improvement of the implementation of voriconazole therapeutic drug monitoring is important considering the pharmacokinetic variability of voriconazole and the relation between trough concentrations and treatment outcome. Collaborative networks of institutions prepared to share data would potentially importantly improve the speed and power to further enhance our scientific knowledge to improve the treatment of these severely ill vulnerable patients.

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