Clinical pharmacology in leishmaniasis: treatment optimization of a neglected disease

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Summary

Leishmaniasis is an infectious disease caused by Leishmania parasites and is transmitted by the bite of minuscule sandflies. It affects only the poorest of the poor in tropical regions worldwide - from the Indian subcontinent to East Africa and Latin America. Leishmaniasis is regarded as a neglected tropical disease, mainly because the options to treat these vulnerable patients have only marginally improved since the disease was discovered more than a century ago. This thesis focuses on the optimization and rationalization of chemotherapy used in the treatment of both cutaneous leishmaniasis (parasitic infection of the skin) and visceral leishmaniasis (parasitic infection of the internal organs), with an emphasis on mathematical-statistical models that describe the fate of the drug in the human body (pharmacokinetics) and the effect of the drug on the human body and parasites (pharmacodynamics). Additionally, we discuss the impact of poor-quality medicines for neglected tropical diseases and propose solutions to prevent the production and distribution of so-called ‘substandard’ medicines in developing countries.

Miltefosine is the first and currently only oral drug available to treat leishmaniasis and it is the primary subject of most of the clinical pharmacological research described in this thesis. As an introduction to this thesis, in chapter 1, a comprehensive overview is provided of all pharmacological aspects of miltefosine, its mechanism of action against Leishmania parasites, and its efficacy and tolerability in leishmaniasis patients. A perspective is provided on the current and future role of miltefosine in the treatment and elimination of leishmaniasis.

In chapter 2, a bioanalytical assay was developed and validated for miltefosine. Using liquid chromatography coupled to tandem mass spectrometry miltefosine could be measured in human blood plasma. This assay was pivotal to assess the pharmacokinetics of miltefosine in leishmaniasis patients, which is described in subsequent chapters.

The general focus of chapter 3 is pharmacokinetics in leishmaniasis patients. In chapter 3.1, the first population pharmacokinetic study of miltefosine is presented, carried out in a cohort of Dutch soldiers who contracted cutaneous leishmaniasis (Leishmania major) in Afghanistan. This pharmacokinetic analysis revealed that miltefosine was eliminated much slower from the body than previously thought and expected, with a terminal elimination half-life of 31 days, resulting in detectable levels of miltefosine up to at least 6 months after end of therapy. The expected impact of these findings on the emergence of drug resistance in parasites and the use of contraception in females are further discussed in this chapter.

Children make up more than 50% of the patient population suffering from cutaneous and visceral leishmaniasis, but typically little attention is attributed to them during the clinical drug development phases. In chapter 3.2, the scarcely
available miltefosine pharmacokinetic data from Indian pediatric patients were used to demonstrate that children are indeed underexposed to miltefosine when they receive a similar mg/kg daily dosage. Population modeling and simulation, also called pharmacometrics, was used to fully take advantage of all sparse data. A new dosing algorithm, based on allometric scaling, is proposed in this chapter, which should alleviate differences in drug exposure between children and adults and should improve clinical outcome in pediatric leishmaniasis patients.

The main safety concern for miltefosine, severely compromising its use in women, is its possible reproductive toxicity to fetus and embryo. As shown in chapter 3.1 and 3.2 miltefosine has a long residence time in the body. Little is known, however, about the duration of contraceptive cover required in women of child-bearing age after miltefosine treatment. In chapter 3.3 a novel translational method is discussed to estimate how long contraception should be provided to prevent any reproductive toxicity after various miltefosine treatment regimens. Following our recommendations, duration of post-treatment contraception should be extended from the currently advised 2 months to 4 months after a standard 28-day miltefosine treatment course. This finding has important implications for the rollout of miltefosine, but also stipulates the need for implementation of shorter combination treatment regimens.

The overall theme of chapter 4 is pharmacodynamics in leishmaniasis patients. In chapter 4.1, a technique is described to monitor parasite dynamics and clearance in lesions of cutaneous leishmaniasis patients. Leishmania parasite biomass was quantitatively monitored over time in repeated biopsies from skin lesions of two European cutaneous leishmaniasis patients, making use of a specific quantitative polymerase chain reaction (qPCR). This study provided not only individual estimates of parasite clearance rates; it also demonstrated that parasites remain in the skin lesions long after end of treatment, corresponding with a slow clinical response.

