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Adverse Effects of Anti-malarial Drugs Used in the Treatment of Malaria Cases Caused by Species Other than *Plasmodium falciparum*: A scoping Review

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Abstract

Antimalarial drugs used in the treatment of malaria caused by species other than Plasmodium falciparum also have adverse effects. The objective of this review is to identify the different molecules used in the treatment of these forms of malaria and the adverse effects they cause in humans. We conducted a scoping review by searching PubMed and Google Scholar data bases as well as gray literature documents. Data were selected, collected and characterized by four reviewers using the methodological guidelines described by Arksey and O'Malley in 2005 and by Levac, Colquhoun and O'Brien in 2010.A total of 37 documents were reviewed. Drugs such as chloroquine and proguanil very rarely have serious adverse effects at recommended doses. Unfortunately, in some parts of the world, these products are no longer effective prophylactic agents. Potentially fatal reactions are caused by the use of pyrimethamine-sulfadoxine and amodiaquine, so these molecules are no longer recommended for prophylaxis. Mefloquine, despite its effects on the central nervous system, is indicated for chemoprophylaxis of malaria caused by all species. The artemether-lumefantrine combination often produces effects that are difficult to distinguish from malaria symptoms, but the most important adverse effect is hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Cinchonism is a common side effect observed after the intake of therapeutic doses of quinine.Regardless ofthe plasmodial species involved, the molecules that can be used in the treatment of malaria are quite similar. However, their side effects can vary from one species to another.

Keywords: Adverse Effects, Antimalarial Drugs, Treatment of Malaria, *Plasmodium Vivax*, *Plasmodium Ovale*, *Plasmodium Malariae*, *Plasmodium Knowlesi*

INTRODUCTION

Malaria is a pathology caused by intracellular protozoan parasites of the genus Plasmodium (P) and transmitted by the bite of a female Anopheles mosquito [Phillips et al., 2017, Cowman et al., 2016]. There are five species responsible for the disease in humans: P. falciparum, *P. vivax, P. malariae, Plasmodium ovale, and P. knowlesi* [Cohee and Laufer, 2017]. The majority of cases are caused by *P. falciparum* [Visser et al., 2014]. Malaria is endemic in 104 tropical and subtropical countries [WHO, 2015], and more than half of the world's population lives in areas where malaria transmission occurs. The disease exacts a heavy public health burden on communities in parts of Africa, Asia, and Central and South America [WHO, 2016]. The population at risk is estimated at 2.57 billion for *P. falciparum* [Gething et al., 2011] and 2.5 billion for *P. vivax* [Gething ., 2010].The literature reveals a very small proportion of infections caused by *P. malariae* and *P. ovale* [Kar et al., 2014]. All of sub-Saharan Africa, most parts of Southeast Asia, as well as the islands of the Western Pacific and the Amazon basin contain communities at risk of *P. malariae* [Karet al., 2014]. Malaria caused by *P. ovale* is widespread in Africa and in the Asia-Pacific regions [Obare et al, 2013, Sutherland et al., 2010]. In remote forested areas of Southeast Asian countries, *P. knowlesi* is a species that causes malaria mainly in primates [Putaporntip et al., 2004, Singh et al., 2004, Van et al., 2009, Vythilingam et al., 2009].

Uncomplicated malaria usually manifests as a nonspecific febrile state, similar to influenza and other common viral infections [Oakley et al, 2011 and Ladhani et al., 2007]. Malaria symptoms are highly variable and may include chills, sweating, headache, lethargy, myalgia, and cough. Gastrointestinal symptoms can be severe, such as nausea, vomiting, diarrhea, and abdominal pain [Gutman and Guarner, 2010]. Physical signs such as pallor, tachycardia, hepato-splenomegaly, jaundice, and increased respiratory rate may also be present in a malaria infection. In cases of cerebral malaria, altered mental status is observed [Trampuz et al., 2013]. The disease may have a slow or fulminant course [Kafai and Odom 2018].

