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Review Article

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. Aschloroquine 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-sulfadoxin 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.

Keywords: Antimalarial drugs, Toxicity, management of poisoning, chemoprophylaxis

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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 antimalarial 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 clinicians 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. The toxicity of antimalarial drugs sets an unusual and interesting problem for the clinician. Unlike most clinical situations, antimalarial drugs are provided to healthy people who are requesting treatment to provide extra security against ill health whilst travelling in malarial areas. Any significant degree of toxicity from these drugs

undermines the whole logic behind the advice given to travellers. A risk-benefit assessment is necessary to decide between different regimens.[3]The toxicity of the drug must be balanced against the risk from malaria, as well as the efficacy of the drug. It has been estimated

that travellers going on short (three week) trips to sub-Saharan Africa, who take some reasonable antimosquito precautions but take no chemoprophylaxis, have only a 1% chance of contracting clinical malaria. Clinical malaria has a mortality of no more than 1% if a policy of seeking medical advice or taking empiric antimalarial treatment for fevers is followed. Overall,

the mortality of travellers who do not take chemoprophylaxis is therefore about 1 in 10000 trips'. Clearly, the risk to travellers going to endemic areas for longer periods or shorter times will be correspondingly higher or lower; and travellers visiting areas of low endemicity will be at much lower risk. Decisions on chemoprophylaxis are normally based on the requirements of the typical traveller. From this, it is clear that any drug which has a frequency of fatal side-effects of 1 in 10 000, should not be used for routine prophylaxis. Furthermore, as non-toxic, though less effective, drugs are available, it is unlikely that drugs with a known frequency of fatal side-effects of less than 1 in 40 000 should be considered for routine use. This theoretical view has been followed in practice whenever toxicity has been measured. In 1985 Fansidar was withdrawn as a recommended drug for routine prophylaxis on the basis of an estimated fatal adverse reaction rate of about 1 in 20000[4]. A year later amodiaquine was withdrawn because of an incidence of fatal neutropenia of about 1 in 20003. Unfortunately, there are few good techniques available to measure rates of severe adverse effects which are lower than 1 in 10 000. Prospective trials are not large enough to reliably detect side effects or adverse effects of such frequencies and the much less reliable techniques of post-marketing surveillance must be used. This depends on using isolated case reports, reports to government agencies and to the pharmaceutical industry. These reports have to be assessed in the context of estimates of overall drug usage. Clearly, such estimates are very imprecise and drugs often have to be used for several years before even this imperfect information can be obtained. In contrast, frequent but mild side effects are much easier to determine. Care is needed in interpreting the nature of mild side-effects because placebo controlled trials have shown that patients often suffer from non-specific side effects such as nausea, dizziness and headaches. In this review, I will attempt to summarise the main knowledge available on the incidence of major adverse effects and an outline of what is known about the minor side effects of the 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[5,6]. Toxicity may range from mild to serious and from reversible to irreversible [5]. 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 some times fatal AEs

Chloroquine and Quinine [7]

Chloroquine and quinine will be considered together as there are similarities in their toxic effects. Both drugs are quickly absorbed by the gastrointestinal tract and symptoms of poisoning usually appear within three hours of ingestion. The clinical features of poisoning include:

- Drowsiness, convulsions and coma and
- Hypotension and cardiac dysrhythmias

(especially ventricular tachycardia and fibrillation) leading to cardiac arrest. Ventricular dysrhythmias may be anticipated from changes on the electrocardiogram (ECG): inversion of T-waves, prolongation of QT interval and widening of the QRS.

- Respiratory failure.
- Diplopia (double vision), blurred vision, narrowing (constriction) of the visual field ("tunnel" vision) and blindness.

The toxic effects on the cardiovascular system tend to be more severe from chloroquine than quinine. Toxicity on the eye (oculotoxicity) is the major problem from quinine poisoning.

The side effects of pharmacological treatment with quinine are common and become exaggerated when the patient has taken a toxic dose:

- Nausea and vomiting,
- Deafness and tinnitus,

Vasodilatation (flushing sensation more obvious in a pale skin). This may be exacerbated by the vasodilatation caused by the malaria itself and so cause postural (orthostatic) hypotension.

