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Drug Interactions with Antimalarial Medications in Older Travelers: A Clinical Guide

Drug interactions with antimalarial medications in older travelers: a clinical guide

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Abstract

Increasingly older adults are traveling to international destinations with malaria as a present risk. Surveillance systems indicate that older adults are more likely to suffer severe complications from malaria. The role of health care providers in selecting an appropriate medication for chemoprophylaxis or treatment of malaria in adults becomes more difficult as older adults undergo physiologic changes that alter the pharmacokinetic and pharmacodynamic nature of medications potentially causing increased drug interactions, adverse events, and altered drug action. A comprehensive literature search from 1970 to present, with a focus on the last 10 years, was conducted on drug interactions, pharmacokinetic and pharmacodynamic effects on antimalarials in adults. It was determined that due to pharmacodynamic and pharmacokinetic changes in older adults, especially renal and cardiovascular, special attention should be given to this population of travelers in order to minimize the likelihood of adverse events or altered drug efficacy. Antimalarial-disease interactions in older adults can occur more often due to QT prolongation, exacerbation of hypoglycemia, decreased renal elimination, and decreased hepatic metabolism. Older antimalarials have well documented drug-drug interactions. Tafenoquine, a new antimalarial, requires G6PD screening like primaquine and monitoring of new potential drug interaction with MATE1 and OCT2 substrates. While drug-drug interactions in older travelers may occur more often as a result of poly-pharmacy, data does not indicate adverse reactions or decreased drug efficacy is greater compared with younger adults. Overall, with the exception of recently approved tafenoquine, much is known about antimalarial drug and disease interactions, but new drugs are always being approved, requiring travel health providers to understand the pharmacokinetics and pharmacodynamics of antimalarial drugs to predict the impact on safety and efficacy in travelers. This guide provides travel health providers with

valuable insights on potential outcomes associated with drug interactions in adults and recommended monitoring or drug regimen modification.

Keywords: older traveler, atovaquone-proguanil, doxycycline, primaquine, tafenoquine, mefloquine, chloroquine, artemisinins, artesunate, artemether, hepatic enzyme induction, QT prolongation

Introduction

Older adults make up an increasingly larger proportion of the traveling population.[1] Those over 60 years of age represent about 8% of ill returned travelers, but of those, more have severe disease compared to younger travelers.[2] In 2016, the U.S. Centers for Disease Control and Prevention (CDC) received 2,078 reports of imported malaria, the most since 1972.[3] While the percentage of adults 65 years and older only accounted for 6.3% of those with malaria in this report, 19.2% of them developed severe malaria, which included cerebral and kidney damage as well as acute respiratory distress syndrome. Studies in Asia and Europe indicate the incidence of hyperparasitemia and renal insufficiency increase with age, and the risk of death due to falciparum malaria increases by 85% per decade of life.[4, 5] It has been suggested that the increased susceptibility to severe malaria might be due to a waning immune system or atherosclerosis, which is more common in older adults.[6] Also, older adults undergo physiologic changes that compromise the pharmacokinetic and pharmacodynamic nature of the medications they take, leading to increased drug-drug interactions, adverse events, and altered drug action.[7] An analysis of TravEpiNet, a large CDC funded pre-travel project, revealed that of potential drug-drug interactions, 61% occurred in those over 50 years of age and 41% had at least three comorbid conditions.[8] Since 1988, the number of medications taken by adults 65 years and older have doubled, and those taking 5 or more medications have tripled.[9] A recent systematic review underscored the need to not only consider the implications of pharmacologic changes associated with aging, but also that older adults are more likely to forego insect protection and may be less likely to adhere to antimalarial regimens.[10] This review aims to address the drug-drug, drug-

disease, physiologic and pharmacokinetic changes in older adults that are critical to protecting this vulnerable population against malaria and its severe complications.

Methods

A comprehensive literature search from 1970 – present, with a focus on the last 10 years, was conducted to identify relevant studies and background information on the use of antimalarials in older adult travelers. Database searches were conducted in PubMed, Cochrane Database of Systematic Reviews, WHO Global Index Medicus, Web of Science, and CINAHL. Searches were conducted using the keywords and mesh terms: aged, antimalarials, artemisinin, atovaquone-proguanil, chemoprophylaxis, chloroquine, doxycycline, drug-drug interactions, malaria, mefloquine, primaquine, tafenoquine, and travel. International trade names for the antimalarials were searched on drugs.com and through the monographs Index Nominum and Martindale: the Complete Drug Reference. Search results were also limited to English-language studies and humans. References of identified articles were reviewed to identify any additional studies not found in the initial search. The search was conducted by four independent authors. After thorough discussion among the authors, articles were selected for inclusion into this manuscript based on their relevance to the topic as well as detailed and complete results.

Results

Pharmacokinetic and Pharmacodynamic Changes

Due to physiological changes associated with aging, the pharmaceutical care of older adults differs from younger adults. Changes in important organ systems like the renal and cardiovascular affect the pharmacokinetics (i.e., drug absorption, distribution, metabolism, and excretion) and pharmacodynamics (i.e., effect of drug at the target site) of medications.[11, 12] For

example, with increased age there is a relative decrease in total body water, lean muscle mass, and increase in percentage of body fat.[11-13] These changes will alter the usual volume of distribution, primarily for lipophilic drugs, resulting in a longer elimination half-life.[12] Hepatic metabolism of drugs in older adults can be reduced by up to 30% while renal excretion can be decreased by 50%.[14] Drug clearance by the liver depends on perfusion and extraction ratio.[12] Since extraction ratio is dependent on the metabolizing capacity of the liver, a decrease in hepatic drug metabolism may also reduce hepatic drug clearance.[12]

Pharmacodynamic changes in older adults usually results in increased or decreased drug sensitivity, depending upon the class of medication.[12] Reasons for pharmacodynamic changes in older adults are less well understood but are most pronounced for cardiovascular and central nervous system effects of various drugs.[11, 15]