Malaria infection can be fatal, and in areas where the index of suspicion is high, management can begin before test results are available or even before they are performed. Health policy in these areas aims to avoid delays in management. Nevertheless, diagnostic specimens should be available, even if presumptive treatment is initiated [Cohee and Laufer, 2017]. In low-resource, nonendemic countries, rapid diagnostic tests (RDTs) for antigen detection are increasingly available for malaria diagnosis. Malaria RDTs detect specific antigens (proteins) produced by malaria parasites in the blood of infected persons. Some RDTs detect monospecific infections (either *P. falciparum* or *P. vivax*), others detect mixed infections (*P. falciparum, P. vivax, P. malariae,* and *P. ovale*), while others distinguish between P. falciparum and non-P. Falciparum infections or specific species. The WHO website provides up-to-date information on available tests and their mechanisms and performance characteristics [WHO, 2020].

Single-molecule approaches to malaria treatment have been shown to significantly contribute to drug resistance and are not recommended [WHO, 2015]. For example, at present, treatment of uncomplicated malaria is not recommended for any plasmodial species, is effectively treated in 3 days with an artemisinin-based combination therapy (Artemisinin-baseCombination Therapy" ACT ") that combines a fast-acting artemisinin derivative with a longer-acting antimalarial drug (artemether + lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, artesunate + SP, dihydroartemisinin + piperaquine) [Phillips et al., 2017, Cowman et al., 2016]. Chloroquine (CQ) is still the standard drug for *P. vivax*, *P. malariae*, and *P. ovale* in most countries [Vanet al., 2011], but *P. vivax* resistance to CQ is emerging in parts of sub-Saharan Africa and Southeast Asia [Baird, 2004]. The World Health Organization (WHO) also recommends the use of ACTs for the treatment of *P. vivax* in affected areas [WHO, 2010]. The use of CQ is avoided in many African countries because of frequently experienced side effects. Artemisinin derivatives are generally well-tolerated [Visser et al., 2014]. Currently, antimalarial drugs in addition to the two described above are available for the treatment of malaria caused by species other than P. falciparum, but these drugs also have adverse effects [Visser et al., 2014].

The objective of this scoping review was to identify the different molecules used in the treatment of malaria caused by species other than *P. falciparum* and the adverse effects that these products cause.

METHODS

The research question we have defined is "What are the adverse effects of antimalarial drugs used in the treatment of malaria caused by species other than *P. falciparum*?"

Research strategy

This review followed the methodological orientations described by Arksey and O'Malley, 2005 and Levac, et al., 2010.We successively 1) defined the research question; 2) conducted a literature research; 3) selected the studies; 4) extracted the data; and 5) summarized and presented the results.

We searched electronic databases (PubMed and Google Scholar) as well as databases containing gray literature, such as health policy documents on malaria. Databases were searched for literature published up to July 2020. Details on search terms and relevant keywords [Medical Subject Headings (MeSH)]were as follows:(((Mefloquine OR Arthemether-Lumefantrine OR Dihydroartemisinin-Piperazine OR Chloroquine OR Primaquine OR Artesunate-amodiaquine OR Atovaquone-Proguanil OR Quinine OR Amodiaquine OR Halofantrine OR Amodiaquine-Sulfadoxine-Pyrimethamine)) AND ((*P. Vivax* OR *P. Malariae* OR *P. Ovalae* OR *P. Knowlesi*))) AND ((Side Effects OR Adverse Effects))))).

We included papers meeting the following inclusion criteria in this review: 1) papers published in English or French and 2) papers addressing the adverse effects of antimalarial drugs used in non-*Plasmodium falciparum* malaria. Exclusion criteria used to filter the documents were as follows: 1) papers published in a language other than French or English, 2) documents or articles dealing with *Plasmodium falciparum* malaria, and 3) documents or articles for which the abstract was unavailable. We did not restrict the study design, the type of article, or the date of publication. We also checked the references of all selected papers to identify others that met the inclusion criteria.