- Abdominal pain (especially epigastric) and
- Visual impairment.
- Hypoglycaemia may result from stimulation of the pancreatic islet beta-cells. This is more common in pregnancy and infants. The risk is reduced by administering the quinine with glucose. However the nursing and medical staff must be aware constantly of the probability of hypoglycaemia.
- Thrombocytopenia may result from an immune mechanism associated with quinine but this is rarely of clinical importance. It may also be part of the disseminated intravascular coagulation syndrome.
- Rashes and angio-oedema have been described. Itching without a rash is a recognized problem affecting a number of Africans.
- Confusional states also occur but distinguishing malaria and quinine as the underlying cause is difficult.
- Black water fever (haemoglobinuria) is a serious complication.
- Hypokalaemia is very common with chloroquine poisoning; even though a facility for serum potassium assay is absent

the hypokalaemia should be assumed. The quantity of chloroquine ingested is a useful predictor of the likely symptoms and problems to expect [7]. The ingestion of over 5 grams of chloroquine and systolic hypotension (less than 80 mmHg) almost always

lead to a fatal. If the plasma concentration of quinine is less than 10 mg/L the symptoms are usually mild but if greater than 15 mg/L the risk of permanent visual damage and cardiac dysrhythmias is high.

Management of poisoning

The priority is always to stabilize the poisoned patient with attention to the Airway, Breathing and Circulation. Ideally management should be carried out in an intensive care facility especially if the patient is shocked with hypotension. Adequate hydration should be established.

Mechanical ventilation may be needed with the added support of very carefully titrated adrenaline [8] particularly if there is chloroquine poisoning. Adrenaline may increase the risk of cardiac dysrhythmias. If the ECG shows an intraventricular block then intravenous 250 ml 8.4% sodium bicarbonate (i.e. 250 mmol) is indicated. Gastric lavage should be considered if the patient arrives at the medical unit within one hour of ingesting quinine or chloroquine. If possible activated charcoal 50 - 100 g should then be given: this dose may need to be repeated every six hours depending on the clinical response. There is no evidence that diazepam is cardiac protective. It is indicated for convulsions. Hypokalaemia may increase the risk of cardiac dysrhythmias. It might be tempting to give routinely an intravenous infusion of potassium. However during the recovery period severe "rebound" hyperkalaemia may develop. Therefore it is probably wise not to give extra potassium unless frequent serum potassium measurements can be made and the results immediately available.

'Safe' antimalarial drugs

Chloroquine

Chloroquine was first used in 1945 and since then has been very widely employed throughout the world. During this time there have been few, if any, reports of severe or fatal adverse effects attributed to the use of the drug at the normal prophylactic dose; thus, it is reasonable to assume, in view of its huge consumption, that instances of fatal adverse effects to chloroquine are substantially less than 1 in a 100 000. This is equivalent to it being safe. [9]

Non-fatal adverse events Chloroquine causes a short term and reversible effect on optical accommodation which can potentially affect eyesight during performance of operators of high performance machinery or cars [10]. The true incidence of this effect has not been determined. Chloroquine binds irreversibly to melanin and long term use of high dose daily chloroquine in patients with rheumatoid arthritis may lead to the accumulation of chloroquine in retina melanin [11]. There are only a few reports of retinopathy which have occurred in patients taking weekly chloroquine for malarial suppression [9]. In these cases the total dose of chloroquine has not been properly assessed. The experience of rheumatologists with higher (500 mg) daily doses of chloroquine suggests that retinopathy, lens and corneal changes can occur after total doses of 100 g; experience with lower (250 mg) daily doses suggests that retinopathy does not occur until over 1000 g have been given. Hydroxychloroquine appears to be better tolerated than

chloroquine [12]

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 [13].

Non-fatal adverse events Since the dose of proguanil has been increased to 200 mg there have been an increasing number of reports of reversible aphthous ulceration [14-17]. It is unclear what the incidence of this effect is, for it has varied from different reports; it is also unclear whether chloroquine taken in combination with proguanil aggravates and is responsible for the increasing incidence of this effect reported since 1986.

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 anti-brilliant 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 [18]. 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 [19]. It is contraindicated in hypersensitivity; epilepsy or seizure disorder; severe psychiatric disorder, and in patients with a diagnosis or treatment for irregular heartbeat. Drugs with potential use as chemoprophylactic agents of unknown toxicity

Doxycycline

The tetracyclines have been in clinical use for many years and have been recently suggested as potential chemoprophylactic drugs. In one randomized study, minor adverse events were reported to be more common than with chloroquine alone: for instance, abdominal symptoms occurred in 40% of patients compared with 15% in the chloroquine group [20]. These suggestions have been made in the absence of reliable data on the incidence of fatal toxicity with this group of drugs.

