Drug Saf (2013) 36:83–91
DOI 10.1007/s40264-013-0017-y

PRACTICAL APPLICATION

Malaria Prophylaxis in Patients with Renal Impairment

A Review

Sabine Amet · Sarah Zimner-Rapuch · Vincent Launay-Vacher · Nicolas Janus · Gilbert Deray

Published online: 1 February 2013

Abstract Malaria is an endemic and potentially lethal disease transmitted by the protozoan parasite *Plasmodium*. It is currently endemic in more than 100 countries, which are visited by 125 million international travellers every year. For dialysis and renal insufficiency patients it becomes increasingly easier to travel to these countries thanks to the recent advances in renal replacement therapy. However, the pharmacokinetics of some prophylactic agents in malaria are altered, which may modify the effectiveness and safety of such treatments and the way they should be prescribed. Clinicians should be aware of these alterations which require subsequent dosage adjustments. This review provides recommendations on the use of antimalarial drugs, alone or in combination, in patients with renal impairment. These recommendations depend on the prevalence of *Plasmodium falciparum* chloroquine resistance, as defined by the WHO. Furthermore, fixed-dose combinations cannot be used in patients with creatinine clearance below 60 mL/min since the tablets available do not allow appropriate dosage adjustment for each drug. Chloroquine and proguanil require dosage adjustments, while atovaquone, doxycycline and mefloquine do not.

S. Amet (✉) · S. Zimner-Rapuch · V. Launay-Vacher · N. Janus
Service ICAR Department, Nephrology Department, Pitié-Salpêtrière Hospital, 47-83 Boulevard de l'Hôpital, 75013 Paris, France
e-mail: sabine.amet@psl.aphp.fr

G. Deray
Nephrology Department, Pitié-Salpêtrière Hospital, 47-83 Boulevard de l'Hôpital, 75013 Paris, France

1 Introduction

Malaria is an endemic disease transmitted by the protozoan parasite *Plasmodium*. More than 300–500 million individuals worldwide are infected by this parasite. About 1.5–2.7 million people a year, for the most part children, die from the infection, according to some authors [1, 2]. In a recent report from the WHO, the estimated number of deaths from malaria ranged from 655,000 to 810,000 during the period 2000–2010, worldwide, most (91 %) in the African region [3]. Malaria is currently endemic in over 100 countries, the majority of which are in the tropical, underdeveloped zones of Africa, Asia and South America. Such countries are visited by more than 125 million international travellers every year [4, 5]. According to the WHO and the results of various studies, each year many international travellers fall ill with malaria whilst visiting these countries, and well over 10,000 people are reported to fall ill after returning home [1, 4, 6]. However, underreporting asserts that the real figure may be as high as 30,000.

Four different species of *Plasmodium* (P) are responsible for malaria: *P. falciparum, P. malariae, P. ovale* and *P. vivax*, but *P. falciparum* causes encephalic forms that can lead to death [6, 7]. Therefore, the best management for such a serious disease is prevention based on chemoprophylaxis in combination with insect repellents. No antimalarial prophylactic regimen gives complete protection, but prescribed at the right dosage it reduces the risk of fatal disease.

Thanks to recent advances in renal replacement therapy, dialysis and renal insufficiency patients can travel more easily. Furthermore, the majority of tourists come from developed countries that are known to have an aging population. Elderly patients have reduced renal function, either due to physiological aging or their diseases and/or medication history [8, 9].

In patients with renal impairment, the pharmacokinetics of the drugs used as prophylactic agents may be altered. It is thus essential to establish recommendations on how to use these drugs in those patients [10]. Moreover, in dialysis patients, drug clearance by dialysis must also be taken into account in order to determine whether drugs should be administered before or after a dialysis session. In this review, detailed pharmacokinetics and dosage adjustments of antimalarial drugs in patients with renal insufficiency are provided.

2 Literature Search Methods

Available data on the pharmacokinetics and dosage adjustments of antimalarial drugs available in most countries (chloroquine, proguanil, atovaquone, mefloquine and doxycycline) in patients with renal insufficiency were collected, studied and synthesized. Primaquine is not included in this review as there are no data regarding the pharmacokinetics of this drug in renal impairment. A review of the literature was carried out in PubMed with no year limit, and all articles in French and English language were considered for analysis. The search for empirical articles was based on the MeSH index (Medical Subject Headings), including the search terms 'renal', 'kidney' AND 'impairment', 'failure', 'insufficiency', 'dialysis', 'pharmacokinetics'. The last literature search was undertaken on 15 January 2012. Based on this analysis of published data, recommendations on dosage adjustments of antimalarial drugs in patients with renal insufficiency according to the severity of chronic kidney disease (CKD), including dialysis patients, have been established.

