Antimalarial Drug Toxicity: A Review

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Abstract

Antimalarial drug toxicity is viewed differently dependingupon whether the clinical indication is for malaria treatmentor prophylaxis. In the treatment of *Plasmodium falciparum*malaria, which has a high mortality if untreated, a greater riskof adverse reactions to antimalarial drugs is inevitable. Aschloroquine resistance has become widespread, alternative agents may be used in treatment regimens, however, thetoxicity of these antimalarial agents should be considered.Quinine is the mainstay for treating severe malaria due to itsrare cardiovascular or CNS toxicity, but its hypoglycemic effectmay be problematic. Mefloquine can cause dose-related serious neuropsychiatric toxicity and pyrimethamine dapsoneis associated with agranulocytosis, especially if therecommended dose is exceeded. Pyrimethamine-sulfadoxineandamodiaquine are associated with a relatively highincidence of potentially fatal reactions, and are no longerrecommended for prophylaxis. Atovaquone/proguanil is anantimalarial combination with good efficacy and tolerabilityas prophylaxis and for treatment. The artemisinin derivatives have remarkable efficacy and an excellent safety record. Prescribing in pregnancy is a particular problem for cliniciansbecause the risk-benefit ratio is often very unclear.

Key Words 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 infectiousdiseases in the world. The current approaches tocurtail this disease include vector control, vaccination, immunotherapy, malaria prevention during pregnancyand chemotherapy. The vector control is achieved by reducingvector density, interrupting their life cycle, andcreating a barrier between the human host and mosquitoes.One of the most important current approaches todevelop new drugs involves the synthesis of chemical librariesand their evaluation against most validated biochemicaltargets of malarial parasites.Avenues of research for the development of new antimalarials include lipid metabolism, degradation of hemoglobinand proteins, interaction with molecule transport, iron metabolism, apicoplasty, and signal transduction. Throughout the course of evolution, microorganisms have thwarted traps set by the environment includingthose designed by man.*P. falciparum,* which is responsible for causing

severeforms of the disease, is also adept at developing resistanceto drugs thereby decreasing their efficacy in treatmentover a period of time. Antimalarial drug toxicity is oneside of the risk-benefit equation and is viewed differentlydepending upon whether the clinical indication for drugadministration is malaria treatment or prophylaxis. Research that leads to drug registration tends to omit twoimportant groups who are particularly vulnerable to malariavery young children and pregnant women. Prescribingin pregnancy is a particular problem for clini-cians because the risk-benefit ratio is often very unclear (Taylor WR and White NJ; 2004). In the prevention of malaria in travelers, a carefulrisk-benefit analysis is required to balance the risk of acquiringpotentially serious malaria against the risk ofharm from the prophylactic agent. The therapeutic ratios for some antimalarials are narrow, and toxicity is frequentwhen recommended treatment dosages are exceeded; parentral administration above the recommendeddose range is especially associated with the hazards of cardiac and neurological toxicity (Luzzi GA and Peto TE; 1993). The purpose of thisreview is to update physicians on the toxicity associatedwith antimalarial drugs.The toxicity of antimalarial drugs sets an unusual andinteresting problem for the clinician. Unlike mostclinical situations, antimalarial drugs are providedto healthy people who are requesting treatment toprovide extra security against ill health whilsttravelling in malarial areas. Any significant degreeof toxicity from these drugs undermines the wholelogic behind the advice given to travelers. A risk-benefit assessment is necessary to decide between different regimens (Peto TEA and Gilks CF; 1986). The toxicity of the drug must is balanced against the risk from malaria, aswell 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 empiricantimalarial treatment for fevers is followed. Overall, the mortality of travelers who do not take chemoprophylaxisis therefore about 1 in 10000 trips'.Clearly, the risk to travellers going to endemic areasfor longer periods or shorter times will be correspondinglyhigher or lower; and travelers visiting areas of low endemicity will be at much lower risk. Decisions on chemoprophylaxis are normally basedon the requirements of the typical traveller. Fromthis, it is clear that any drug which has a frequencyof fatal side-effects of 1 in 10 000, should not be usedfor routine prophylaxis. Furthermore, as non-toxic,though less effective, drugs are available, it isunlikely that drugs with a known frequency of side-effects of less than 1 in 40 000 should beconsidered for routine use.This theoretical view has been followed in

