Antimalarial Drug Toxicity: A Review

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Abstract
Antimalarial drug toxicity is viewed differently depending upon whether the clinical indication is for malaria treatment or prophylaxis. In the treatment of Plasmodium falciparum malaria, which has a high mortality if untreated, a greater risk of adverse reactions to antimalarial drugs is inevitable. As chloroquine resistance has become widespread, alternative agents may be used in treatment regimens, however, the toxicity of these antimalarial agents should be considered. Quinine is the mainstay for treating severe malaria due to its rare cardiovascular or CNS toxicity, but its hypoglycemic effect may be problematic. Mefloquine can cause dose-related serious neuropsychiatric toxicity and pyrimethamine-dapsone is associated with agranulocytosis, especially if the recommended dose is exceeded. Pyrimethamine-sulfadoxine and amodiaquine are associated with a relatively high incidence of potentially fatal reactions, and are no longer recommended for prophylaxis. Atovaquone/proguanil is an antimalarial combination with good efficacy and tolerability as prophylaxis and for treatment. The artemisinin derivatives have remarkable efficacy and an excellent safety record. Prescribing in pregnancy is a particular problem for clinicians because the risk-benefit ratio is often very unclear.

Introduction
Malaria, caused mostly by Plasmodium falciparum and P. vivax, remains one of the most important infectious diseases in the world. The current approaches to curtail this disease include vector control, vaccination, immunotherapy, malaria prevention during pregnancy and chemotherapy. The vector control is achieved by reducing vector density, interrupting their life cycle, and creating a barrier between the human host and mosquitoes. One of the most important current approaches to develop new drugs involves the synthesis of chemical libraries and their evaluation against most validated biochemical targets of malarial parasites.

Avenues of research for the development of new antimalarials include lipid metabolism, degradation of hemoglobin and proteins, interaction with molecule transport, iron metabolism, apicoplasty, and signal transduction. Throughout the course of evolution, microorganisms have thwarted traps set by the environment including those designed by man.

P. falciparum, which is responsible for causing severe forms of the disease, is also adept at developing resistance to drugs thereby decreasing their efficacy in treatment over a period of time. Antimalarial drug toxicity is one side of the risk-benefit equation and is viewed differently depending upon whether the clinical indication for drug administration is malaria treatment or prophylaxis. Research that leads to drug registration tends to omit two important groups who are particularly vulnerable to malaria – very young children and pregnant women. Prescribing in pregnancy is a particular problem for clini-
icians because the risk-benefit ratio is often very unclear [1]. In the prevention of malaria in travelers, a careful risk-benefit analysis is required to balance the risk of acquiring potentially serious malaria against the risk of harm from the prophylactic agent. The therapeutic ratios for some antimalarials are narrow, and toxicity is frequent when recommended treatment dosages are exceeded; parenteral administration above the recommended dose range is especially associated with the hazards of cardiac and neurological toxicity [2]. The purpose of this review is to update physicians on the toxicity associated with antimalarial drugs.

Toxicity

All drugs cause toxicity. Type A adverse effects (AEs) result from excessive responses to a drug; these AEs are predictable from the known effects of the drug and are dose or concentration related. In contrast, type B AEs are not predictable from the known effects of the drug; there may be an immunological basis to the AE, and there is often no clear relationship with the dose or concentration of drug. Furthermore, certain patient groups are at particular risk of severe AEs — including the elderly, the very young, glucose-6-phosphate dehydrogenase (G6PD)-deficient people and HIV-positive people — and these may not be well represented in submissions to regulatory authorities [3, 4]. Toxicity may range from mild to serious and from reversible to irreversible [3]. Adequate clinical response is defined as rare toxicities, e.g. those which occur in <1% of patients using the agent, uncommon in 1–10%, and common in >10%.

Toxicity of Antimalarial Drugs

All drugs used for malaria therapy or prophylaxis have common AEs, in addition to rare, mild-to-severe and/or sometimes fatal AEs [5].