3 Selection of Antimalarial Drugs According to WHO Recommendations

The risk of contracting malaria is highly variable from country to country, and appropriate preventive measures depend upon the destination. For malaria chemoprophylaxis, countries are sorted by the WHO in three groups based upon the presence of *P. falciparum* and its chloroquine resistance (see Table 1). Nevertheless, *P. vivax* is developing chloroquine resistance. It is still rare but increasing and was first reported in the late 1980s in Indonesia and Papua New Guinea. Focal chloroquine resistance or prophylactic and/or treatment failure has since also been observed in Brazil, Colombia, Ethiopia, Guyana, India, Myanmar, Peru, the Republic of Korea, Solomon Islands, Thailand and Turkey. Chloroquine-resistant *P. malariae* has also been reported from Indonesia. Moreover, mefloquine-resistant *P. falciparum* has been reported in Oriental Timor, in forest zones on each side of the Thailand-Cambodia border, in Myanmar (ex-Burma) and in Laos [6, 56].

Travellers must be reminded that no antimalarial prophylactic regimen gives complete protection. They should also take preventive measures against mosquito bites after sunset, the simplest being to wear loose clothes with long sleeves and pants covering as much skin area as possible, tight to the neck, wrists and ankles. Applying repellents on exposed skin and using an insecticide-treated mosquito net are other preventive measures.

4 Routine Assessment of Renal Function

Many patients could be at risk of renal impairment (patients with diabetes mellitus, patients with high blood pressure, patients taking nephrotoxic drugs, patients with cancer, etc.). Furthermore, in our developed countries the aging population has a number of these comorbidities. Besides, the NHANES (National Health and Nutrition Examination Survey) data on the epidemiology of renal insufficiency in the US estimated that 60 % of people have a glomerular filtration rate (GFR) inferior to 90 mL/min [11]. Thus, renal function should be routinely assessed in all patients, at least by calculation of creatinine clearance (CL_{CR}) in every patient, even when serum creatinine (SCr) is within the normal range. Assessment of renal function can be carried out in many ways. The gold standard is the measurement of GFR using radiomarked 51-chrome-ethylene-diamine-tetra-acetic acid (51Cr-EDTA); however, use of this radiomarked method in all patients is unfeasible. As a result, it is recommended that the GFR be estimated. Nevertheless, the raw value of SCr should not be used for its production depends on age, weight and muscular mass. Estimation of GFR (or CL_{CR}, which is assumed to be an acceptable estimate of the GFR) allows an appropriate evaluation of renal function. This estimation can be realized with several formulae, two of which should be considered. The Cockcroft-Gault (CG) equation [12] is still the most used formula. It gives an estimation of CL_{CR}, with a result expressed in mL/min. A more recently introduced equation is the Modification of Diet in Renal Disease (MDRD) study formula and, in routine practice, the abbreviated MDRD (aMDRD) formula [13]. The aMDRD formula estimates the GFR, with a result expressed in mL/min/1.73 m^2.

Renal clearance of 51Cr-EDTA was compared with GFR estimated using either the CG equation or the aMDRD formula in a large cohort study [14]. Analysis of the standard deviation of the mean difference between estimated and measured GFR showed that both formulas lacked precision; the CG formula was less precise than the

Table 1 Selection of the malaria chemoprophylaxis according to country risk, as defined by the WHO (adapted from the Institut de veille Sanitaire [55] and WHO [6])