practicewhenever toxicity has been measured. In 1985Fansidar was withdrawn as a recommended drug forroutine prophylaxis on the basis of an estimated fataladverse reaction rate of about 1 in 20000 (Anonymous; 1985). A year later a modiaquine was withdrawn because of anincidence of fatal neutropenia of about 1 in 20003.Unfortunately, there are few good techniquesavailable to measure rates of severe adverse effectswhich are lower than 1 in 10 000. Prospective trialsare not large enough to reliably detect side effects oradverse effects of such frequencies and the much lessreliable techniques of post-marketing surveillancemust be used. This depends on using isolated casereports, reports to government agencies and to thepharmaceutical industry. These reports have to beassessed in the context of estimates of overall drugusage. Clearly, such estimates are very imprecise anddrugs often have to be used for several years beforeeven this imperfect information can be obtained. Incontrast, frequent but mild side effects are mucheasier to determine. Care is needed in interpreting the nature of mild side-effects because placebocontrolled trials have shown that patients often sufferfrom non-specific side effects such as nausea, dizzinessand headaches.In this review, I will attempt to summaries the main knowledge available on the incidence of major adverseeffects and an outline of what is known about theminor 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 arepredictable from the known effects of the drug and aredose or concentration related. In contrast, type B AEs arenot predictable from the known effects of the drug; theremay be an immunological basis to the AE, and there isoften no clear relationship with the dose or concentrationof drug. Furthermore, certain patient groups are at particularrisk of severe AEs – including the elderly, the veryyoung, glucose-6-phosphate dehydrogenase (G6PD)-deficientpeople and HIV-positive people – and these maynot be well represented in submissions to regulatory authorities. Toxicity may range from mild to seriousand from reversible to irreversible (Winstanley P, etal; 2004). Adequate clinicalresponse is defined as rare toxicities, e.g. those whichoccur in 1% of patients using the agent, uncommon in1–10%, and common in 1 10%.

Toxicity of Antimalarial Drugs

All drugs used for malaria therapy or prophylaxis havecommon AEs, in addition to rare, mild to-severe and/orsometimes fatal AEs

Chloroquine and Quinine (Jaeger, A; 2012)

Chloroquine1 and quinine will be considered togetheras there are similarities in their toxic effects. Both drugsare quickly absorbed by the gastrointestinal tract andsymptoms of poisoning usually appear within three hoursof 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 dysrhythmiasmay be anticipated from changes on theelectrocardiogram (ECG): inversion of T-waves, prolongation of QT interval and widening of theQRS; 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 tobe more severe from chloroquine than quinine. Toxicityon the eye (oculotoxicity) is the major problem fromquinine poisoning.

The side effects of pharmacological treatment withquinine are common and become exaggerated when thepatient has taken a toxic dose- Nausea and vomiting, Deafness and tinnitus, Vasodilatation (flushing sensation more obviousin a pale skin). This may be exacerbated by thevasodilatation caused by the malaria itself and socause postural (orthostatic) hypotension, Abdominal pain (especially epigastric) and Visual impairment; Hypoglycaemia may results from stimulation ofthe pancreatic islet beta-cells. This is more commonin 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 hypoglycemia; Thrombocytopenia may result from an immune mechanism associated with quinine but this israrely of clinical importance. It may also be partof the disseminated intravascular coagulation syndrome; Rashes and angio-oedemahave been described.Itching without a rash is a recognised problem affecting a number of Africans; Confusional states also occur but distinguishingmalaria and quinine as the underlying cause is difficult; Blackwater fever (haemoglobinuria) is a seriouscomplication; Hypokalaemiais very common with chloroquinepoisoning: even though a facility for serum