The principal investigator developed and conducted this literature search. First, he checked each document using the title and abstract to discern those that met the inclusion criteria. For all abstracts that met the inclusion criteria, the complete documents were retrieved. Then, the full text of the selected papers was read. Finally, three other investigators

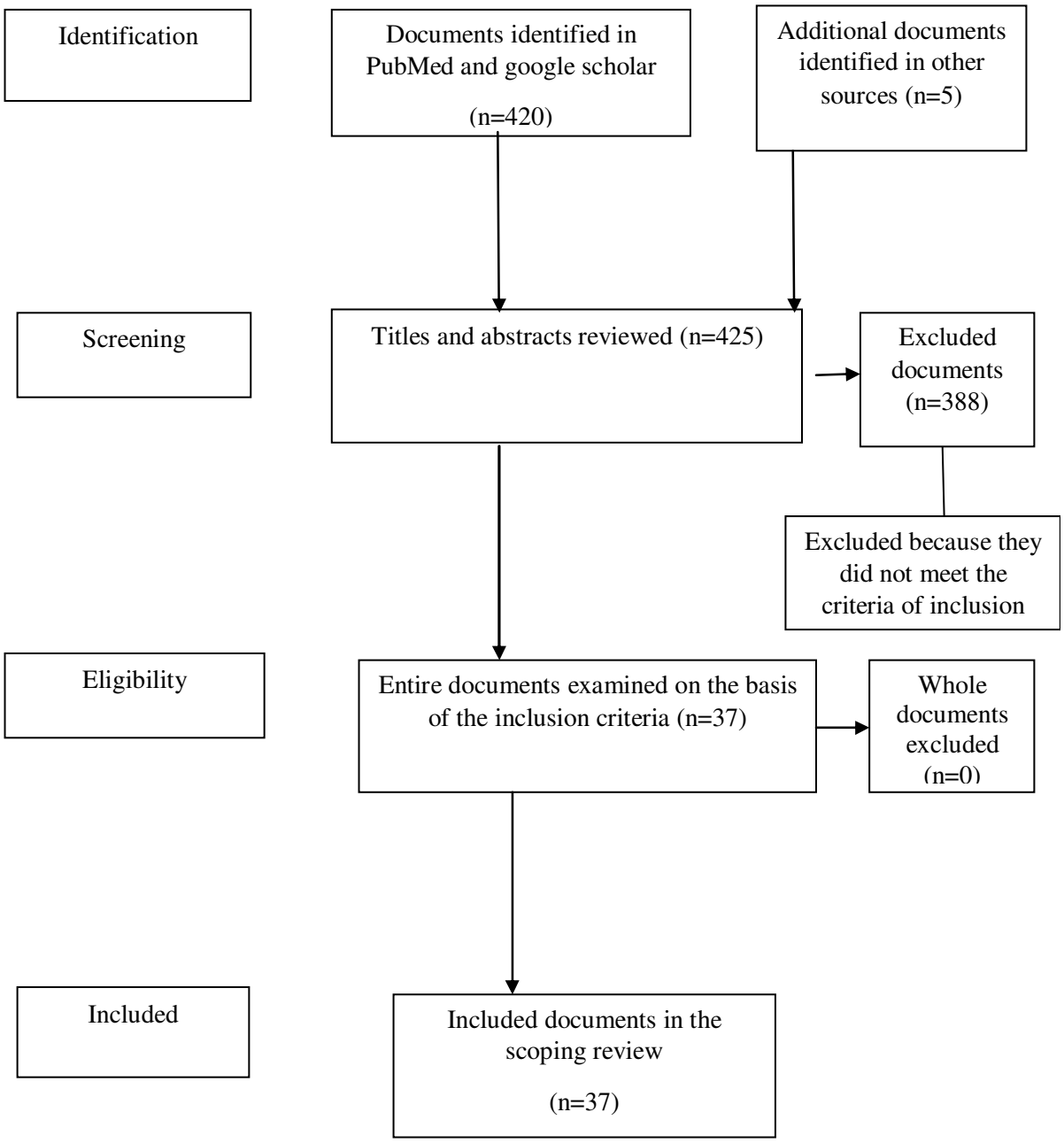

Figure 1: PRISMA diagram for document selection.

partnered with the principal investigator to extract data from the included documents and enter them into a data collection form to collect relevant information on adverse effects of antimalarial drugs used in non-*P. falciparum* malaria. Figure 1 shows a schematic of the selection process for the documents considered in this review.

RESULTS

Four hundred twenty-five documents were identified from the search strategy, of which 388 were excluded and 37 included for data extraction. Of the 37 documents included, 21 were original articles, 5 were case reports, 7 were simple reviews, 3 were systematic reviews, and the last was a health policy document.