Group	Characteristics of *Plasmodium (P)*	Countries	Recommended chemoprophylaxis
I	No *P. falciparum* No chloroquine resistance	Argentina (north-west and border with Paraguay), Belize, Bolivia (except Amazonia), China (north-east), Costa Rica, Guatemala, Haiti, Honduras, Iraq (Duhok, Erbil, Sulaimaniya), Iran (except south-east), Jamaica (Kingston city), Mexico (Yucatan), Nicaragua, Panama (west), Paraguay (east), Peru (except Amazonia), Dominican Republic, El Salvador, Venezuela (except Amazonia), Yemen (Socotra Island)	Chloroquine
II	Prevalence of chloroquine-resistant *P. falciparum*	Colombia (except Amazonia), India (except north-west), Madagascar, Nepal (Teraï), Sri Lanka, Tajikistan	Chloroquine/proguanil or atovaquone/proguanil
III	High prevalence of chloroquine-resistant *P. falciparum* Multiresistant *P. falciparum*	Afghanistan, Angola, Bangladesh (except Dhaka), Benin, Bolivia (Amazonia), Botswana, Brazil (Amazonia), Burkina Faso, Burundi, Bhutan, Cambodia, Cameroun, Chad, China (Yunnan et Hainan), Colombia (Amazonia), Comoros, Congo, Ivory Coast, Djibouti, Equateur (Amazonia), Eritrea, Ethiopia, Gabon, Gambia, Ghana, equatorial Guinea, Guinea, Guinea-Bissau, Guyana, French Guyana (except coasts), India (north-west), Solomon Islands, Indonesia (except Bali), Iran (south-east), Kenya, Laos, Liberia, Malawi, Malaysia (except coasts and cities), Mali, Mauritania, Mayotte, Mozambique, Myanmar, Namibia, Niger, Nigeria, Sao Tome et Principe, Uganda, Pakistan, Panama (east), Papua New Guinea, Peru (Amazonia), Philippines, Central African Republic, Rwanda, Solomon Islands, Saudi Arabia (south, west), Senegal, Sierra Leone, Somalia, Soudan, South Africa (north-west), Surinam, Swaziland, Tanzania, Thailand (border area), Timor Leste, Togo, Vanuatu, Venezuela (Amazonia), Vietnam (except coasts and deltas), Yemen (except Socotra Island), Zaire, Zambia, Zimbabwe	Mefloquine or doxycycline or atovaquone/proguanil

aMDRD formula in most cases. In the majority of patients, both formulae give similar results in estimating renal function. However, there are some populations of patients in whom the CG formula should not be used, including patients older than 65 years of age and those with a body mass index (BMI) greater than 30 kg/m^2. Indeed, in these patients, estimation of the GFR using CL_{CR} may be false compared with their current GFR, and the aMDRD formula may allow a more precise estimation of their renal function. In the case of cachexia (BMI <18.5 kg/m^2), no single tool is really accurate. In these patients, the best estimate of GFR is provided by direct methods such as (51)Cr-EDTA [14].

The US National Kidney Foundation (Kidney Disease Outcomes Quality Initiative) [15] (KDOQI) and the international working group Kidney Disease: Improving Global Outcomes [16] (KDIGO) have defined and stratified the severity of CKD (see Table 2) according to the GFR. The result of the aMDRD formula allows the stage of CKD to be defined. Lastly, when making a drug dosage adjustment, the calculated GFR with aMDRD formula should be adjusted to the patient's body surface in order to obtain a result in mL/min [17]. If the CG formula is used, no adjustment to body surface is necessary as the unit of this formula is mL/min.

5 The Effects of Renal Impairment on Drug Pharmacokinetics

In patients with kidney impairment, all stages of the pharmacokinetics, absorption, distribution, metabolism and excretion may be modified. For example, the renal excretion of a drug and/or its metabolites may be impaired, leading to excessive accumulation in the body. Furthermore, in patients with CKD, the plasma protein binding of drugs may be significantly reduced, influencing the pharmacokinetic processes of distribution and elimination. Moreover, the activity of several drug-metabolizing enzymes and drug transporters has also been shown to be impaired in patients with chronic renal impairment [18]. Therefore, it is essential to study the pharmacokinetics of drugs in patients with impaired renal function in order to prescribe drugs at the right dosage, thus improving the tolerance and efficiency of the drugs among these patients [19, 20]. Considering only the pharmacokinetics data in

Table 2 Kidney Disease Outcomes Quality Initiative and Kidney Disease: Improving Global Outcomes definition and classification of chronic kidney disease in adults [15, 16]

Stage	Description	GFR (mL/min/1.73 m^2)
At increased risk	Risk factors for kidney disease (e.g. diabetes, high blood pressure, family history, older age, ethnic group)	≥90
1	Markers of kidney damage[a] and normal GFR	≥90
2	Markers of kidney damage[a] and mild decrease in GFR	60–89
3	Moderate decrease in GFR	30–59
4	Severe decrease in GFR	15–29
5	Kidney failure (dialysis or kidney transplant needed)	<15

[a] Albuminuria, proteinuria, haematuria, structural abnormalities detected by imaging

GFR glomerular filtration rate

normal renal function patients is not advisable to anticipate drug dosage adjustment in patients with CKD. Individual drug literature analysis should be performed.