Chloroquine

Chloroquine is effective against P. vivax, P. ovale, P. malariae, and drug-sensitive P. falciparum. It is used for treatment or as prophylaxis. Chloroquine is usually well tolerated. Mild side effects, such as nausea and headache, may occur. Africans rather than African-Canadians may experience generalized pruritus, which is not indicative of drug allergy. Fehintola et al. [6] observed an incidence of 24.7% of chloroquine-induced pruritus in African children. Ademowo and Sodeinde [7] recorded a higher incidence of 41.3%, but patient age ranged from 1 to 33 years. Chloroquine-induced pruritus is thought to involve a complex interaction between the host, the parasite and the drug. Some genetic markers, notably hemoglobin genotype and G6PD, have been found to be associated with chloroquine-induced pruritus. Retinal toxic effects, which may occur with long-term daily doses of chloroquine (>100 g total dose) used in the treatment of other diseases, are extremely unlikely with chloroquine given as weekly chemoprophylaxis. Chloroquine may worsen psoriasis and, rarely, is associated with seizures and psychosis. Acute toxicity is most frequently encountered when therapeutic or high doses are administered too rapidly by parenteral routes. Cardiovascular effects include hypotension, vasodilatation, suppressed myocardial function, cardiac arrhythmias, and cardiac arrest. Confusion, convulsions and coma indicate central nervous dysfunction. Chloroquine doses of more than 5 g given parenterally are usually fatal [8]. Parenteral administration can cause hypotension, cardiac depression and arrhythmias. A number of case reports in the medical literature have suggested an association between seizures and parenteral chloroquine, both at therapeutic concentrations and overdose. Seizures may occur within a few hours of overdose or between 1 day and several weeks after the start of therapy [9]. Chloroquine is contraindicated in individuals with a history of epilepsy or generalized psoriasis.

Primaquine

Primaquine is often administered for the hypnozoite stage of P. vivax and P. ovale to prevent relapse and after departure from a malaria-risk area for prophylaxis. Therapeutic or higher doses of primaquine can cause hemolytic anemia or fatal hemolysis in G6PD-deficient persons. In Arab populations living in malaria-risk areas, more than 30% of the patients will show evidence of this deficiency in general, with an incidence of about 10–20%. In patients having the sickle cell trait, G6PD deficiency is more commonly seen. Large doses cause epigastric distress and mild-to-moderate abdominal distress. Mild anemia, cyanosis (methemoglobinemia), and leukocytosis are less common. High doses (60–240 mg of primaquine daily) accentuate the abdominal symptoms and cause methemoglobinemia in most subjects and leukopenia in some. Methemoglobinemia can occur even with common doses of primaquine and can be severe in persons with congenital deficiency of nicotinamide adenine dinucleotide methemoglobin reductase [10]. Granulocy-
topenia and granulocytosis are rare complications of therapy and usually associated with overdosing. Hypertension, arrhythmia and symptoms involving the central nervous system including depression and confusion are further rare complications [11].

**Mefloquine**

Mefloquine is structurally similar to quinine. It is used for treatment or prophylaxis of drug-resistant malaria. It may have cardiac depressant effects and antifibrillar activity, and may result in marked gastrointestinal or CNS AEs and is, therefore, not recommended as first-line treatment; nausea, strange dreams, seizures (rare), and psychosis may also occur [12]. Severe CNS events requiring hospitalization (e.g. seizures and hallucinations) occur in 1:10,000 patients taking mefloquine as chemoprophylaxis. However, milder CNS events (e.g. dizziness, headache, insomnia, and vivid dreams) are more frequently observed, occurring in up to 25% of patients. The higher incidence of AEs observed when the drug is used at the higher doses needed for malaria treatment implies a dose effect [13]. It is contraindicated in hypersensitivity; epilepsy or seizure disorder; severe psychiatric disorder, and in patients with a diagnosis or treatment for irregular heartbeat.

**Amodiaquine**

Amodiaquine is thought to have the same mechanism of action as its analogue chloroquine. Hepatitis and agranulocytosis were seen in patients taking amodiaquine for prophylaxis, and the drug is no longer recommended for this indication. Amodiaquine-quinoneimine can be generated from amodiaquine both spontaneously, when the drugs is in aqueous solution, and as a result of enzyme activity. The quinoneimine is highly reactive and haptenates proteins, generating antigen to which an immune response may be mounted. Repeated exposure to this antigen may be important in the generation of organ damage [3].

**Doxycycline**

Doxycycline is used as part of combination therapy or as prophylaxis of malaria. Photosensitivity may occur with prolonged exposure to sunlight or tanning equipment. In renal impairment, dose reductions are indicated. Doxycycline may cause gastrointestinal upset and rarely esophageal ulceration. It is photosensitizing and may make the skin more susceptible to sunburns. Although tetracyclines and other antibiotics have been cited as a cause of oral contraceptive failure [8, 14], a recent case-control analysis failed to demonstrate any significant association. However, the long-term safety (>3 months) of doxycycline has not been established. Adjustment of the doxycycline dosage may be necessary with either a twice daily dosing schedule (100 mg b.i.d.) or 200 mg daily [14].