Changes in older adults are important considerations when selecting an antimalarial medication for prophylaxis or treatment. Some common adverse events with antimalarial agents that warrant more consideration in older adults are a risk for QT prolongation and hypoglycemia. Many antimalarial drugs can cause QT prolongation and in older adults there is increased risk of this due to pre-existing cardiovascular disease, use of concurrent QT-prolonging drugs and age-related increases in QT interval.[11, 15, 16] Some antimalarial drugs can cause insulin production resulting in increased risk of hypoglycemia especially in older adults on concurrent anti-diabetic medications.[17, 18] There is also strong concern for drug-drug and drug-disease interactions in older adults due to increased medication use and comorbidities with age.[11]

Atovaquone-proguanil

Atovaquone-proguanil is indicated for prophylaxis and treatment of uncomplicated malaria in adults and children weighing 5 kg or greater.

Pharmacologic/Pharmacokinetic Effects

Atovaquone and proguanil are both active against all stages of the malaria parasite life cycle.[19, 20] Atovaquone is a hydroxynaphthoquinone and is a ubiquinone analogue that disrupts the cytochrome electron transport system and hinders the transport of several parasite enzymes which lowers the mitochondrial membrane potential.[20, 21] Proguanil must be converted into the active metabolite, cycloguanil, which inhibits dihydrofolate reductase in the *Plasmodium* species leading to the inhibition of deoxythymidylate synthesis.[22]

Atovaquone is a lipophilic compound, and thus, it is poorly absorbed from the GI tract. In older adults, lipophilic drugs may have a larger volume of distribution with a longer half-life resulting in greater systemic exposure and an increased risk for adverse effects.[14] Proguanil is readily absorbed from the GI tract. To increase absorption, atovaquone-proguanil should be taken with food, preferably a fatty meal, at the same time every day, which increases the bioavailability to 21-23%.[23, 24] Atovaquone has a half-life of about 2-3 days in adults due to enterohepatic recycling.[23] While it is highly protein bound (>99%), atovaquone does not seem to displace other highly protein-bound drugs in vitro.[23] Proguanil is 75% protein bound and it has a half-life of 12-21 hours.[23] According to the manufacturer, single-dose pharmacokinetics of atovaquone, proguanil, and cycloguanil were studied in 13 elderly subjects (65-79 years of age) and compared to 13 younger subjects (30-45 years of age).[23] Systemic exposure, or area under the curve, of cycloguanil was higher in the older adult population (point estimate 2.36, 95% CI 1.70 to 3.28). The Tmax and elimination half-life were longer in the older adult population when

compared to the younger population (8 hours vs 4 hours and 14.9 hours vs 8.3 hours, respectively).[23, 25] When using atovaquone-proguanil in older adults the possibility of higher systemic exposure to the medication should be considered as the likelihood for adverse effects may be greater.

Undetectable amounts (<0.6%) of atovaquone pass through the kidney.[26] About 40-60% of proguanil is excreted renally.[23, 25] In patients with severe renal impairment there is a risk for pancytopenia which can result from proguanil accumulation.[27] Thus, for patients with CrCl <30 mL/min prophylaxis with atovaquone-proguanil is contraindicated and treatment of malaria with atovaquone-proguanil should only be used if the benefits outweigh the risks. These are important considerations in older adults as they are more likely to have renal impairment than younger individuals.[12]

Atovaquone is almost primarily excreted via the liver.[26] It has been postulated that some of atovaquone also undergoes enterohepatic recirculation.[26] Proguanil undergoes hepatic metabolism via CYP2C19 and CYP3A4 at which time it is converted into cycloguanil.[23, 28] There are currently no dosage adjustment recommendations for atovaquone-proguanil in patients with mild to moderate hepatic impairment. Studies have not been conducted in patients with severe hepatic impairment taking atovaquone-proguanil.[23]

Pharmacodynamic Effects

Although mostly well-tolerated, atovaquone-proguanil may cause gastrointestinal (GI) disturbances such as abdominal pain, nausea, vomiting, and diarrhea.[23] Rarely, allergic reactions, blood disorders, photosensitivity, rash, increased liver enzymes, hepatitis, and hepatic failure may occur.[23]

Drug-drug Interactions

Rifampin and rifabutin can decrease plasma concentrations of atovaquone by up to 52%.[23, 29] (Table 1) The mechanism of this interaction is not known, but it has been suggested that the ability of rifamycin to induce hepatic enzymes and drug transporters may be responsible.[26] Certain HIV medications such as efavirenz, lopinavir/ritonavir, and atazanavir/ritonavir have also been shown to lead to lower plasma concentrations of atovaquone and proguanil.[30, 31] (Table 1) Although not demonstrated, studies have suggested that this may be due to atovaquone plasma protein displacement of these drugs.[26, 30] Similarly, the plasma concentration of atovaquone may be reduced by 40% when taken with tetracycline and the bioavailability of atovaquone may be lower if taken with metoclopramide.[23] (Table 1) If these drug interactions cannot be avoided, dosage adjustments and closer monitoring of patients for the development of malaria is warranted. Atovaquone may increase the plasma concentrations of zidovudine, by inhibiting its metabolism through glucuronidation, and etravirine and saquinavir, by interfering with CYP450 mediated metabolism, possibly on the 2C isoenzymes.[32, 33] Atovaquone-proguanil may potentiate the anticoagulant effect of warfarin by increasing the free warfarin concentrations through plasma protein displacement.[26, 34-36] (Table 1) Closer monitoring of the warfarin dose is necessary to avoid excessive bleeding. Proguanil, at twice the dose used in the adult formulation of atovaquone-proguanil, may decrease the efficacy of the oral typhoid vaccine due to in vitro antibacterial activity that decreases replication of the vaccine strain in vivo, which in turn, diminishes vaccine efficacy.[37] However, subsequent work in children using atovaquone-proguanil showed no decrease in the immunogenicity of the oral typhoid vaccine and

thus the Centers for Disease Control and Prevention state it may be given together or at any interval.[38, 39]

Drug-disease Interactions and Considerations in Older Adults

For patients with HIV and those patients taking rifampin, rifabutin, or warfarin an alternative agent should be considered for malaria prophylaxis or treatment. An increase in age leads to an increase in potential for comorbidities and the need for anticoagulation.[40] Thus, older adults are more likely to be on warfarin therapy and this should be a consideration with atovaquone-proguanil. INR should be closely monitored at baseline and throughout therapy. Kidney function should also be evaluated prior to start of therapy.