potassium assay is absent the hypokalaemiashouldbeassumed.The quantity of chloroquine ingested is a usefulpredictor of the likely symptoms and problems to expect The ingestion of over 5 grams of chloroquine andsystolic hypotension (less than 80mmHg) almost always lead to a fatal If the plasma concentration of quinine is less than 10mg/L the symptoms are usually mild but if greater than15mg/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 addedsupport of very carefully titrated adrenaline particularly if there is chloroquine poisoning (Jaeger, A; 1987). Adrenalinemay increase the risk of cardiac dysrhythmias.If the ECG shows

an intraventricular block thenintravenous 250ml 8.4% sodium bicarbonate (i.e. 250mmol) is indicated. Gastric lavage should be considered if the patientarrives at the medical unit within one hour of ingestingquinine or chloroquine. If possible activated charcoal50 – 100G should then be given: this dose may need tobe repeated every six hours depending on the clinicalresponse.There is no evidence that diazepam is cardiacprotective. It is indicated for convulsions. Hypokalaemia may increase the risk of cardiacdysrhythmias. It might be tempting to give routinely anintravenous infusion of potassium. However during therecovery period severe "rebound" hyperkalaemia may develop. Therefore it is probably wise not to give extrapotassium unless frequent serum potassium measurementscan be made and the results immediately available.

'Safe' Antimalarial Drugs

Chloroquine

Chloroquine was first used in 1945 and since then hasbeen very widely employed throughout the world.During this time there have been few, if any, reportsof severe or fatal adverse effects attributed to the useof the drug at the normal prophylactic dose; thus, itis reasonable to assume, in view of its hugeconsumption, that instances of fatal adverse effects to chloroquine are substantially less than 1 in a100 000. This is equivalent to it being safe (Kelsey JH; 1977).

Non fatal adverse events Chloroquine causes a short-term and reversible effect on optical accommodationwhich can potentially affect eyesight during performanceof operators of high performance machinery or cars (Cook GC; 1986). The true incidence of this effect has notbeen determined. Chloroquine binds irreversibly tomelanin and long term use of high dose dailychloroquine in patients with rheumatoid arthritismay lead to the accumulation of chloroquine in retinal melanin (Bernstein HN; 1983). There are only a few reports of retinopathy which have occurred in patients taking weeklychloroquine for malarial suppression. In these casesthe total dose of chloroquine has not been properlyassessed. The experience of rheumatologist's withhigher (500 mg) daily doses of chloroquine suggeststhat retinopathy, lens and corneal changes can occurafter total doses of 100 g5; experience with lower (250 mg) daily doses suggests that retinopathy doesnot occur until over 1000 g have been given. Hydroxychloroquineappears to be better tolerated than chloroquine (McKenzie AH; 1983).

Proguanil

Proguanil marketed in combination with atovaquoneis used for both the treatment of uncomplicated *P. falciparum*and prophylaxis of mild chloroquine-resistantmalaria. The most common AEs reported in 1 10% of patients taking atovaquone/proguanil for treatment of malaria

are abdominal pain, nausea, vomiting, and headachein adults, and vomiting in children; for

prophylaxisof malaria AEs include headache and abdominal painand vomiting in children. It is well tolerated, and although oral aphthous ulcerations are not uncommon, they are rarely severe enough to warrant discontinuingthis medication. Proguanil is considered safe duringpregnancy and breastfeeding, but insufficient drug is excretedin the milk to protect a breastfed infant (Schlagenhauf P: Mefloquine; 1999).

non-fatal adverse events Since the dose of proguanilhas been increased to 200 mg there have been anincreasing number of reports of reversible aphthous ulceration (Davidson N McD; 1986, Harries AD; 1988, Handson SN, et al 1989, Fogh S; 1988). It is unclear what the incidence ofthis effect is, for it has varied from different reports;it is also unclear whether chloroquine taken incombination with proguanil aggravates and is responsiblefor the increasing incidence of this effectreported since 1986.