**Proguanil**

Proguanil marketed in combination with atovaquone is used for both the treatment of uncomplicated *P. falciparum* and prophylaxis of mild chloroquine-resistant malaria. The most common AEs reported in >10% of patients taking atovaquone/proguanil for treatment of malaria are abdominal pain, nausea, vomiting, and headache in adults, and vomiting in children; for prophylaxis of malaria AEs include headache and abdominal pain and vomiting in children. It is well tolerated, and although oral aphthous ulcerations are not uncommon, they are rarely severe enough to warrant discontinuing this medication. Proguanil is considered safe during pregnancy and breastfeeding, but insufficient drug is excreted in the milk to protect a breastfed infant [15].

**Diaminopyrimidines (Antifolates)**

Pyrimethamine-sulfadoxine can be used to treat malaria. It is no longer considered a first-line agent for prophylaxis because of the AE profile. Co-trimoxazole can be used in combination with rifampicin and isoniazid in resistant *P. falciparum* [16]. Antimalarial doses of pyrimethamine alone cause little toxicity except occasional skin rashes and decreased hematopoiesis. Excessive doses produce megaloblastic anemia, resembling folate deficiency, that responds readily to drug withdrawal or treatment with folinic acid. It causes severe to even fetal cutaneous reactions, such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, dermatitis, serum sickness-type reactions, and hepatitis. Toxic sulfamethoxazole metabolites may elicit hypersensitivity reactions. Trimethoprim can inhibit renal creatinine secretion, leading to high serum creatinine levels. Trimethoprim also inhibits dihydrofolate reductase, causing decreased dopamine production, which may lead to parkinsonian symptoms [17]. The drug is contraindicated in persons with a history of intolerance to sulfonamides and in infants ≤2 months [18].

**Quinine**

Quinine sulfate is used for malaria treatment only, has no role in prophylaxis and is used with a second agent in drug-resistant *P. falciparum*. Hemolytic anemia may occur in patients with G6PD deficiency.
Quinine is associated with a triad of dose-related toxicities when it is given at full therapeutic or excessive doses, e.g. cinchonism, hypoglycemia, and hypotension. Quinine has an α-adrenergic blocking effect, and hypotension may occur as a result of vasodilation, myocardial depression, or dysrhythmia [19]. Mild forms of cinchonism, e.g. tinnitus, high-tone deafness, visual disturbances, headache, dysphoria, nausea, vomiting, and postural hypertension, occur frequently and disappear soon after the drug is withdrawn. Hypoglycemia is also common [20]. Symptoms appear when the total plasma concentration of quinine is about 5 mg/l, i.e. at the lower limit of the therapeutic range of the drug, which is 5–15 mg/l. Dose-related cardiovascular, gastrointestinal and central nervous system effects may arise following excessive infusion or from accumulation following oral administration. Severe hypotension may develop if the drug is injected too rapidly. A single dose of quinine of >3 g is capable of causing serious and potentially fatal intoxication in adults, preceded by central nervous system involvement and seizures. Much smaller doses can be lethal in children. Dysrhythmias, hypotension and cardiac arrest can result from the cardiotoxic action, and visual disorders may be severe, leading to blindness in rare cases. Plasma concentrations >5 µg/ml cause cinchonism, >10 µg/ml visual impairment, >15 µg/ml cardiac arrhythmias, and >22.2 µg/ml death [21].

Artemisinin and Its Derivates

Artemether-lumefantrine, a new fixed-dose oral antimalarial drug which combines the fast onset of action of artemether (an artemisinin derivative) in terms of parasite clearance with the high cure rate of lumefantrine in the treatment of acute uncomplicated *P. falciparum* malaria. The most commonly reported AEs following artemether-lumefantrine therapy are abdominal pain, anorexia, nausea, vomiting, diarrhea and CNS involvement (headache and dizziness). Pruritus and rash were reported by <2% of patients. Artemether-lumefantrine can thus be expected to show, both in children and in adults, a favorable safety profile for the treatment of acute, uncomplicated, *P. falciparum* malaria; it could as well be an alternative treatment option for travelers to endemic countries. Oral artesunate and artemether alone were very well tolerated. There was no difference in the incidence of possible AEs between the two drugs, and no evidence that either derivative caused allergic, neurologic or psychiatric reactions, or cardiovascular or dermatologic toxicity [22]. Piperaquine has a mode of action similar to quinine and is used in combination with artemisinin.