Doxycycline

Doxycycline is indicated for chemoprophylaxis and treatment of severe or uncomplicated malaria.

Pharmacologic/Pharmacokinetic Effects

Doxycycline is a broad-spectrum antibiotic. It is synthetically derived from oxytetracycline which makes it related to tetracycline.[19] The dosage for chemoprophylaxis of malaria is 100 mg once daily, whereas for many other indications, it is given twice daily. Thus, the magnitude of pharmacodynamic effects for non-malaria dose studies should be interpreted with caution. Doxcycline has a longer half-life than tetracycline and a better absorption profile.[19] As an anti-malarial medication, it interrupts the apicoplast function in plasmodium thereby inhibiting protein synthesis.[41, 42] After oral administration, doxycycline is quickly and almost entirely absorbed.[43] Divalent cations, such as calcium in dairy products, and trivalent cations decrease

doxycycline absorption, but otherwise, doxycycline is not affected by food.[44, 45] It does undergo enterohepatic recirculation which may slow clearance of the medication and it is primarily excreted by chelation in the GI tract.[43] One study found that the apparent volume of distribution of doxycycline was higher in older adults 65-90 years of age (mean 76.3 ±6 years) compared to younger individuals.[46]

The clearance of doxycycline is similar in individuals with normal renal function and in those with renal impairment.[47] No dosage modifications are needed for hepatic insufficiency.

Pharmacodynamic

Gastrointestinal

Doxycycline may cause gastric irritation. Doxycycline hyclate has been shown to cause more gastrointestinal side effects than doxycycline monohydrate and the incidence of esophageal ulcers is higher with doxycycline hyclate capsules than with tablets.[43, 48] Because of this, GI disturbances such as nausea and abdominal pain commonly occur as well as vomiting and diarrhea, which are less common.[43] To lessen the likelihood of this adverse effect and to avoid esophagitis, doxycycline should be taken with food, a full glass of water and in an upright position.[49] Dysphagia, esophageal ulceration, dry mouth, glossitis, enterocolitis, and stomatitis have also been reported.[9] While once thought to increase the rate of *Clostridium difficile* infection, newer evidence suggests it may decrease the rate.[50]

Dermatologic

Photosensitivity is a common adverse effect of doxycycline. Patients should avoid excessive sun exposure while on this medication and ensure the use of sunscreen when going outdoors. Other adverse effects include inflammatory lesions in the ano-genital region, skin

reactions, exfoliative dermatitis, and hypersensitivity reactions.[19] Case reports mention skin-hyperpigmentation, post-inflammatory elastolysis, and tooth discoloration with long-term doxycycline use.[43]

Other

Although not reported in patients taking doxycycline for malaria prevention, doxycycline has rarely been associated with benign intracranial hypertension.[43] Hematologic abnormalities have been reported in rare cases.[51]

Drug-drug Interactions

Dairy products, such as milk, decrease the absorption of doxycycline due to their calcium content. Antacids, bismuth subsalicylate, proton pump inhibitors, and oral iron products also decrease the absorption of doxycycline.[52-54] (Table 1) In addition, older adults are at higher risk for adverse effects with PPIs.[55, 56] In a Gallup Survey, 22% of responders who were greater than 50 years old stated they used antacids and other anti-dyspepsia agents two or more times per week.[57] In this same poll, only 9% of the responders younger than 50 admitted to doing the same.[57] Since older adults are more likely to be taking these agents, and many are over the counter, health care providers should discontinue or seek alternatives to these types of medications prior to prescribing doxycycline.

Hepatic enzyme inducers such as certain antiepileptic drugs, rifampicin, and chronic alcohol use may increase the metabolism of doxycycline.[58-62] (Table 1) Another major interaction that has been described in literature is the competitive plasma protein displacement of methotrexate by doxycycline leading methotrexate toxicity.[36] (Table 1) Over anticoagulation can occur when warfarin and doxycycline are given together through pharmacodynamic inhibition of

vitamin K dependent coagulation factors, and pharmacokinetic, protein binding displacement, mechanisms.[63] (Table 1)

Drug-disease Interactions and Considerations in Older Adults

Anticoagulation

With increasing age, there is an increased likelihood for comorbidities, such as atrial fibrillation, and the need for anticoagulation and older adults are also at an increased risk for hemorrhage from anticoagulation therapy.[40, 64] Doxycycline should be avoided or the INR needs to be monitored closely with the concomitant use of warfarin, especially in older adults.

Fungal infections

Due to the suppression of vaginal bacterial flora, doxycycline has been implicated in the development of candidal vulvovaginitis.[43] Individuals predisposed to candidal vulvovaginitis, such as those with diabetes mellitus, or prior medical history of recurring vulvovaginitis, may benefit from carrying a course of antifungal treatment on their trip.[43, 65] Elevated blood sugars may predispose patients to candida infections. Older adults are more likely to have diabetes and thus, they should be counseled regarding the increased risk for candida infections especially if they will take doxycycline for a prolonged period of time.[66]

Photosensitivity

As older adults are more likely to have comorbid conditions such as diabetes and hypertension, they may already be taking certain medications such as thiazide diuretics and sulfonylureas which may cause photosensitivity.[40, 51, 66] As doxycycline may also cause photosensitivity[51], patients should be counseled to wear extra sunscreen while traveling.