In the following lines, we described in detail each molecule and its side effects that we also summarize in Table 1.

Chloroquine

Chloroquine is an antimalarial drug indicated for the treatment of uncomplicated malaria caused by *P. vivax, P. malariae, P. ovale*, and *P. knowlesi* [Krafts and Hempelmann, 2012]. This molecule is still recommended for the prevention of *plasmodium vivax* infections. Chloroquine is generally well tolerated under therapeutic doses [WHO, 2015]. The results of this review revealed adverse events [WHO, 2015, Chu and White 2016, Villegas et al., 2007, Ballut et al., 2013, Gebreyohannes et al., 2017, Navaratnam et al., 2009, Grigg et al., 2018], the most frequent of which was pruritus. This effect is more severe in dark-skinned people [WHO, 2015]. Other less frequent adverse events reported in this review included headache, liver damage in the form of hepatitis, gastrointestinal disorders (anorexia, nausea, vomiting, diarrhea, abdominal pain on an empty stomach), oral inflammation, skin rashes, and elevated liver enzymes. More rarely, central nervous system toxicity manifested by convulsions, mental changes, sleep disturbances and dizziness may occur. This research also identified the occurrence of visual disturbances, fatigue, dizziness, cough, sore throat, joint pain, flushing, and shortness of breath. Furthermore, chloroquine may cause a slight widening of the QRS complex and QT intervals in electrocardiography. Additional rare effects reported by other authors include myopathy, hearing loss, photosensitivity and hair loss. Extremely rare effects include blood disorders (aplastic anemia) [WHO, 2015].

Artemether-lumefantrine

The combination of artemether-lumefantrine is also indicated for the treatment of *P. vivax, P. ovale, P. knowlesi* and *P. malariae malaria* [WHO, 2015]. Several documents revealed that artemether-lumefantrine has adverse effects, such as gastrointestinal disorders (nausea, anorexia, vomiting, diarrhea, mouth inflammation, abdominal pain) [WHO, 2015, Ballut et al., 2013,Braga et al., 2016, Abdallah et al., 2012,]. Side effects, such as dizziness, headache, asthenia or fatigue, joint pain, dizziness, skin rashes, cough, chills, hyperhydrosis, vision and hearing problems and shortness of breath, in some patients have also been reported in the literature [WHO, 2015, Ballut et al., 2013,, 34]. Some signs are not easily distinguishable from malaria symptoms.
As a monotherapy, artemether has adverse effects similar to other artemisinin derivatives, such as hypersensitivity reactions, minor gastrointestinal disturbances, dizziness, reticulocytopenia, neutropenia and increased liver enzyme activity. Studies reported bradycardia and a very slight prolongation of the QT interval [WHO, 2015,].

Primaquine

Primaquine is a drug indicated for the radical cure of *P. vivax* or *P. ovale malaria*, for the presumptive treatment of relapses in people with high exposure to *P. vivax* or *P. ovale*, and as an alternative to primary prophylaxis against all species of malaria [WHO, 2015,]. The drug is generally well tolerated. From the documents consulted [WHO, 2015,, Chu and White, 2016, Hatz et al., 2008, Daher et al., 2018, Chu et al., 2017, Pasaribu et al., 2006, Rebholz et al., 2008, Betuela et al., 2012, Redht et al., 2018 chu et al., 2018, Taylor et al., 2019, Fernando et al., 2011], the scoping review revealed several undesirable effects during the use/intake of this molecule. These include gastrointestinal discomfort, abdominal pain, nausea, vomiting, generalized urticarial rash, lack of appetite, meso or hypogastric pain, choluria, weakness or malaise, headache, myalgia or arthralgia, fever, dizziness, shortness of breath, and bronchospasm. The most important adverse effect was hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and the degree of hemolysiswas proportional to dose, duration of exposure and degree of G6PD deficiency. Rarely, hypertension and cardiac arrhythmia have been reported. This research shows, through the documents consulted, the occurrence of leukopenia, methemoglobinemia with cyanosis and granulocytopenia.