Atovaquone

Atovaquone causes few side effects that required withdrawal of therapy. The most common reactions are rash, fever, vomiting, diarrhea, abdominal pain, and headache. Patients treated with atovaquone only occasionally exhibit abnormalities in serum transaminase and amylase levels. Atovaquone/proguanil should not be used in infants <11 kg, pregnant women, women breast-feeding infants <11 kg, or patients with severe renal impairment (creatinine clearance <30 ml/min). Apparently, a few acute AEs are caused, but more clinical evaluation of the drug is needed, especially to detect possible rare, unusual, or long-term toxicity [23].

Toxicity of Antimalarial Drugs

Cardiovascular Toxicity

Chloroquine has three main cardiovascular effects: membrane stabilization, direct negative inotropic effects, and direct arterial vasodilation. The data also suggest a role for nitric oxide and histamine release in mediating this response leading to hypotension/postural hypotension. These effects are manifested as rhythm and conductance disturbances, myocardiopathy, or vasoplegic shocks. Quinine and halofantrine are capable of prolonging the QT interval. Quinine prolongs the QT interval at standard doses, similar to halofantrine. Halofantrine induces a dose-related prolongation of the QT interval whereas mefloquine has no effect on the QT interval. However, the risk of significant QT prolongation was greater if halofantrine was given as a re-treatment following mefloquine failure than as primary treatment. Cardiotoxicity of antimalarials is increased in patients with acute renal failure, especially after 3 days of treatment. This is partly because the degree of QT prolongation is dependent on the plasma concentration of halofantrine. The frequency of QT interval prolongations following artemether-lumefantrine treatment was similar to or lower than that observed with chloroquine, mefloquine, or artesunate + mefloquine; these changes were considerably less frequent than with quinine or halofantrine [24, 25].

Ocular Toxicity

Ocular toxicity caused by antimalarials was first described in the literature as early as 1957. As antimalarials were also found to be effective in the treatment of rheumatoid diseases apart from the treatment and prophylaxis of malaria, the risk of ocular toxicity is increased.
The incidence of early retinopathy in ophthalmologically unmonitored patients was estimated by Bernstein [26] to be 10% for chloroquine and 3–4% for hydroxychloroquine. Advanced retinopathy had an incidence of 0.5%. These risks might be reduced substantially by regular observation and testing [27]. The major toxicity of antimalarial agents is retinal damage (rare), which can lead to visual impairment. The major risk factor for retinal toxicity appears to be the combination of cumulative doses >800 g and age >70 years (presumably due to the increased prevalence of macular disease in the elderly). In the absence of risk factors, it is recommended that an ophthalmologic examination and central field testing be performed every 6–12 months. The central 10° of the visual field is the initial site of antimalarial retinal toxicity. There is a higher risk of visual loss when plasma concentrations of quinine exceed 15 mg/l at any stage of overdosage. Blurred vision may proceed to complete blindness within a few hours. As vision is lost, the pupils become dilated and unresponsive to light. Initially, only narrowing of the retinal arterioles may be seen on fundoscopy but after 3 days retinal edema may appear [28]. Hirst et al. [29] reported that a 34-year-old man treated with >250 g of amodiaquine hydrochloride during 1 year was noted to have diffuse conjunctival and corneal changes and also demonstrated abnormal results in retinal function tests.

**Myopathy**
Factors increasing the risk of muscle disorders may depend on concomitant disease (diabetes, hypothyroidism, renal and hepatic disease), advanced age and dose. Myopathy has rarely been reported with these agents [30]. Clinicians should be aware that treatment may lead to neuromyopathy as well as irreversible retinopathy with chronic use. Usually patients complain of muscle weakness with or without muscle pain. Peripheral sensory abnormalities, such as lack of deep tendon reflexes, may be noted on examination. Muscle enzymes are normal or slightly elevated. In cases suspected of drug-induced myopathy, plasma concentrations of cellular contents released from damaged muscle are assessed. These laboratory parameters include creatine kinase, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, aldolase myoglobin, and potassium and phosphorus, both of which increase with muscle injury. Serum creatine kinase is considered to be the most sensitive indicator, but its lack of specificity is a major limitation. In the presence of drug-induced myopathy, serum creatine kinase may be normal, slightly elevated, or as high as 10–20 times the upper normal limit [31]. Myopathy and cardiomyopathy are thought to be caused by damage to the mitochondria in muscle cells.