Some combination therapies associating two drugs in one tablet have been developed. Whilst these fixed-dose combinations generally provide convenience and ease of use for patients, it is important to understand that their use may be inappropriate in patients with renal insufficiency. Indeed, fixed-dose combinations can contain only one drug for which dosage adjustment is required.

In patients with acute renal failure, the pharmacokinetics of drugs are modified; however, the extent of those modifications are difficult to anticipate as renal function is not stable. In those patients, malaria prophylaxis should, if possible, be withheld until renal function is stable, either normal or chronically impaired. The chronicity of renal impairment is defined by the KDOQI-KDIGO [15, 16] by a stable GFR for at least 3 months.

In case of acute renal failure occurring in a patient with baseline chronic renal insufficiency, the decision to treat patients should be assessed with a benefit-risk balance between the risk of malaria infection and the risk of drug-related adverse effects.

6 Individual Drug Literature Analysis

This work will review only the most-used drugs for malaria prophylaxis, as recommended by the WHO: chloroquine, proguanil, atovaquone, mefloquine and doxycycline (see Table 1) and for which there are data in CKD patients. Primaquine is not included in this review as there are no data regarding the pharmacokinetics of primaquine in renal impairment.

6.1 Chloroquine

Chloroquine is used for the prophylaxis of malaria in endemic areas of group I and in combination with proguanil in endemic areas of group II (see Table 1). It has limited value as a prophylactic agent because of widespread resistance to the falciparum malaria parasite. According to the WHO recommendations, chloroquine should only be prescribed for travellers going to countries where malaria species are 100 % *P. vivax* and/or to countries where there is absolutely no drug resistance to *P. falciparum* [6].

The usual dosage of chloroquine in patients with normal renal function is 100 mg/day orally, from the day of departure until 4 weeks after returning from the malaria-endemic area. According to the Summary of Product Characteristics (SmPC) of Nivaquine® (Sanofi-Aventis, Paris, France) there is an alternative dosing schedule consisting of 300 mg twice a week, 1 week before departure and until 4 weeks after returning [21].

In patients with normal renal function, chloroquine is mainly metabolized by the hepatic microsomal system. Metabolism does not result in a loss of antimalarial action of the molecule because the main metabolite, monodesethylchloroquine (MDEC), has appreciable antimalarial action and has been shown to have an additive effect on the antimalarial actions of chloroquine [22]. Urinary excretion accounts for 55 % of the orally administered drug, with 70 % as unchanged drug and 23 % as MDEC [23].

In patients with renal impairment, the pharmacokinetics of chloroquine are altered. In one study of the pharmacokinetics of chloroquine in patients with CKD, the plasma half-life of chloroquine was significantly higher in patients with renal impairment than in controls [24]. This suggests

Table 3 Preventative malaria treatment in adults in the general population and patients with renal impairment travelling in countries in group I according to the WHO grading of countries at risk of malaria [10, 21, 25]

Creatinine clearance (mL/min)	Chloroquine base (Nivaquine®) [tablet 100 mg; syrup 25 mg/5 mL]
Normal renal function	100 mg/day
89 to 60	100 mg/day
59 to 30	50 mg/day
29 to 15	25 mg/day
<15 and HD	25 mg every 48 h[a]
CADP	25 mg every 48 h

[a] Administered after the dialysis session

CADP continuous ambulatory dialysis patients, *HD* haemodialysis patients

Table 4 Preventative malaria treatment in adults in the general population and patients with renal impairment travelling in countries in group II according to the WHO grading of countries at risk of malaria [10, 28, 31–33]

Creatinine clearance (mL/min)	Chloroquine base (tablet 100 mg; syrup 25 mg/5 mL)	Proguanil (tablet 100 mg)	Chloroquine base/proguanil (tablet 100 mg/200 mg)	Proguanil/atovaquone (tablet 100 mg/250 mg)
Normal renal function	100 mg/day	200 mg/day	1 tablet/day	1 tablet/day
89 to 60	100 mg/day	200 mg/day	1 tablet/day	1 tablet/day
59 to 30	50 mg/day	100 mg/day	Chloroquine and proguanil both require dosage adjustment Because the tablet is not divisible, drugs must be administered separately	Impossible to use
29 to 15	25 mg/day	50 mg every 48 hours		Dosage adjustment is required for proguanil but not for atovaquone
<15 and HD	25 mg every 48 hours[a]	50 mg/week[a]		There is no pharmaceutical form of atovaquone that allows its use in this indication
CAPD	25 mg every 48 hours	50 mg/week		Choose a therapeutic alternative

[a] Administered after the dialysis session

CAPD continuous ambulatory peritoneal dialysis patients, *HD* haemodialysis patients

that renal insufficiency may lead to the accumulation of chloroquine in the body and that chloroquine dosage should be reduced according to the degree of renal impairment (see Tables 3 and 4) [10].