Dihydroartemisinin-piperazine

This combination of dihydroartemisinin and piperazine is also indicated for the treatment of *P. vivax malaria*, and the literature also indicates that it is likely to be very effective against *P. ovale, P. knowlesi* and *P. malariae* [WHO, 2015,]. Reported side effects include nausea, diarrhea, vomiting, anorexia, anemia, dizziness, headache, sleep disturbance, cough, dizziness, and itching. Another adverse effect is highlighted by the intensive use of dihydroartemisinin-piperazine, where in piperazine prolongs the QT interval on electrocardiography [Visser et al., 2014, WHO, 2015, Pasaribu et al., 2013, Tjitra et al., 2012].

Table 1. Summary of the side effects of antimalarial drugs and their indications according to plasmodium species

Plasmodial species involved	Indicated molecule	Side effects/molecule	Comments
P. vivax, P. Ovale, P. Malariae, P. Knowlesi	Chloroquine	Pruritus, Headache, Hepatitis, Gastrointestinal disorders, Oral inflammation, Elevated liver enzymes, Convulsions, Mental changes, Sleep disturbance, Dizziness, Visual disturbances, Fatigue, Dizziness, Cough, Sore throat, Joint pain, Flushing, Shortness of breath, Slight enlargement of QRS complex and QT intervals, Myopathy, Decreased hearing, Photosensitivity and hair loss, Blood disorders.	Pruritus is the most important side effect.
	Artemether - lumefantrine	Nausea, anorexia, vomiting, diarrhea, inflammation of the mouth, abdominal pain, dizziness, headache, asthenia or fatigue, joint pain, dizziness, skin rashes, cough, chills, hyperhydrosis, vision and hearing problems, shortness of breath.	
	Artemether in monotherapy	Minor gastrointestinal disorders, dizziness, reticulocytopenia, neutropenia, increased liver enzyme activity, bradycardia and very slight prolongation of the QT interval.	
	Dihydroartemisinin - piperazine	Nausea, diarrhea, vomiting, anorexia, anemia, dizziness, headache, sleep disturbances, cough, dizziness, itching, prolongation of QT interval on electrocardiography.	
	Artesunate-amodiaquine	Gastrointestinal disorders (nausea, abdominal pain), cough, anorexia, insomnia, fatigue, weakness, headache, dizziness, diarrhea, arrhythmia, bradycardia, vomiting, extrapyramidal effects, pruritus, eye disorders and irreversible retinopathy.	
P. vivax, P. Ovale, P. Malariae, P. Knowlesi	Artesunate in monotherapy	Hypersensitivity reactions, gastrointestinal disorders, cough, skin rashes, arthralgia, dizziness, delayed hemolysis, dose-dependent neutropenia	
	Amodiaquine	Neutropenia, elevated serum aminotransferase levels, bradycardia, pruritus and excessive drowsiness.	
	Amodiaquine combined with Sulfadoxine-Pyrimethamine	Vomiting, loss of appetite, fever, and mild to moderate skin reactions.	
	Sulfadoxin-Pyrimethamine	Gastrointestinal disorders, headache, dizziness, photosensitivity, rash, pruritus, hives, mild hair loss, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, leukopenia, thrombocytopenia, megaloblastic anemia, hemolyticanemia, crystalluria, hematuria, oliguria, hepatitis, serum sickness, allergic pericarditis and pulmonary infiltrates.	

Table 1 contd.