Mefloquine

Mefloquine is indicated for the prophylaxis of malaria and the treatment of mild-to-moderate, uncomplicated, chloroquine-resistant *P. vivax* and uncomplicated *P. falciparum* malaria in combination with Artesunate.

Pharmacologic//Pharmacokinetic Effects

Mefloquine is a quinoline-methanol compound structurally similar to quinine. Mefloquine acts as a blood schizonticide but its exact mechanism of action is not known. It is a 4-aminoquinoline with a fairly large volume of distribution, is highly protein bound and is primarily distributed in the tissue.[42, 67] With increased age, protein binding can potentially be affected. Healthy older adults will have normal concentrations of important proteins like albumin and alpha-1-acid glycoprotein which may be decreased by malnutrition and frailty.[11] While mefloquine is a highly protein bound drug, no changes in dosing based on weight or composition are currently recommended.[68]

Mefloquine is primarily metabolized via CYP enzymes in the liver.[69] Although the natural decrease in liver function that occurs with aging will not usually affect mefloquine use, caution should be taken in patients with liver disease.[70] There are currently no dose adjustment recommendations for hepatic impairment; however, the half-life is increased leading to prolonged plasma levels.[70] With increased drug exposure there is increased risk for adverse effects including headache, gastrointestinal disturbances, nervousness, fatigue, disorders of sleep, mood, memory and concentration, and occasionally psychosis.[71]

As only a small amount of mefloquine is renally eliminated, no major renal considerations exist for the use of mefloquine.

Pharmacodynamic Effects

Mefloquine may cause bradyarrhythmia, gastrointestinal issues, dizziness, headache, insomnia, hallucinations and anxiety.[72] Mefloquine has also been associated with other serious side effects which include QT interval prolongation, seizures, suicidal ideations, and pneumonitis.[72]

Drug-drug Interactions

As most drugs are hepatically metabolized, mefloquine does interact with other drugs that rely on similar metabolism routes in the body. Both ketoconazole and ampicillin lead to higher concentrations of mefloquine by decreasing its metabolism in the liver.[67, 73] (Table 1) Conversely, CYP enzyme inducers such as rifampin can lead to decreased mefloquine concentrations.[74] (Table 1) Ritonavir and mefloquine seem to interfere which each other's metabolism to varying extents but the clinical impact is unclear.[75]

Mefloquine can affect cardiac conduction, specifically slowing the heart rate and increasing risk for QT prolongation.[76, 77] Given this risk the WHO recommends caution when using mefloquine with drugs that also affect cardiac conduction such as calcium channel blockers, digoxin, amiodarone, quinolones, β-blockers, and other quinines.[42] (Table 1)

Drug-disease interactions and Considerations in Older Adults

Neuropsychiatric

Mefloquine use is contraindicated in patients with epilepsy.[78] Additionally, one of the major concerns with mefloquine is the rare risk for neuropsychiatric adverse events including anxiety, depression, mood changes, panic attacks, forgetfulness, confusion, hallucinations,

aggression, psychotic or paranoid reactions.[79] The CDC recommends avoiding use of mefloquine in patients with pre-existing psychiatric disease or a strong family history of psychiatric disease.[80] This caution should especially be exercised in older adults as data shows 52% of patients with first onset of a mood disorder at age 60 or older.[81] There is no evidence to suggest older adults are at higher risk of neuropsychiatric adverse events, however they should appropriately be screened for mood disorders prior to use of mefloquine especially when used for long term prophylaxis.

Cardiac

As the incidence of cardiovascular disease such as arrhythmias and the use of antiarrhythmic drugs increases with age, older adults may be at a greater risk for cardiotoxicity especially if taking mefloquine with a medication that affects cardiac conduction.[82] Caution should be exercised if prescribing mefloquine to ensure that drug-drug interactions, especially those that affect cardiac conduction, are not present.

Primaquine

Primaquine is indicated for the prophylaxis of malaria and treatment, including radical cure of *Plasmodium vivax* and *P. ovale* infections and presumptive anti-relapse therapy.

Pharmacologic/Pharmacokinetic Effects

Primaquine phosphate is an 8-aminoquinoline active against malaria parasites in the erythrocytic, hepatic, and gamete phase of the plasmodium's life cycle.[83]

Primaquine is broken down by monoamine oxidase into a predominant inactive metabolite, carboxyprimaquine, which lacks efficacy and toxicity, as well as by CYP2C19,

CYP2D6, and CYP3A4 enzymes into metabolites which are responsible for the antimalarial and hemolytic toxicity of primaquine.[84-86] The CYP2D6 enzyme may be essential for antimalarial efficacy of primaquine, and thus, the reduction in its activity may result in treatment failure.[86] Once it is distributed in the body, primaquine is found in erythrocytes in high concentrations. Primaquine is readily absorbed from the GI tract with 96% bioavailability.[87] Primaquine and carboxyprimaquine are primarily excreted through the biliary tract; however, some of primaquine is also excreted unchanged in the urine.[88] The elimination half-life is 4 to 7 hours and no dosage adjustment is needed for renal insufficiency.[89, 90] Although clinical studies have not identified differences in response to treatment with primaquine in older adults versus younger patients, the manufacturer recommends starting with low doses of this drug due to potential physiologic changes in older adults.[83]

Pharmacodynamic Effects

Primaquine is usually well-tolerated. It may cause some GI discomfort which may be dose-related.[83] If this occurs, patients can take primaquine with food. Rarely, hypertension, QT prolongation and cardiac arrhythmias occur.[83]