Chloroquine is dialyzable: in one study, the chloroquine plasma clearance was 412–560 mL/min when administered either orally or intravenously in subjects with normal renal function compared with an average haemodialysis clearance (CL_{HD}) of 58 mL/min in four patients with chronic renal impairment [25]. As a result, the proportion of an absorbed dose of chloroquine that is eliminated by haemodialysis (F_{HD}) ranges from 9.4 % to 12.3 %. F_{HD} represents the participation of dialysis in the overall elimination of the drug in a dialyzed patient (dialysis and extra-renal), and is derived from the total body clearance (CL) and CL_{HD} of a drug: $F_{HD} = CL_{HD}/CL$. The influence of haemodialysis is clinically relevant if F_{HD} exceeds 25 % [26]; However, the F_{HD} of chloroquine is less than 25 %, suggesting that it could be administered before or after the session on haemodialysis days.

Adverse effects caused by overdosage of chloroquine include headache, visual changes, cardiovascular collapse, seizures, abdominal cramps, vomiting, cyanosis, methaemoglobinaemia, leukopenia, and respiratory and cardiac arrest. It is important to monitor these symptoms because chloroquine has a narrow therapeutic index and has caused many fatal, accidental poisonings [25].

6.2 Proguanil

Proguanil is used in combination with chloroquine in the prophylaxis of malaria in endemic areas of group II and in combination with atovaquone in endemic areas of group III (see Table 1). The usual dosage in patients with normal renal function is 200 mg/day orally, on the day prior to departure and until 4 weeks after returning from the malaria-endemic area.

Proguanil can be considered as a prodrug of the active triazine metabolite, cycloguanil, which is poorly absorbed when given orally [27, 28]. In patients with normal renal function, after oral administration, 59 % of the proguanil dose is recovered in the urine, comprising 62 % proguanil, 30 % cycloguanil and 8 % as p-chlorophenylbiguanide, the antimalarial activity of which has not yet been determined but is likely to be low. Accumulation of the drug should thus be anticipated in patients with severe renal impairment who are given normal dosage regimens. These patients should consequently receive a lower proguanil dose for prophylaxis. They could therefore avoid accumulation and overdosage signs such as haematological toxicity, megaloblastic anaemia and pancytopenia.

Indeed, in a study involving two patients with chronic renal impairment, one of whom was receiving haemodialysis, the authors suggested that proguanil treatment was responsible for the clinical (vomiting, diarrhoea) and haematological abnormalities (severe megaloblastic anaemia associated with pancytopenia) observed in both patients, one of whom received 100 mg/day (patient on haemodialysis) and the other 200 mg/day [29]. However, even with considerable overdose, proguanil usually produces few symptoms in subjects with normal renal function. This lack of adverse effects is no doubt due in part to prompt excretion that may not occur in patients with renal impairment. Indeed in these two patients, because of the severe degree of renal impairment, the retention of

proguanil and its metabolites induced the megaloblastic anaemia. Other studies confirm these results by reporting cases of poor haematological and digestive tolerance of proguanil in patients with renal impairment [20, 28, 30].

The proguanil dosage depends on the degree of renal impairment [10]. The usual dosage may be used as long as renal function is over 60 mL/min. For lower levels of renal function, the dose must be reduced (see Table 4). The SmPC of Paludrine® (Astrazeneca, Rueil-Malmaison, France) reports the same conclusions [31].

In one case report, a haemodialyzed patient presented with toxic proguanil blood levels that persisted for 1–2 weeks despite regular haemodialysis twice weekly [28]. This suggests that proguanil is not dialyzable, but because of a lack of more accurate information on its CL_{HD} it is recommended to administer the drug after the haemodialysis session or on a day without haemodialysis.

