Rational use of antibiotics

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CHAPTER 11

RECAPUTILATION AND GENERAL DISCUSSION

The scope of this thesis was to investigate some measures to optimize antibiotic treatment that can be applied to combat the increasing antibiotic resistance. The historical background sketched in the introduction of this thesis showed a timeline, from the time point of the discovery of penicillin in 1928 towards the development of more than 30 antibiotics between 1950 and 1980. However, nowadays, the 'back side', i.e. antibiotic resistance, is considered as one of the biggest threats to global health. At present, the WHO marks antibiotic resistance as a major threat to mankind, ranked along with climate change and terrorism[1]. Several actions have been suggested to tackle the emergence of antibiotic resistance. Cornerstones of an effective strategy to respond to antibiotic resistance include:

1. refining stewardship of existing antimicrobials
2. re-introducing old antibiotics within the framework of antimicrobial stewardship
3. introducing new antimicrobial agents

This thesis focuses on ways to stimulate rational and effective use of antimicrobials, by following the first two action points: (1) refining stewardship of existing antimicrobials and (2) re-introducing old antibiotics within the framework of antimicrobial stewardship.

Refining stewardship of existing antimicrobials

Chapter 2 and **chapter 3** focused on the oral absorption of flucloxacillin. This antibiotic is used specifically to treat infections caused by methicillin susceptible *Staphylococcus aureus* strains, in countries with low prevalence of MRSA, such as in the Netherlands[2]. In case of severe infections flucloxacillin is administered initially intravenously, followed by oral administration. The fraction of flucloxacillin that is absorbed after oral administration is highly variable[3]. Therefore, it is necessary to assure that patients absorb sufficient flucloxacillin, in order to attain efficacy. In case of sufficient absorption, intravenous administration can be switched to oral flucloxacillin. To assess the oral absorption flucloxacillin, therapeutic drug monitoring (TDM) was introduced in LUMC. This test starts after an overnight interruption of intravenous flucloxacillin while the patient fasted. Thereafter, an oral test dose of 1 gram of flucloxacillin is given. Blood samples before and 1 and 2 hours after the oral dose are taken to measure the concentration of flucloxacillin (test A). Though this test worked well, it has the disadvantages of proneness to human error and it is rather laborious. Therefore, we developed an alternative test considering that the therapeutic index of flucloxacillin is wide and hence toxicity at this high concentrations does not occur. This allowed to design a simplified absorption test in which 1 gram of flucloxacillin was administrated orally in the morning with the patient in a common fasted state (eg before breakfast) while the intravenous flucloxacillin was continued, and blood samples were taken before and 1 and 2 hours after the oral dose (test B). To compare the tests a study was performed in 43 patients, data of 19 patients that were previously subjected to test A were compared to data of 24 patients subjected to the new test B. The patient groups were comparable. It was found that the average maximal increase in flucloxacillin levels for both tests were similar, and both tests identified approximately 10% of the patients as poor absorbers. We concluded that the simpler test B yielded similar results compared to the more elaborate test A.

Therefore, the new flucloxacillin absorption test (test B) was introduced in the LUMC and a follow-up study was performed in a larger population (chapter 3). This study was performed in 196 patients receiving intravenous flucloxacillin and for whom oral maintenance therapy was considered. Upon analysis, it was noted that still some old tests A were performed (n=28), but in the majority of the patients (n=168) the new test was performed, Both groups were comparable regarding the baseline characteristics. We found that the average increase in flucloxacillin concentration was 22.0 and 21.5 mg/L for test A and B, respectively. Twenty-six (13%) patients were identified as insufficient absorbers. In this larger study we thus confirmed that both tests yield similar outcomes, and that TDM is indeed needed to assure effective continuation of therapy via the oral route. In conclusion, we advocate the use of the simplified flucloxacillin absorption test. These studies show how rational use of TDM can aid in antibiotic stewardship, and at the same time reduces the chance of infusion errors and prevents an undesirable drop in flucloxacillin concentrations. Thus, it can be used as tool to optimize the use of small spectrum antibiotics, while avoiding rather complicated procedures.

In **chapter 4** we investigated the absorption of oral penicillin, which is known to have large inter-individual and intra-individual variability in bioavailability (4). In the LUMC, an oral penicillin (pheneticillin) absorption test has been integrated in clinical practice. In this thesis, the oral absorption test, executed in 88 hospitalized patients, was evaluated. In brief, patients treated with intravenous penicillin were given an oral dose of 1 gram of pheneticillin in the fasted state and blood samples were taken at 1 and 2 hours. We found that 36% patients absorbed pheneticillin poorly, confirming previous findings and emphasizing the need for TDM in case of switching from intravenous penicillin to pheneticillin. When absorption testing is not available, we advise not to use pheneticillin, but to choose another antibiotic, for instance oral amoxicillin, which is known to be absorbed well.[9-11] With this approach the chance of improper antibiotic use is reduced; it improves patient outcome, reduces the risk on antimicrobial resistance and lastly it reduces medical costs.