Drug-drug interactions

There are no clinically significant drug interactions resulting in toxicity with currently marked drugs and primaquine. Quinine use may decrease the plasma concentration of carboxyprimaquine, an inactive metabolite, by interfering with the production and elimination of carboxyprimaquine.[91] Dihydroartemisin-piperaquine and artesunate-pyronaridine may increase the levels of primaquine and carboxyprimaquine by displacing bound primaquine and

carboxyprimaquine from the tissues.[85, 91] Chloroquine has also been shown to increase primaquine geometric mean plasma concentration by 63%, which does not result in toxicity but may have a synergistic effect.[92] While no recent studies confirm these interactions, the manufacturer of primaquine reports interactions with quinacrine and myeloid suppressive drugs. (Table 1)[83]

Drug-disease Interactions and Considerations in Older Adults

G6PD deficiency

The most important adverse effect with primaquine is hemolysis which results when patients are G6PD deficient. There are different variants of G6PD deficiency and these are associated with different risks for hemolysis. In G6PD deficient people, hemolysis usually occurs 2 to 3 days after primaquine initiation. Both qualitative and quantitative point-of-care G6PD testing is now available. The CDC states that quantitative G6PD deficiency testing must be done prior to primaquine use.[93] The severity of hemolysis depends on the dose, length of therapy, and degree of G6PD deficiency. As primaquine is rapidly eliminated from the body, hemolysis stops shortly after drug discontinuation. If primaquine must be used, it can be dose adjusted depending upon the degree of G6PD deficiency.[94] Hemolytic anemia, leukopenia, methemoglobinemia, and granulocytopenia may also occur independently of G6PD deficiency.[89]

Rheumatoid arthritis and SLE

Primaquine use is contraindicated in acutely ill patients with granulocytopenia such as patients with a severe subset of rheumatoid arthritis (RA) and SLE.[95] This is an important consideration especially in older adults who are more likely to suffer from RA than younger individuals.[95]

Other

Loss of efficacy has been observed in patients with poor and intermediate P450 CYP2D6 activity phenotypes since isoenzyme 2D6 may be primarily responsible for metabolizing primaquine into active metabolites against hypnozoites in the liver.[96]

Drug Name: Tafenoquine

Arakoda® (US trade name) and Kodatef® (Australian trade name) are indicated for the prophylaxis of malaria. Krintafel® (US trade name) and Kozenis® (Australian trade name) are indicated for radical cure of *P.vivax* malaria.

Pharmacologic/Pharmacokinetic Effects

Similar to primaquine, tafenoquine is an 8-aminoquinoline.[97, 98] It is active against all stages of the parasite, including dormant liver stages of *P.vivax* and erythrocytic phase, having a similar efficacy to mefloquine for prophylaxis.[99]

Unlike primaquine, tafenoquine is eliminated from the body at a much slower rate. The terminal half-life of tafenoquine is 12-15 days, and co-administration with a high-fat meal increases systemic exposure by 41%.[94, 100] The longer half-life allows for weekly dosing where primaquine must be dosed daily. Age does not appear to impact the pharmacokinetics of tafenoquine.[101, 102]

Tafenoquine has not been studied in patients with renal and hepatic disease, however renal and hepatic function should be monitored in patients with pre-existing disease.[94]

Pharmacodynamic Effects

Gastrointestinal

The adverse effect profile of tafenoquine is like that of primaquine. GI disturbances such as nausea, diarrhea, vomiting and motion sickness have occurred. If taken with food, the GI adverse effects of tafenoquine may be minimized.

Hematologic

Moderate methemoglobinemia has been reported but is likely due to higher doses (>200 mg) daily or weekly.[94] When used as a single dose, this adverse effect is very rare.[94]

Ophthalmic

Corneal deposits or epithelial keratopathy with prolonged use can occur with tafenoquine. This was observed in 25% of individuals taking the drug for 6 months and it resolved within 12-48 weeks upon discontinuation of the drug.[94, 103]

Other

Depression, photophobia, increased serum creatinine and serum alanine aminotransferase, insomnia, and decreased hemoglobin have also been reported but with lesser frequency.[104]

Drug-drug Interactions

Tafenoquine may increase the levels of multidrug and toxin extrusion (MATE1) substrates and organic cation transporter (OCT2) substrates, which are renal transporters important in renal elimination of drugs.[105] If one or both renal transporters are inhibited as is the case with tafenoquine, this can lead to toxicity of the substrates. Therefore, a combination of tafenoquine with MATE1 or OCT2 substrates should be avoided. However, if the drugs must be

given together a dose reduction of MATE1 or OCT2 substrates should be considered to avoid toxicity. Cisplatin, oxaliplatin, and metformin are a few examples of OCT2 and MATE2 substrates that have increased plasma levels when given with tafenoquine.[105-107] (Table 1) As the likelihood for diabetes increases with age[108], this may be an important consideration to take note of since many patients with diabetes are often prescribed metformin for management of diabetes.[109] Tafenoquine has little effect on cytochrome P450 metabolized drugs like primaquine, nor does it affect the pharmacokinetics of chloroquine when co-administered.[110] Tafenoquine has not been adequately studied in older adults.

Drug-disease interactions and Considerations in Older Adults

G6PD deficiency

As with primaquine, G6PD deficiency must be screened for prior to administration of tafenoquine due to increased risk for hemolytic anemia.[104] Females with a quantitative activity of G6PD ≥30% to <70% are considered to be in the intermediate category, but because tafenoquine has dose dependent hemolysis, males and females should have a quantitative test done to ensure the activity is greater than 70% before it can be used for prophylaxis or treatment.[94]

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common genetic disorder in humans.[94] Since the G6PD gene lies on the X chromosome, males with a mutation on the X chromosome and females with a mutation on both X chromosomes will have full phenotypic expression of the deficiency.[94] Females with a mixture of G6PD normal and G6PD deficient red cells will have varying levels of G6PD deficiency.[94] Qualitative testing for G6PD deficiency is sufficient for males as they are either G6PD deficient or normal.[94] However, for females, a quantitative test must be done because of the possibility of having an intermediate

level of G6PD deficiency.[94] The threshold for normal G6PD qualitative test is ≥30%.[94] Thus a female heterozygous patient testing "normal" may still have up to 70% of their red blood cells G6PD deficient.[111] As most patients with G6PD deficiency remain asymptomatic, it is possible that an older adult does not know their G6PD status.[112]