6.3 Fixed Combination of Chloroquine/Proguanil

A fixed combination of proguanil and chloroquine is often used for malaria prophylaxis in countries belonging to group II (see Table 1).

As previously demonstrated in patients with renal impairment, doses of proguanil and chloroquine both need to be adjusted; however, the tablet of the fixed-dose combination therapy is not divisible [32]. Therefore, the fixed combination of chloroquine/proguanil cannot be used in CKD patients whose renal function is below 60 mL/min. It is thus necessary to administer chloroquine and proguanil separately (see Tables 3 and 4).

6.4 Fixed Combination of Atovaquone/Proguanil

Atovaquone is used in fixed combination with proguanil for the prophylaxis of malaria in endemic areas of groups II and III (see Table 1). According to the SmPC of Malarone® (GlaxoSmithKline, Marly-Le-Roi, France), the usual dosage in patients with normal renal function is 250 mg of atovaquone in association with 100 mg of proguanil per day, to be taken during meals, on the day prior to leaving and until 7 days after returning from the malaria-endemic area [33].

The pharmacokinetics of atovaquone have been studied in a radiolabelling study involving four healthy male volunteers [34]. Radioactivity was eliminated almost exclusively via the faeces. The entire radioactivity in plasma, urine and faeces was accounted for by atovaquone, with no evidence of metabolites. The drug is essentially not metabolized, with 94 % of an oral dose excreted unchanged in the faeces over 21 days, and less than 0.6 % of a dose excreted in the urine [35, 36].

Although no specific study has been conducted among patients with renal insufficiency, but given the small amount excreted by the kidneys, renal disease would not be expected to significantly affect plasma concentrations [10, 37]. As a result, it does not appear to be necessary to adjust the dosage of atovaquone in patients with renal impairment (see Tables 4 and 5). Similarly, there are no available data for atovaquone CL_{HD}, so it is recommended to administer the drug after the haemodialysis session on haemodialysis days. No cases of overdose have been reported following administration of this drug.

In the indication of malaria prophylaxis, atovaquone is always used in association with proguanil. According to the SmPC of Malarone® [33], pharmacokinetic studies indicate that no dosage adjustments are needed in patients with mild-to-moderate renal impairment (GFR >30 mL/min/1.73 m^2). Indeed, in these patients the oral clearance and/or area under the concentration curve (AUC) data for atovaquone, proguanil and cycloguanil are within the range of values observed in patients with normal renal function;

Table 5 Preventative malaria treatment in adults in the general population and patients with renal impairment travelling in countries in group III according to the WHO grading of countries at risk of malaria [10, 33, 39, 42, 45, 51–53]

Creatinine clearance (mL/min)	Proguanil/atovaquone (tablet 100 mg/250 mg)	Mefloquine (tablet 250 mg) [mg/wk]	Doxycycline monohydrate (tablet 100 mg) [mg/day]
Normal renal function	1 tablet/day	250	100
89 to 60	1 tablet/day	250	100
59 to 30	Impossible to use	250	100
29 to 15	Dosage adjustment is required for proguanil but not for atovaquone	250	100
<15 and HD		250[a]	100 not dialyzable
CAPD	There is no pharmaceutical form of atovaquone that allows its use in this indication	250	100
	Choose a therapeutic alternative		

[a] Administered after the dialysis session

CAPD continuous ambulatory peritoneal dialysis patients, *HD* haemodialysis patients

however, there are no data on the pharmacokinetics of the fixed combination of atovaquone/proguanil in patients with more severe renal impairment. A case report of a 49-year-old woman with renal impairment (estimated GFR 36–50 mL/min/1.73 m^2) showed she received malaria chemoprophylaxis consisting of one tablet of the fixed combination of atovaquone/proguanil per day [38]. This patient developed pancytopenia within 48 hours following the beginning of treatment. Overdosage of proguanil was suspected by the authors as the half-life of proguanil was doubled in this patient [38]. As mentioned previously and in contrast to atovaquone, proguanil dose depends on the degree of renal impairment. In patients with CL_{CR} <60 mL/min, as only the proguanil dose should be adapted, these two drugs must be administered separately (see Tables 4 and 5). Since there is no pharmaceutical form of atovaquone that allows administration of a 250-mg dose alone, alternatives to the fixed combination of atovaquone/proguanil are recommended in patients in whom the CL_{CR} is under 60 mL/min [10].