In **chapter 5** we evaluated the absorption of the antibiotic rifampicin, a potent antibiotic against a variety of pathogens, including mycobacteria. Rifampicin is mainly used in the first-line treatment of active or latent tuberculosis (TB), due to its high activity against *Mycobacterium tuberculosis*. The worldwide use of rifampicin together with the high risk of developing rifamycin-resistance among all susceptible bacteria is a pervasive concern.[12] In particular, rifamycins are prone to 'endogenous resistance development'[13] resulting from mutations in the target

sites of *Mycobacteria*.[12] This may be aggravated by extrinsic factors resulting in wide-spread resistance of *Mycobacterium tuberculosis* to rifamycins.[14] For the latter, insufficient serum concentrations of rifampin are particularly important in the development of drug resistance.[15,16] Notwithstanding, TDM of rifampin is not part of routine clinical practice. This prompted us to measure rifampicin levels in serum (chapter 5). We conducted a study in 90 patients to measure serum concentrations of rifampin at 0, 3 and 6 hours after drug intake. Furthermore, criteria for interpretation of serum concentrations were established. We found that 63 out of 90 patients (79%) had adequate rifampicin levels in their blood samples drawn at 3 hours after intake. In conclusion, rifampin levels varied but were mostly within the targeted range and a single measurement at 3 hours after intake provided the required information in most cases, indicating that serial measurements could be reserved for specific situations only. We encourage the introduction of a single measurement in clinical practice.

Re-introducing old antibiotics within the framework of antimicrobial stewardship

In addition to improving the use of existing drugs – as described in the first chapters of this thesis – revival of old drugs previously discontinued in routine clinical practice constitutes an opportunity to combat antimicrobial resistance. Polymyxins and fosfomycin are examples of these antibiotics that have barely been used in clinical practice since the seventies of the last century in The Netherlands. After publications about significant side effects – especially nephrotoxicity and neurotoxicity[10] – colistin disappeared from clinical practice in the seventies of the previous century, it was introduced again in first decade of this century due to the need to combat multiple drug resistant organisms. An overview of the potential uses and of the remaining gaps in our knowledge concerning polymyxin E (colistin) is given in **chapter 6**.

At present intravenous colistin is considered as rescue treatment for critically ill patients with infections caused by multidrug resistant Gram-negative bacteria. Further, strict guidelines in terms of antibiotic stewardship have been developed to promote colistin's efficacy and to prevent the emergence of resistance against colistin. No major forms of nephrotoxicity and neurotoxicity, reasons for their earlier withdrawal, have recently been reported.

As before, colistin is currently is mainly used as therapy for the treatment of pulmonary infection by multidrug resistant *Pseudomonas aeruginosa* especially in Cystic Fibrosis patients. Intravenous treatment with colistin is administered in hospitals. To explore whether colistin is suitable for prolonged intravenous administration at patients' homes, we investigated the stability of colistin methanesulfonate (CMS) in **chapter 7**. We found that CMS infusion solution is sufficiently stable for a period of 7 days when refrigerated plus one additional day kept at room temperature. In conclusion, it does appear that CMS is stable for a reasonable time to allow administration of colistin at home, which provides a real benefit for the patient.

Fosfomycin is another antibiotic for which renewed interest is shown. Fosfomycin was discovered in 1969 and is described in detail in **chapter 8**. Fosfomycin has a broad spectrum of activity, including MDR bacteria. In the Netherlands, fosfomycin is currently registered as oral treatment for uncomplicated urinary tract infections. Recently, an intravenous formulation of fosfomycin has been registered for use in the Netherlands.

The oral dose regimen for the treatment of uncomplicated cystitis is unlikely to result effective serum and tissue concentrations for the treatment of complicated systemic infections. To substantiate this assumption, first more detailed information on the pharmacokinetics (PK) of the drug is required. In **Chapter 9** different fosfomycin-dosing regimens were subjected to PK-modelling using surrogate pharmacodynamic (PD) indices to evaluate possible treatment regimens for treatment of systemic infections. Our PK/PD model provided quantitative evidence that a dosing regimen of 6–12 g per day divided in 3 doses is required to obtain effective concentrations in the treatment of systemic multi-drug-resistant bacterial infections.