	Quinine	"Cinchonism" (with mild forms are characterized by tinnitus, slight hearing impairment, headaches, nausea, dizziness, dysphoria and sometimes vision problems), dizziness, vomiting, abdominal pain, diarrhea, marked hearing loss, visual symptoms, including vision loss, hyperinsulinemic hypoglycemia, QTc prolongation, hypotension, cardiac arrest, urticaria, bronchospasm, skin rash, fever, antibody-mediated thrombocytopenia, hemolyticanemia, hemolytic-uremic syndrome, liver damage and psychosis.	Commonly, "Cinchonism" is the side effect observed after the administration of treatment doses.
	Halofantrine	Bradycardia, atrioventricular block, unacceptable risk of arrhythmia and excessive QT prolongation.	
	Atovaquone- Proguanil	Headache, cough, gastrointestinal disorders, dizziness, mouth ulceration, allergic reactions (anaphylaxis, angioedema, Stevens-Johnson syndrome, vasculitis), neutropenia, anemia, photosensitivity rash, erythema multiforme, increased liver enzyme activity, hepatitis, liver failure, pancytopenia.	
	Mefloquine	Convulsions, anxiety, irritability, dizziness, paranoia, suicidal ideation, depression, hallucinations, violence, vomiting, gastrointestinal disorders, hepatitis, polyneuropathy, thrombocytopenia, pneumonia, skin rash or irritation, sinus bradycardia and visual impairment.	
P. vivax, P. Ovale, P. Malariae, P. Knowlesi	Primaquine	Gastrointestinal discomfort, abdominal pain, nausea, vomiting, generalized urticarial rash, lack of appetite, meso or hypogastric pain, choluria, weakness or malaise, headache, myalgia or arthralgia, fever, dizziness, shortness of breath, bronchospasm, hemolysis, hypertension, cardiac arrhythmia, leukopenia, methemoglobinemia with cyanosis and granulocytopenia.	Hemolysis is the most important side effect.

Artesunate-amodiaquine

Artesunate-amodiaquine is also indicated for the treatment of uncomplicated *P. vivax* malaria and is considered effective against *P. ovale, P. knowlesi* and *P. malariae.* This combination produces a higher incidence of side effects, such as gastrointestinal disorders (nausea, abdominal pain). Other commonly reported side effects include cough, anorexia, insomnia, fatigue and weakness, headache, dizziness, diarrhea. Less common side effects of artesunate-amodiaquine are arrhythmia, bradycardia, vomiting, extrapyramidal effects and pruritus. This review also reports adverse effects in the form of eye disorders and, very rarely, irreversible retinopathy [WHO, 2015, Chu et al., 2017, Adjei et al., 2008, Adjei et al., 2012, Brasseur et al., 2012, Haeusler et al., 2018].

Artesunate used as monotherapy has similar side effects to other artemisinin derivatives, such as hypersensitivity

reactions, gastrointestinal disorderscough rashes, arthralgia, dizziness and delayed hemolysis. Clinically, hemolysis has been reported up to weeks after treatment. The literature also reveals dose-dependent neutropenia as an adverse effect [WHO, 2015].

Amodiaquine

Adverse reactions related to the use of amodiaquine monotherapy have been reported in the literature. These include neutropenia, elevated serum aminotransferase levels, bradycardia, pruritus and excessive drowsiness [WHO, 2015, Adjei et al., 2008, Adjei et al., 2012, Haeusler et al., 2018].

Amodiaquine-sulfadoxine-pyrimethamine (SP)

Amodiaquine combined with sulfadoxine-pyrimethamine causes some side effects, such as vomiting, loss of appetite, fever and mild to moderate skin reactions [WHO, 2015].
The adverse effects of MS reported in the literature [WHO, 2015, Maokola et al., 2011, Mutabingwa et al., 2009] are primarily those associated with sulfonamides (gastrointestinal disorders, headaches, dizziness and skin reactions such as photosensitivity, rashes, pruritus, hives and slight hair loss). Adverse reactions also include life-threatening skin reactions, such as erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. Other side effects, such as leukopenia, thrombocytopenia, megaloblastic anemia, hemolyticanemia, crystalluria, hematuria, oliguria and hepatitis, have been reported in the literature. Furthermore, serum sickness, allergic pericarditis and pulmonary infiltrates resembling eosinophilic or allergic alveolitis have been reported.

Quinine

Quinine is a gametocytocidal agent against *P. vivax, P. ovale* and *P. malariae* [WHO, 2015]. This molecule has frequent side effects [WHO, 2015, Krudsood et al., 2005 Achan et al., 2011, Haeusler et al., 2018]. Commonly, side effects after the administration of therapeutic doses are called "Cinchonism", with mild forms characterized by tinnitus, slight hearing impairment, headaches, nausea, dizziness, dysphoria and sometimes visual disturbances. High tone hearing impairment is usually concentration-dependent and reversible. The literature highlights more serious manifestations, including dizziness, vomiting, abdominal pain, diarrhea, marked hearing loss and visual symptoms, including vision loss. A major adverse effect of quinine reported is hyperinsulinemic hypoglycemia. This hypoglycemia is particularly common in young children, pregnant women and elderly patients. Prolongation of the QTc interval is also reported as an adverse reaction to quinine. When the product is administered too quickly, certain adverse effects occur, such as hypotension and cardiac arrest. This study also revealed the occurrence of quinine hypersensitivity reactions, such as urticaria, bronchospasm, skin rash, fever, antibody-mediated thrombocytopenia, hemolyticanemia and hemolytic-uremic syndrome. Rarely, liver damage and psychosis may occur.