**Neurotoxicity**
Serial audiometry was performed in 10 patients receiving quinine treatment for acute *P. falciparum* malaria. Quinine reduced high-tone auditory responses. Tinnitus was reported in 7 patients after plasma concentrations >5 mg/ml, but the high-tone loss resolved completely after treatment was completed. Neuropsychiatric AEs of mefloquine range from anxiety and paranoia to depression, hallucinations, psychotic behavior and possibly suicide [32]. A number of case reports in the medical literature have suggested an association between seizures and parenteral chloroquine, both at therapeutic concentrations and overdosage. Seizures may occur within a few hours of overdosage or between 1 day and several weeks after the start of therapy. Seizures complicate the clinical course of >30% of patients admitted to hospital for cerebral malaria and are associated with an increased risk of death and neurological sequelae. There are many explanations for seizures in malaria. Due to high tissue binding, the concentration of chloroquine within the brain is approximately 4 times that of plasma, and experimental evidence suggests that chloroquine may precipitate seizures by attenuation of γ-aminobutyric acid pathways (GABAergic mechanism) and enhancement of dopaminergic neurotransmission [33, 34]. Auditory deficits include transient tinnitus and eighth bilateral nerve damage after overdose. Deafness and mutism occurred in a 14-year-old child who ingested approximately 6.5–7.8 g of quinine sulfate. Symptoms lasted for approximately 3 days. Benign intracranial hypertension is a rare but potentially serious condition. It has been documented in association with a variety of drugs, particularly tetracyclines [35, 36].

**Hepatotoxicity**
Amodiaquine can cause AEs including liver damage. The observed drug toxicity is believed to involve the formation of an electrophilic metabolite, amodiaquine-quinoneimine, which can bind to cellular macromolecules and initiate hypersensitivity reactions. Since hepatitis and agranulocytosis occurred in prophylactically treated patients, it is no longer recommended as prophylactic treatment of malaria. Repeated exposure to the quinoneimine-generated antigen may be important in the generation of organ damage [37]. Mainra and Card [38] reported on a 24-year-old woman with severe liver failure...
following trimethoprim-sulfamethoxazole treatment, demonstrating the possible severity of the drug hypersensitivity syndrome associated with trimethoprim-sulfamethoxazole. The abrupt onset of hepatic failure, 5 days after the start of doxycycline, and the rapid normalization after drug discontinuation leads to suspect a causal relationship between doxycycline and liver insufficiency [39]. Williams [40] found significant changes in the proportions of plasma proteins in malarious birds 8 days after infection; albumin and $\alpha_2$-globulin were reduced, while $\gamma_1$- and $\gamma_2$-globulin were increased. Those changes coincided with significant increases in the plasma concentrations of total protein and enzymes (aspartate aminotransferase, glutamate dehydrogenase and $\gamma$-glutamyltransferase), and a decrease in creatinine. A prospective study done in 216 children with complicated P. falciparum malaria showed hepatopathy in 33.3% of cases, with a higher incidence in children aged $\geq$5 years. Bilirubin and alanine aminotransferase were moderately raised in most cases [40].

Pregnancy

The US Centers for Disease Control and Prevention consider that chloroquine is safe throughout pregnancy, and mefloquine is safe in the second and third trimesters, with limited data suggesting safety in the first trimester [41]. Malaria often occurs in chloroquine-resistant regions, thus the pregnant traveler cannot generally choose chloroquine. Effectively, she has the choice of mefloquine in the second and third trimester, and nothing for the first trimester. The data suggest that mefloquine may lead to stillbirths if administered in the first trimester [42]. Published data on 607 pregnancies in which artemisinin compounds were given during the 2nd or 3rd trimesters indicated no evidence of treatment-related, adverse pregnancy outcomes. Similar data show normal outcomes in 124 pregnancies exposed to artemisinin compounds in the 1st trimester. Artemisinin compounds cannot be recommended for treatment of malaria in the first trimester. Because the safety data are limited, artemisinin compounds should only be used in the second and third trimester. Artesunate-atovaquone-proguanil is a well-tolerated, effective, practical, but expensive treatment for multidrug-resistant P. falciparum malaria during the second or third trimester of pregnancy [43]. Very small amounts of antimalarial drugs have been discovered in the breast milk, but the amount of drug transferred is not thought to be harmful to the infant. Because the quantity of antimalarials transferred in breast milk is insufficient to provide adequate protection against malaria, infants who require treatment or chemoprophylaxis should obtain the recommended antimalarial dosages.

References