Chapter 10 describes a prospective clinical trial in patients with recurrent urinary tract infections who were prescribed fosfomycin 3 gram once every three days for at least two weeks. Patients were dosed with 3 gram oral and intravenous administration and blood and urine samples were taken. Based on the finding that fosfomycin urine levels were above an MIC of 8 mg/L for 72 hours, it appears that a dose regimen of 3 gram fosfomycin orally every 72 hours is appropriate to treat patients with recurrent urinary tract infections, who are otherwise unresponsive.

How to combat antibiotics resistance

Now we have explored some cornerstones that could be instrumental in a successful strategy towards the rational use of antibiotics, the following recommendations could be distilled from the results described in this thesis:

- The rules of antibiotic stewardship are essential and must be implemented and maintained in all disciplines of medicine.
- Reliable and easy to use protocols using validated assays for appropriate matrices with a short turn-around time are of great importance to successfully implement therapeutic drug monitoring (TDM) and may overcome practical objections that currently obstruct rational use of antibiotics.
- TDM should involve the assessment of drug concentrations in plasma or serum, and if possible also at the site of the infection
- Assays should measure unbound concentrations of antimicrobials.
- It does seem that personalized antibiotic treatment for patients is best achieved when combining concentration and effect of antibiotics and this should be performed by close collaboration between pharmacies (TDM) and medical

microbiology laboratory (name and MIC of the microorganism), supervised by an antibiotic team that integrates the results and provides therapeutic advice. Our plea is to optimally use the already available infrastructure to implement this.

- More prospective clinical trials, including clinically relevant outcomes, should be performed. The most important reasons that TDM is not commonly used for all antibiotic classes are unclear therapeutic PK/PD targets, the lack of clinical outcome studies and the unavailability of an assay in the hospital.[12-18]
- Both PK studies and PK/PD modeling studies should be performed during drug development for proof-of-concept, for dose and interval selection for clinical trials in humans, to determine susceptibility breakpoints, and evaluation the clinical meaning of antibiotic resistance.[19]

From the results of the studies presented in this thesis, more specific antibiotic-specific recommendations can be generated. We advise the universal introduction in clinical practice of the simple flucloxacillin absorption test that we developed. We advocate to switch from intravenous penicillin to pheneticillin in patients with severe infections after individual proof of sufficient absorption. When absorption testing is not available, we advise not to use pheneticillin, but to choose another antibiotic, for instance oral amoxicillin, which is known to be absorbed well.[4,20,21] With this approach, preferred use of small spectrum antibiotics when available, the chance of improper antibiotic use is reduced; it improves patient outcome, reduces the risk on antimicrobial resistance and, lastly, it reduces medical costs. We also encourage the introduction of a single measurement of rifampin in clinical practice to mitigate the development of resistance to rifampicin during treatment of tuberculosis, a major burden of disease still, particularly in low- and middle income countries.

Old antimicrobial agents have the potential to help combat the result of the emergence of antibiotic resistance, i.e. infections due to multiple drug resistant microorganisms. Colistin can be used parenterally outside the hospital setting, and fosfomycin can be used orally for the treatment of recurrent urinary tract infections, infections which would be difficult to treat without these new regimens applying old antimicrobial agents. It is recommended that re-introduction of these compounds will be based upon population PK/PD models designed for optimal clinical efficacy and for the better prevention of the emergence of antimicrobial resistances due to these therapies.

The third cornerstone of an effective strategy towards antibiotics resistance is the introduction of new agents. Although studies with new antimicrobial drugs have been published[22,23] showing the recent increased activity in the discovery and development of new drugs including plazomicin, a next generation aminoglycoside[23], the pharmaceutical pipeline is quite empty. Although this development possibly marks the beginning of a new era, it can only be part of the solution to overcome resistance to antibiotics.

Last but not least, medical doctors should be more educated in PK/PD and modelling. Extended clinical pharmacology education for medical doctors would give them better insight into dosing recommendations based on modelling and simulation studies, clinical breakpoints and TDM. Therefore, good pharmacology education and education on clinical breakpoints and TDM is highly recommended to improve antimicrobial therapy in clinical practice.

CONCLUSIONS

In conclusion, we conclude that antibiotic stewardship with TDM may assist for the rational use of antibiotics, and may be part of the solution to tackle the problem of increasing antibiotic resistance. Future prospective clinical pharmacological trials are an indispensable part of this strategy. Old antimicrobial agents in combination with PK/PD modeling studies could be helpful to re-use this forgotten antibiotics. Rational use of antibiotics must be on top of the scientific agenda, given the expected disaster of an estimate number of 10 million casualties per year, worldwide in 2050 due to antibiotic resistance.[1]

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