Halofantrine

The adverse effects highlighted in the literature that occur after taking halofantrine include bradycardia, atrioventricular block, unacceptable arrhythmogenic risk and excessive QT prolongation [Bindschedler et al., 2010].

Atovaquone-proguanil

Atovaquone is a hydroxynaphthoquinone with anti-malarial activity against all stages of all species of Plasmodium, and proguanilis a biguanide compound that acts against all stages of the life cycle of the malaria parasite. This review reports adverse effects [WHO, 2015, Mutabingwa et al., 2009, Jolink et al., 2010], and common effects are headache, cough and gastrointestinal disorders (abdominal pain, nausea, vomiting and diarrhea). Rarely, the literature highlights additional side effects, such as dizziness, mouth ulceration, and allergic reactions, such as anaphylaxis, angioedema, Stevens-Johnson syndrome and vasculitis. Very rarely, authors identified certain adverse effects, such as blood disorders (neutropenia and anemia) and skin reactions (photosensitivity rash and erythema multiforme). Liver damage has been reported in the form of increased liver enzyme activity, hepatitis and liver failure. In patients with severe renal impairment treated with proguanil, pancytopenia has also been observed.

Mefloquine

Mefloquine is indicated for the chemoprophylaxis of malaria caused by all species. Adverse reactions to this drug have been reported in the literature [WHO, 2015, Fernando et al., 2011, Chester et al., 2011,Fiaccadori et al.,2006, Crotf et al., 2006, Udry et al.,2002, Soentjens et al., Cui et al., 2015]. Mefloquine produces adverse central nervous system effects (convulsions, anxiety, irritability, dizziness, paranoia, suicidal ideation, depression, hallucinations and violence in patients treated for malaria and in people under long-term prophylaxis with mefloquine), and these neuropsychiatric adverse effects usually disappear after discontinuation of mefloquine. This review also reveals gastrointestinal side effects. Vomiting and gastrointestinal disorders were frequently reported. Rarely, mefloquine causes hepatitis, polyneuropathy, thrombocytopenia, pneumonia, skin rash or irritation, sinus bradycardia and visual impairment.

DISCUSSION

The primary finding of our review is that there are several antimalarial drugs used in the treatment of malaria caused by species other than P. falciparum. These drugs produce adverse effects in humans.

This scoping review has a limitation. We did not consult paid documents in the data sources, and they could certainly contain additional useful information.

Chloroquine in combination with primaquine remains the first-line treatment for radical cure of *P. vivax* malaria in most areas [Cui et al., 2015]. It has been the gold standard for the treatment of uncomplicated malaria for many years but is no longer appropriate for the treatment of P. falciparum malaria in nearly all areas due to drug resistance [Cui et al., 2015]. It is generally well tolerated at the standard dose of 25 mg base/kg over 3 days for *P. vivax* infection [Taylor et al., 2015]. The literature highlights that in Indonesia, increased chloroquine resistance to *P. vivax* prompted a policy change to ACTs for this type of malaria [Baird et al., 2011]. Chloroquine doses used for prophylaxis or treatment of P. vivax, P. ovale or P. malaria are considered 'safe doses' during pregnancy [WHO, 2015]. This molecule should be used with caution in patients with psoriasis, neurological, retinal or gastrointestinal disorders,as well as those with liver failure, because it can exacerbate these underlying pathologies [WHO, 2015].

The combination of artemether and lumefantrine often produces effects that are difficult to distinguish from the symptoms of malaria itself [WHO, 2015]. This combination should not be used in patients with hypersensitivity to artemether or lumefantrine. In addition to the known side effects of this combination, there are also precautions to be taken, such as close monitoring of patients over 65 years of age and children under 5 years of age [WHO, 2015]. This medicine is not recommended in patients with congenital or clinical conditions that cause prolongation of the QTc interval, a family history of congenital long QT syndrome or sudden death, or those with electrolyte abnormalities, such as hypokalemia or hypomagnesemia [Norvatis, 2009].