The theoretical risks are great: doxycycline can produce photosensitivity, allergic skin reactions, skeletal deposition with dental staining, oesophagitis, candida infections, pseudomembranous colitis, and perhaps enhancement of shigella and salmonella enteritis. The use of this drug in young children and in pregnancy is contraindicated because of discolouration of the teeth and possible adverse effects on development [20-23].

Halofantrine

Halofantrine has only been used much more recently and the numbers are not large enough to be able to detect the incidence of severe adverse events[24].

Antimalarial drugs withdrawn from use due to adverse effects

Mepacrine

Mepacrine was first used in 1935 and was widely employed throughout the Second World War. Severe cases of aplastic anaemia, transient psychotic reactions and exfoliative dermatitis have been described, together with more minor adverse events including yellow skin pigmentation and gastrointestinal disturbances. The incidence of adverse events is unknown. It is likely that the drug was withdrawn because of the high frequency of minor adverse events rather than the high frequency of life-threatening events. Also, at the time of withdrawal, the non-toxic drugs chloroquine and proguanil became widely available.

Sulphonamides

The use of sulphonamides was started in the 1930s. The problems of severe skin reactions and neutropenia were well described. Nevertheless, a combination of pyrimethamine and sulfadoxine

(Fansidar) was introduced in 1965. Twenty-two cases of Stevens-Johnson syndrome were observed with three deaths. In 1985, reports of severe skin reactions with six fatalities were reported in the United States² and a corresponding number of nine cases (four fatal) in UK were also reported[25]. From an estimation of the frequency of the reported reactions and the number of tablets sold within the US, an incidence of fatal reactions of a frequency of 1 in 18 to 1 in 24 000 (with 95% confidence limits about 1 in 10-50 000) has been reported[26]. It is unlikely that this toxicity is due to combination treatment as similar frequencies were observed in Beira when single doses of sulphadoxine were given to 150 000 people². Examples of neutropenia have also been recorded with Fansidar, although the frequency of this has not been properly measured. Many studies suggest that this occurs approximately as frequently as severe skin reactions[27]. One dissenting Swiss study shows a much lower (1 in 150 000) incidence of severe adverse effects. The reason for this difference remains obscure, although it may simply reflect over-estimates of drug usage[28]. It is unclear whether different formulations of sulphonamides have a significantly different incidence of severe adverse effects but, as these effects are so rare, it is unlikely that any high quality data will ever be produced that can be used to disprove this hypothesis.

Dapsone

Dapsone had been used since 1965 as prophylaxis against malaria and, ever since, its use has been associated with neutropenia. Originally, it was used in combination with chloroquine and primaquine at doses of 25 mg a day, and neutropenia occurred in 1 in 10 000 cases, 40% of which died[29]. Since then the combination of 12.5 mg pyrimethamine and 100 mg dapsone (Maloprim) at a dose of two tablets a week has been shown to be associated with agranulocytosis. A dose of one Maloprim tablet a day has also been associated with four cases of neutropenia, including two deaths¹. Dapsone is also associated with specific minor side-effects, in particular methaemoglobinemia. The toxicity of low dose Maloprim (one a week) is still contentious as only a few reports of neutropenia have been associated with low dose use. Maloprim is not licensed in the US and is only

used by a minority of travellers who are advised in Britain and Australia. Thus, in spite of the few cases reported, the frequency of fatal adverse effects is likely to lie in the grey area of 1 in 20 to 1 in 50 000, where the benefits of prophylaxis may not outweigh the toxicity.

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, myocardopathy, 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[30,31].

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 [32]. 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 over dosage. 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 [33]. Hirst et al. reported that a 34-year-old man treated with 1250 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. 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.

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 15 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]

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 [35].

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 [36]. 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 [37]. Published data on 607 pregnancies in which artemisinin compounds were given during the 2nd or 3rd trimesters indicate 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.

Conclusions

There are very little reliable data on the frequency of serious adverse effects with antimalarial drugs. Such data are very difficult to obtain and will never be available for newly marketed drugs. This means that great caution should be

exercised before new drugs are recommended for widespread use by routine travellers who may have only a low (eg 1 to 10 000) risk of death from malaria without chemoprophylaxis. Furthermore, there is an urgent need for doctors to organize some morbidity assessment of the travelers that they have advised, on their return home, in order to provide accurate monitoring of the safety of currently recommended antimalarial regimens.

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