6.5 Mefloquine

Mefloquine is used for malaria prophylaxis in endemic areas of group III (see Table 1). According to the SmPC of Lariam® (Roche, Boulogne-Billancourt, France), the usual dosage of mefloquine in patients with normal renal function is 250 mg orally on a fixed day once weekly, starting 10 days before departure until 3 weeks after returning from the malaria-endemic area [39].

In patients with normal renal function, less than 50 % of the mefloquine dose is metabolized in the liver into two metabolites which are devoid of antimalarial activity [40]. Excretion is mainly through the bile into the faeces, with less than 10 % of the dose recovered unchanged in the urine [23, 41–43]; therefore, it does not seem necessary to adjust the mefloquine dosage in patients with renal impairment.

In one study, two patients on haemodialysis were given an oral dose of 250 mg of mefloquine 2 weeks before departure and continued prophylaxis throughout their 3-week stay in Africa and for 1 week after returning to Austria [42]. No clinical adverse effects attributable to mefloquine administration were observed in these patients. This report confirms that mefloquine may be administered at its usual dose, whatever the degree of renal impairment is [10] (see Table 5).

In this study, the authors also suggested that the prophylactic dose of mefloquine could be given before, during or after the haemodialysis session [42]. Nevertheless, because of the lack of more accurate data, it is recommended to administer the drug after the haemodialysis session, or on a day without haemodialysis [10].

Mefloquine is generally well tolerated. The most common adverse effects are neuropsychiatric, gastrointestinal, dermatological and cardiovascular disorders [44].

6.6 Doxycycline

Doxycycline is used in the prophylaxis of malaria in endemic areas of group III (see Table 1) in case of resistance, contraindication or intolerance to mefloquine. According to the SmPC of Vibramycin® (Sinclair Pharma, Paris, France), the usual dosage of doxycycline in patients with normal renal function is 100 mg daily, which should be started 1–2 days before departure and maintained for 4 weeks after returning from the malaria-endemic area [45, 46].

In patients with normal renal function, doxycycline is eliminated in the urine and in the bile. Forty percent of the active drug is excreted in the urine within 3 days and 32 % in the faeces over the same time period [46, 47]. Although patients with renal insufficiency are expected to have a delayed elimination of this drug, one study involving anephric patients and patients with varying degrees of renal function showed that the plasma elimination half-life of biologically active doxycycline was not significantly extended [48]. Another study on healthy patients and patients with renal insufficiency confirmed that there were no statistically significant different serum levels between the two groups [49, 50]. Moreover, in renal impairment, the urinary excretion of the drug is significantly reduced but is made up for by an increase in faecal elimination [51–53]. These data suggest that the dose of doxycycline does not depend on the degree of renal impairment [10] (see Table 5).

Doxycycline is 82–93 % protein bound and its apparent volume of distribution is 0.7–1.9 L/kg in healthy volunteers [54]. Doxycycline CL_{HD} is only 10 mL/min or less [48]. The removal rate of the drug by haemodialysis is thus likely to be insignificant. However, available data does not allow F_{HD} calculation so it is recommended that doxycycline should be administered after the haemodialysis session.

No cases of doxycycline overdose have been reported. Overdose of other tetracyclines as a result of renal impairment (liver toxicity, azotemia, hyperphosphatemia, acidosis) have been reported but are not likely to occur with doxycycline because blood levels of the drug are independent of kidney function.

7 Conclusion

Travelling in regions where malaria is endemic has become common. Physicians of patients with renal insufficiency,

even on dialysis, should pay particular attention to the dosage of drugs used in malaria prophylaxis. In these patients, it is important to give the right drug at the right dose according to the country of destination, the prevalence of drug-resistant organisms, and the degree of renal impairment.

Pharmacokinetics of chloroquine and proguanil are altered in patients with renal insufficiency and dosage adjustments are thus necessary according to renal function and to the mode of dialysis. For mefloquine, atovaquone and doxycycline, no pharmacokinetic alterations have been reported and no dosage adjustments are necessary. Consequently, fixed-dose combinations may be unsuitable in some patients.

Clinicians should be aware of these pharmacokinetic alterations that require subsequent dosage adjustments. Further pharmacokinetic investigations need to be performed in haemodialysis and in peritoneal dialysis patients, for whom the data are still scanty.

Acknowledgements Native English editing and manuscript styling was provided by Andrea Bothwell of *in*Science Communications, a Wolters Kluwer business, with funding by Astellas.

The authors have no conflicts of interest to declare that are directly relevant to this article.

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