Chapter 4.2 reports a randomized clinical trial comparing different single doses of AmBisome® with a multiple dose regimen of AmBisome® for the treatment of visceral leishmaniasis in East Africa (Sudan and Ethiopia). In this study, the clearance of parasites was studied in repetitive blood samples of patients during their treatment. Despite small patient numbers, significant differences in clearance of the blood parasite biomass (Leishmania rRNA measured by qPCR) could be observed between single and multiple doses of AmBisome®, within the first few days of treatment. These differences in parasite clearance rates were predictive for the observed differences in clinical cure rates, which had led to early discontinuation of this trial. These pharmacodynamic results prompted the implementation of this qPCR methodology in various clinical trials on VL currently ongoing in East Africa.

It is currently unknown to what extent leishmaniasis patients need to be exposed to miltefosine in order to result in either cure or failure of therapy. In chapter 4.3, a first attempt is made to capture this exposure-effect relationship by investigating the association between miltefosine drug exposure and high treatment
failure rates in visceral leishmaniasis patients in Nepal. We demonstrated that the period of time patients were exposed to a threshold miltefosine concentration was associated with an increased probability of treatment failure. This study confirmed that Nepalese children were less exposed to miltefosine and had a higher risk to experience a disease relapse, while they received the same mg/kg body weight dosage. These findings are a major impetus to introduce the optimal miltefosine dosing schedule that was proposed in chapter 3.2.

In leishmaniasis, final cure is typically evaluated by following patients for several months after end of therapy to verify whether parasite biomass, and thus clinical symptoms, do return (i.e. relapse of disease) or will permanently subside. This clinical algorithm is far from ideal in the remote settings where leishmaniasis is endemic. Biomarkers that could indicate eventual clinical outcome early on during treatment and are able to monitor treatment efficacy are urgently needed to evaluate and compare new treatments and treatment combinations. In chapter 4.4, a systematic inventory is provided of potential and plausible pharmacodynamic biomarkers for cutaneous and visceral leishmaniasis to monitor therapeutic response. In this chapter we also provide a benchmark of specifications for pharmacodynamic biomarkers, defining priorities for future research in this direction.

Poor-quality medicines are particularly prevalent in low- and middle-income countries. In chapter 5 the impact of the quality of medicines in neglected tropical diseases is further discussed and global solutions are proposed. A miltefosine product without any active pharmaceutical ingredient was discovered in Bangladesh for use in the national elimination programme for visceral leishmaniasis. In chapter 5.1, a complimentary platform of forensic analytical chemical techniques is presented to characterize poor-quality miltefosine products. Most notably, a simple colorimetric test is presented which can be used in field circumstances to demonstrate semi-quantitatively the presence or absence of miltefosine in a pharmaceutical product. The discovery and its aftermath of the Bangladeshi miltefosine product not containing any miltefosine is further described in chapter 5.2, together with a critical discussion of the currently used terminology for poor-quality drugs and corresponding prioritizations in solving this global problem. The emphasis on intellectual property issues has led the international community to prioritize the fight against counterfeit medicines (e.g. produced by frauds with a criminal intent), in favour of so-called substandard medicines (e.g. produced by regular companies structurally neglected quality standards), which we believe to be a fallacy, since this latter category is equally dangerous for patients and thus equally important. In chapter 5.3 and 5.4 we discuss these issues and argue that neglected tropical diseases are particularly vulnerable for substandard drugs due to the typical public procurement of this category of medicines. Instead of a posteriori detection, a priori solutions to prevent poor-quality medicines should be prioritized. Preventive measures should be put in place, with an emphasis on strengthening of regulatory oversight in developing countries, so-called prequalification of drugs for neglected tropical diseases and
better public access to technical expertise on quality standards.

Manufacturers of medicines for neglected tropical diseases often cease or interrupt production, or the products that need to be used are labelled for different clinical indications, leading to confusion in guidelines and dose recommendations. In **chapter 5.5**, such an instance is illustrated for confusion in the dosage of pentamidine in used in clinical trials and guidelines for the treatment of leishmaniasis and human African trypanosomiasis, which arose during the past five decades due to the availability of two different pentamidine salts.

In conclusion, this thesis presents various novel applications of clinical pharmacokinetics and pharmacodynamics in the treatment of leishmaniasis, by which diverse clinically relevant issues, mainly related to the efficacy and safety of miltefosine, could be elucidated. Throughout this thesis, the added value of population modeling and simulation in clinical pharmacology has been exemplified, for instance by making full use of sparse datasets, translational preclinical-to-clinical extrapolation of toxicity and drug exposure, and design and *in silico* evaluation of optimal dosing regimens specifically aimed at pediatric populations. Additionally, investigations into the issues of poor-quality medicines for the treatment of neglected tropical diseases are presented and global solutions against this looming threat are discussed. This thesis has attempted to further improve the treatment for patients suffering from the neglected tropical disease leishmaniasis by optimizing the available treatment options and making them safer to use.