Hematologic

Methemoglobin elevations have been reported with tafenoquine use and this should be considered prior to prescribing the medication, especially if used at higher doses.[110]

Neurologic

Tafenoquine should also be used with caution in patients with psychiatric disorders. With higher doses of tafenoquine, serious psychiatric adverse events have been reported in patients with a past medical history of psychiatric disorders.[113] Anxiety, abnormal dreams, mood changes, and trouble sleeping have been observed.[104] These effects may have a delayed onset due to longer half-life and longer time to Cmax of the drug.[101] This is an especially important consideration in older adults as data shows that the first onset of a mood disorder occurs at age 60 or older in 52% of patients.[81] Patients with a history of psychotic disorders or current psychotic symptoms, especially in deployed military personnel, should not use this drug.[97, 114]

Artemisinins Artesunate and Artemether

Artesunate is administered intravenously for the treatment of severe malaria and Artemether with Lumefantrine (AL), with the trade name of Coartem® in US and Africa and Riamet® in Europe, is used orally for treatment and standby emergency treatment of uncomplicated malaria.

Pharmacologic/Pharmacokinetic Effects

Both artemether and artesunate have similar pharmacodynamic properties as other artemisinin derivatives.[115] The mechanism of action of the artemisinins is hypothesized to involve an iron-mediated cleavage of the endoperoxide bridge, which produces oxygen free radicals, which then react with nearby molecules, interfering with parasite function.[116] Both artesunate and artemether are prodrugs that are rapidly hydrolyzed by plasma esterases to an active metabolite, dihydroartemisinin (DHA), which then undergoes hepatic metabolism via CYP2B6, CYP2C19, and CYP3A4 to inactive metabolites.[117] Bodyweight has been linked to differences in dosage necessary of artesunate, with children requiring higher dosages due to a larger volume of distribution.[42] No enhanced measures are recommended for older adults with lower body weight. The exact mechanism of action of lumefantrine is unknown but it is thought to prevent the formation of β-hematin by complexing with hemin, inhibiting nucleic acid and protein synthesis, and eliminating residual parasites. While artemether clears most of the parasitemia, lumefantrine concentrations that remain at the end of the 3- to 5-day course, due to its long half-life of 3-6 days, are responsible for eliminating residual parasites.[118] There is no renal or hepatic dose modification necessary with the artemisinins, but they should be used cautiously in severe impairment. A high-fat meal, as little as 1.2 g, can significantly increase the AUC of lumefantrine, 5 fold, and artemether.[119, 120]

Pharmacodynamic Effects

Hypersensitivity reactions, some gastrointestinal disturbances, dizziness, reticulocytopenia, and an increase in liver enzymes have been reported.[42]

Drug-drug interactions

Similar to other antimalarials previously discussed, the artemesins and DHA, the active metabolite, interact with potent CYP 3A4 inducers and inhibitors as noted. With the short half-life of intravenous artesunate, it is unlikely to incur clinically significant drug-drug interactions.[121] The drug-drug interactions with the best documentation are between AL and ketoconazole and rifampin.[122] Ketoconazole can increase levels of AL and DHA by CYP 3A4 inhibition 1.6 to 2.3 fold, leading to QT interval prolongation.[120] Rifampicin, on the other hand, is a CYP 3A4 enzyme inducer, thus, theoretically, leading to a decrease in AL plasma levels and a potential decrease in antimalarial efficacy.[123] The pharmacokinetic decrease of DHA with ritonavir and similar drugs is thought to be due to the induction of uridine diphosphate-glucuronosyltransferases (UGTs), the main route of elimination of DHA, by ritonavir. [124] Decreased exposure of DHA observed with ritonavir may negatively impact efficacy of antimalarial therapy. Lumefantrine is also mainly metabolized by CYP3A4. Administration with potent inducers of CYP3A4 may result in lower lumefantrine, artemether and DHA exposure and potential failure of treatment. In clinical studies, artemether and DHA exposure were substantially lower with concomitant use of nevirapine (NVP) and efavirenz (EFV).[125, 126] Efavirenz, is a potent CYP 3A4 inducer and has shown to decrease the AUC of DHA by 50%, potentially leading to AL treatment failure.[127] Results with lumefantrine and NVP have been mixed as NVP is a less potent inducer of CYP3A4 than EFV. In the South African and Tanzanian studies, they found lumefantrine exposure increased at the end of a simulated 7-day course, but a Ugandan study found a decrease in lumefantrine AUC.[125, 126, 128] Speculation as to the difference in effect on lumefantrine in the South African study is they provided a high fat meal to participants and extended the regimen, which may be necessary to overcome this

interaction with NVP.[128] Conversely, when lumefantrine and the HIV drug lopinavir/ritonavir were co-administered to HIV positive study participants, lumefantrine plasma concentrations were 10 times greater with no documented increase in adverse effects.[129] Whether this interaction leads to better efficacy needs further study. A summary of drug-drug interactions and artemisinins is listed in Table 1.

Drug-disease interactions and Considerations in Older Adults

Cardiac

While lumefantrine is structurally similar to halofantrine, which is known to cause significant cardiotoxicity, pharmacologic modifications to the drug have borne out no increase in QT prolongation.[130, 131] The manufacturer, however, recommends against use in patients with congenital QT prolongation and patients receiving other drugs known to affect the QT interval.[120] As mentioned previously, older adults may be at a greater risk for cardiotoxicity as the incidence of cardiovascular disease such as arrhythmias and the use of antiarrhythmic drugs increases with age.[82]

Chloroquine

Due to the high prevalence of chloroquine resistant *P. falciparum* malaria in most parts of the world, chloroquine use has significantly declined over the years. Chloroquine is indicated for malaria prophylaxis and treatment of susceptible plasmodium species. Hydroxychloroquine is not commonly used for malaria prevention or treatment, but the adverse effect profile and drug-drug interactions are similar to chloroquine.