Mefloquine

Mefloquine is structurally similar to quinine. It isused for treatment or prophylaxis of drug resistant malaria.It may have cardiac depressant effects and antifibrillary activity, and may result in marked gastrointestinalor CNS AEs and is, therefore, not recommended asfirst-line treatment; nausea, strange dreams, seizures(rare), and psychosis may also occur (Palmer KJ; 1993). Severe CNS events requiring hospitalization (e.g. seizures and hallucinations) occur in 1: 10,000 patients taking mefloquineas chemoprophylaxis. However, milder CNS events (e.g.dizziness, headache, insomnia, and vivid dreams) aremore frequently observed, occurring in up to 25% of patients.The higher incidence of AEs observed when thedrug is used at the higher doses needed for malaria treatmentimplies a dose effect (Phillips-Howard PA; 1995). It is contraindicated in hypersensitivity; epilepsy or seizure disorder; severe psychiatricdisorder, and in patients with a diagnosis or treatmentfor irregular heartbeat.Drugs with potential use as chemo-prophylactic agents of unknown toxicity.

Doxycycline

The tetracyclines have been in clinical use formany years and have been recently suggested as potential chemo-prophylactic drugs. In onerandomized study, minor adverse events werereported to be more common than with chloroquinealone: for instance, abdominal symptoms occurred in40% of patients compared with 15% in the chloroquine group (Pang LW; 1987). These suggestions have been made in theabsence of reliable data on the incidence of fataltoxicity 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, pseudo membranous colitis, and perhaps enhancement of shigella and salmonella enteritis. The use of this drug in young children and in pregnancy is contraindicated because of discoloration of the

teeth andpossible adverse effects on development (Rickman KH; 1987, Pang L; 1988).

Halofantrine

Halofantrine has only been used much more recentlyand the numbers are not large enough to be able todetect the incidence of severe adverse events (Peters W; 1987).

Antimalarial drugs withdrawn from use due to adverse effects

Mepacrine

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

Sulphonamides

The use of sulphonamides was started in the1930s. 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 casesof Stevens-Johnson syndrome were observed withthree deaths. In 1985, reports of severe skinreactions with six fatalities were reported in the United States and a corresponding number of ninecases (four fatal) in UK were also reported (Phillips-Howard PA; 1990). Froman estimation of the frequency of the reportedreactions and the number of tablets sold within theUS, an incidence of fatal reactions of a frequency of1 in 18 to 1 in 24 000 (with 95% confidence limitsabout 1 in 10-50,000) has been reported (Hernborg A; 1985). It is unlikely that this toxicity is due to combinationtreatment as similar frequencies were observed inBeira when single doses of sulphadoxine were given to 150 000 people2. Examples of neutropenia havealso been recorded with Fansidar, although the frequency of this has not been properly measured.Many studies suggest that this occurs approximatelyas frequently as severe skin reactions. One dissentingSwiss study shows a much lower (1 in150000) incidence of severe adverse effects. Thereason for this difference remains obscure, althoughit may simply reflect over-estimates of drug usage (Steffen R, Somaini B; 1986).It is unclear whether different formulations of sulphonamides have a significantly different incidenceof severe adverse effects but, as these effectsare so rare, it is un likely that any high quality datawill ever be produced that can be used to disprove thishypothesis.

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 (Ognibene AJ; 1970). 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 deaths'. Dapsone is also associated with specific minor side-effects, in particular methaemoglobinaemia. 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 out weight 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, 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. Halofantrineinduces 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-treatmentfollowingmefloquine 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 (Yap YG, Camm AJ; 2003).

Ocular Toxicity

Ocular toxicity caused by antimalarials was first described in the literature as early as 1957. As antimalarialswere 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 ophthalmologicallyunmonitored patients was estimated by Bernstein 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 (Neubauer AS, et al; 2003) . 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 fundoscopybut after 3 days retinal edema may appear (Canning CR; 1988). 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 andpossibly suicide (Stuiver PC; 1989).

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 (Winstanley PA *et al*; 1990).

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 (Phillips-Howard PA; 1998). Malaria often occurs in chloroquine-resistant regions, thus the pregnant traveler cannot generally choose chloroquine. Effectively, she has the choice of mefloquinein 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 (White NJ; 2000). 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-proguanilis a well-tolerated, effective, practical, but expensive treatment for multidrugresistant*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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