Primaquine is an aminoquinolone that has been used for several decades as a prophylaxis and treatment for malaria [Novartis, 2009].The most important side effect of primaquine is hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and severe anemia. G6PD deficiency is very common, with a prevalence ranging from 3% to 35% in tropical areas [WHO, 2015]. The extent of hemolysis with primaquine depends on the degree of G6PD deficiency and the dose of primaquine. Two of the most prevalent G6PD variants represent the two extremes of the severity spectrum, with the Mediterranean variant (the primary variant found in Europe, West and Central Asia and northern India) being among the most severe and the African variant A- (found in sub-Saharan Africa and among African Americans) being among the mildest. There is also substantial variation in G6PD activity among individuals of the same genotype and even within the same individual over time [WHO, 2015].

This review also indicates that piperazine prolongs the QT interval on electrocardiography when intensively used. Significant QTc prolongation can cause life-threatening ventricular tachyarrhythmia, but there is no evidence that this has occurred with piperazine, despite its intensive use [WHO, 2015].

Combinations of artesunate-amodiaquine, artesunate-mefloquine or artesunate-SP are indicated for the treatment of *P. vivax, P. ovale, P. knowlesi* and *P. malariae*. Artesunate is generally well-tolerated [WHO, 2015,]. It has similar side effects to other artemisinin derivatives and is contraindicated in patients with known hypersensitivity to artesunate or artemisinin derivatives. The literature recommends caution in treating patients with renal or hepatic impairment. The combination of artesunate-amodiaquine produces a higher incidence of gastrointestinal disorders [WHO, 2015,]. Fatal skin reactions, such as Stevens-Johnson syndrome, are sometimes produced when sulfadoxine-pyrimethamine is administered [WHO, 2015,].

Quinine kills large asexual ring and trophozoite parasites and is gametocytocidal against *P. vivax, P. ovale* and *P. malariae* but not against P. falciparum malaria [Achan et al., 2011]. Quinine has a low therapeutic index, and the adverse effects associated with its use are significant [WHO, 2000]. Commonly, side effects called "Cinchonism" are

observed when taking quinine and the most important side effect caused by this molecule is hyperinsulinemic hypoglycemia.Quinine is contraindicated in patients with known hypersensitivity to quinine or to one of the quinine alkaloids [WHO, 2015].

Halofantrine causes excessive QT prolongation after it is taken by patients, and atovaquone-proguanil frequently causes gastrointestinal disorders. Atovaquone is a hydroxynaphthoquinone with antimalarial activity against all stages of all Plasmodium species [WHO, 2015]. The literature reveals that this combination results in transient elevations of serum enzymes and rare cases of clinically apparent liver damage [Novartis et al., 2009]. Atovaquone-proguanil is rarely used in endemic areas because of the propensity for the emergence of high-grade resistance to atovaquone from single mutations in the cyt b gene [WHO, 2015].

Results also show that mefloquine often causes undesirable effects on the central nervous system, which limits its use [LiverTox, 2017]. The molecule is indicated for chemoprophylaxis of malaria caused by all species [WHO, 2015].

CONCLUSIONS

Several products with adverse effects are widely used in the prophylaxis and treatment of malaria caused by species other than P. falciparum. Regardless of the plasmodial species involved, the molecules that can be used are the same. However, their side effects can vary from one species to another.

Drugs such as chloroquine and proguanil are very rarely associated with serious adverse effects at the recommended doses. Unfortunately, in some parts of the world, these products are no longer effective prophylactic agents. Pyrimethamine-sulfadoxine and amodiaquine are associated with life-threatening reactions and are no longer recommended for prophylaxis. Mefloquine, despite its effects on the central nervous system, is indicated for chemoprophylaxis of malaria caused by all species. Because of the almost generalized resistance to chloroquine, other drugs, such as quinine, mefloquine, pyrimethamine-sulfadoxine, halofantrine and artemisinin,as well as its derivatives, can be used in therapeutic management.

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