Pharmacologic/Pharmacokinetic Effects

Chloroquine is a 4-aminoquinoline and an anti-protozoal agent. While the exact mechanism of action of chloroquine is not well known, it is thought to kill plasmodium in the erythrocytes by the prevention of the polymerization of heme, leading to accumulation in the parasite, which is toxic. Chloroquine is readily absorbed from the GI tract, and it is extensively distributed in tissues such as liver, spleen, kidney, and lung.[22] It is metabolized in the liver by CYP2C8 and CYP3A4 enzymes, and about 55% of the medication is renally eliminated.[19, 132, 133]

There are currently no dosage adjustment recommendations for chloroquine. However, it has been recommended to administer 50% of the chloroquine dose if the patient's CrCl is less than 10 mL/min.[134]

Pharmacodynamic Effects

Dermatologic

Pruritis can occur with chloroquine use and has a higher frequency in dark-skinned individuals.[135] Administration of an antihistamine at the same time as the administration of chloroquine may help decrease the incidence of pruritis in susceptible individuals.[136] However, the American Geriatrics Society (AGS) 2019 Updated AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults states that first-generation antihistamines should be avoided due to increased risk of adverse effects.[15] Some examples of first-generation antihistamines are brompheniramine, chlorpheniramine, diphenhydramine, doxylamine, hydroxyzine, and meclizine.

Cardiac

Although rare, QRS complex and QT interval prolongation along with cardiotoxicity have been observed with chloroquine use.[137] Older adults may be at a greater risk for cardiotoxicity as the incidence of cardiovascular disease such as arrhythmias and the use of antiarrhythmic drugs increases with age.[82]

Other

Rarely, chloroquine may cause GI disturbances such as nausea, vomiting, and diarrhea, hypoglycemia, hepatitis, elevated liver enzymes, and headache.[138] Taking chloroquine with food may help alleviate any GI adverse effects. Other adverse effects that may occur very seldom are central nervous system changes, myopathy, photosensitivity, hearing loss, and blood disorders.[138] If used chronically for long term prophylaxis, keratopathy and retinopathy may occur. For indications other than acute malaria, the use of chloroquine is contraindicated in the presence of retinal or visual field changes.[139]

Drug-drug Interactions

Chloroquine should be used cautiously with cimetidine, ampicillin, praziquantel, thyroxine, cyclosporine, methotrexate, and antiepileptic medications due to drug interactions using different mechanisms.[140-146] (Table 1) It has been postulated that cimetidine may inhibit the elimination of chloroquine and that chloroquine may decrease gastric emptying and gut motility resulting in decreased ampicillin bioavailability.[140, 141] The interaction between chloroquine and praziquantel is not well understood, but it has been proposed that chloroquine may increase the catabolism of thyroid hormones via enzymatic induction.[143, 144] Chloroquine may increase cyclosporine levels by inhibiting its metabolism through direct enzyme inhibition or by enzyme competition.[142, 147] Chloroquine may reduce the bioavailability of methotrexate when co-

administered.[146] Carbamazepine was reported to antagonize the effect of chloroquine.[138] Chloroquine may also increase the risk for acute dystonic reactions when taken with metronidazole, and it should be taken at least 4 hours apart from antacids as antacids may decrease the absorption of chloroquine.[148, 149] (Table 1) Some medications (ie. antipsychotic medications, cisapride, dronedarone, etc) are contraindicated with chloroquine due to the increased risk for QT prolongation.[138] (Table 1) Antidepressant medications such as citalopram, escitalopram, fluoxetine, and some tricyclic antidepressants also pose a great risk for QT prolongation with chloroquine.[36] (Table 1)

Drug-disease interactions and Considerations in Older Adults

G6PD deficiency

Chloroquine may also cause hemolysis in glucose-6 phosphate dehydrogenase (G6PD) deficient individuals and especially if these patients are taking medications which can also cause hemolysis. These medications include dapsone, methylene blue, nitrofurantoin, phenazopyridine, primaquine, rasburicase, and tolonium chloride.[150] While it is not recommended to perform G6PD testing, if the individual has the enzyme deficiency, it should not be used. Periodic checks of complete blood cell counts are important if patients are taking chloroquine for an extended period of time.

Cardiac

A scientific statement by the American Heart Association in 2016 concluded that chloroquine might cause myocardial toxicity or exacerbate underlying myocardial dysfunction in cases of long-term use and with high doses.[137] Older adults, female sex, long duration of therapy (3 months – 27 years; mean > 10 years), high doses, preexisting cardiac disease, and renal

insufficiency are all risk factors for cardiotoxicity.[137, 151, 152] Drug-drug interaction should always be checked with chloroquine especially in older adults to ensure that the risk for QT prolongation and cardiotoxicity is minimized.

Hypoglycemia

Hypoglycemia has been reported with chloroquine. As older adults are at a higher risk for hypoglycemia during treatment for diabetes with glucose lowering medications, close monitoring of blood sugars is warranted if chloroquine is used for malaria prevention or treatment.[18]

Ophthalmic

The risk of retinopathy is also increased if a patient has decreased renal function or is taking tamoxifen.[153, 154] Older adults should have normal renal function when taking chloroquine as these individuals are more prone to renal impairment.[12] Age, however, does not seem to correlate to retinal toxicity.[154] The American Academy of Ophthalmology (AAO) recommends baseline screening for retinal toxicity and annual screening for patients taking chloroquine for longer than 5 years as the risk of retinal toxicity increases from less than 1% over 5 years to 2% up to 10 years, and to 20% after 20 years.[153]

Other

Chloroquine may exacerbate psoriasis, neurological, retinal, or gastrointestinal disorders.[138] Exacerbation and, rarely, induction of plaque-type psoriasis can occur, typically after 4 to 12 weeks of use, but the actual risk is unknown.[155] Chloroquine should be used with caution in patients with hepatic impairment as it may accumulate in the liver, thereby resulting in hepatic toxicity. This is an important consideration in older adults as they are more likely to have multiple co-morbid conditions, including decreased hepatic function.[12, 66]

As older adults may have more comorbid conditions such as diabetes mellitus, heart disease, and retinopathy, the risk for hypoglycemia, cardiotoxicity, QT interval prolongation, and retinopathy with chloroquine should be considered prior to prescribing chloroquine for these individuals.[108, 156] This is especially true if an older adult requires long term malaria prophylaxis.

Limitations

Limited data was found on drug-drug interactions in older patients once the literature search was performed. The limited data and lack of recent literature prevented the authors from performing a systematic review or meta-analysis due to the lack of heterogeneity in the evidence.

Conclusion

While the proportion of older adults traveling to malarious areas is small compared to younger groups, special attention is warranted due to their unique changes in physiology and how drugs are affected by their pharmacokinetic parameters. In addition, older adults are more likely to take multiple medications and have chronic medical conditions. As a result, older adults may be at a higher risk for drug-drug and drug-disease interactions such as cardiotoxicity or over anticoagulation. With some exceptions, older adults are not more likely to experience adverse effects or decreased efficacy due to drug-drug interactions any differently than younger groups.

Author Statements

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Author Contributions

- All authors read and approved the final manuscript.
- All authors collaborated on the conceptualization, methodology design, writing the manuscript, revising the manuscript and providing comments to the manuscript.

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Table 1. Summary of Antimalarial Drug-Drug Interactions

Generic Drug Name	High Risk Interacting Drugs	Quality of Documentation/Recommended action[ł]	Drug-Drug Considerations

Mefloquine	• QT prolongation drugs	Quality of documentation varies based on drug/Contraindicated or use with extreme caution	• Caution with drugs that affect cardiac conduction (B-blocker, digoxin, amiodarone, etc.) due to QT prolongation
	• Rifampin	Good/Avoid concurrent use	• Decreased exposure with concurrent rifampin
	• Ketoconazole	Good/Contraindicated	• Increased exposure with concurrent ketoconazole and increased risk for cardiotoxicity
Chloroquine	• Cyclosporine (↑)	Good/Avoid concurrent use	• Monitor cyclosporine levels for toxicity
	• Tamoxifen	Fair/Avoid concurrent use	• Increased risk for retinopathy
	• QT prolongation drugs	Quality of documentation varies based on drug/Contraindicated or use with extreme caution	• Augmentation of QT prolongation effect (ie. some antidepressants, antiarrhythmics, certain antipsychotics, some HIV medications, certain antiemetics, etc.)
	• Cimetidine (↑)	Good/Avoid concurrent use	• Suggest switching to another anti-ulcer medication with less potential to alter the pharmacokinetics of chloroquine
	• Carbamazepine (↓)	Fair/Avoid concurrent use	
	• Praziquantel (↓) • Thyroxine (↓)	Good/Precaution	• Decreased bioavailability of these agents • Consider dose increase of praziquantel is patient is not responding to treatment • Monitor TSH levels when starting and discontinuing chloroquine therapy
	• Antacids	Good/Avoid concurrent use	• Reduced absorption with antacids

			• Administration should be separated by at least four hours
Doxycycline	• Antacids • Bismuth subsalicylate • Oral iron	Good/Avoid concurrent use	• Doxycycline should be taken at least one to two hours before aluminum, calcium or magnesium containing products • Doxycycline should be taken at least two to three hours before the bismuth subsalicylate dose • Iron salts should be given not less than three hours before or two hours after the doxycycline dose
	• Rifampin	Good/Avoid concurrent use	• May decrease plasma concentration of doxycycline
	• Carbamazepine • Phenytoin • Phenobarbital	Fair/Avoid concurrent use	• May decrease plasma concentration of doxycycline
	• Warfarin (↑)	Fair/Precaution	• Closely monitor INR at initiation and withdrawal of doxycycline therapy and reassess periodically during concurrent therapy
	• Methotrexate (↑)	Good/Use with caution	• Closely monitor for evidence of methotrexate toxicity especially at high methotrexate doses; consider an alternative to doxycycline
Primaquine	• Quinacrine	Contraindicated (PI)	• Manufacturer recommendation (may increase toxicity of primaquine)
Atovaquone-proguanil	• Ritonavir, efavirenz, rifamycins	Good/Use not recommended	• Decreased plasma concentration of atovaquone/proguanil
	• Tetracycline	Good/Use not recommended	• Decreased plasma concentration of atovaquone/proguanil

	• Metoclopramide	Fair/Use with caution only if other options not available	• Decreased bioavailability of atovaquone/proguanil
	• Warfarin (↑)	Good/Precaution	• Closely monitor INR at initiation and withdrawal of antimalarial therapy
Tafenoquine	• Cisplatin • Metformin • Oxaliplatin	Fair/ Precaution	• Increases levels of multidrug and toxin extrusion (MATE1) substrates and organic cation transporter 2 (OCT2) substrates
Artemisinins (Artesunate, Artemether/Lumefantrine)	• Rifampin (↓) • Ketoconazole (↑) • QT prolongation drugs	Excellent/Contraindicated	• Avoid with potent CYP 3A4 inducers or inhibitors • Augmentation of QT prolongation effect
	• Darunavir, ritonavir, lopinavir, ritonavir, nevirapine, efavirenz, etravirine	Fair/Precaution	• Caution with potent CYP 3A4 inducers or inhibitors

[±] Classification and strength of evidence adapted from Micromedex Online Solutions. Greenwood Village, CO: Truven Health Analytics. http://micromedex.com/. Accessed date August 2019