clinical pharmacology

Interactions between malaria chemoprophylaxis and other drug treatment

With the massive rise in international travel over the last 10 years, the world has become a smaller place and it is probably easier nowadays to contract an infectious disease than in years gone by. Malaria kills up to 2 million people worldwide every year, the majority of whom are Africans. Effective prophylaxis against malaria is widely available and deserves to be prescribed diligently by health professionals for travellers to malaria areas. Of course, the use of mosquito repellants and other physical protectants with the oral prophylaxis is mandatory.

Medicines may interact with one another, sometimes to one's advantage, but more often adversely, with potentially serious consequences. The drug interaction table below lists the currently recommended malaria chemoprophylaxis options together with common medicines that travellers may be taking. This table is limited to potential drug interactions with the three malaria prophylaxis options currently recommended in South Africa to prevent *P. falciparum* malaria (atovaquone/proguanil, doxycycline and mefloquine). Widespread chloroquine resistance precludes it being used alone or in combination with proguanil to prevent falciparum malaria; this prophylaxis should only be considered for areas with exclusively non-falciparum malaria transmission (for details on malaria risk in individual countries see www.who.int/ith/en). It is important to remember that drug interactions are only one among a number of precautions to consider when prescribing malaria chemoprophylaxis.

Please note that this table does not include all possible interactions with malaria chemoprophylactic drugs. Please contact the Medicines Information Centre on 086 110 0531 or 021 406 6785 or pha-mic@uct.ac.za or the Amayeza Info Centre on 011 678 2332 or amayeza@amayeza-info.co.za if you require any assistance.

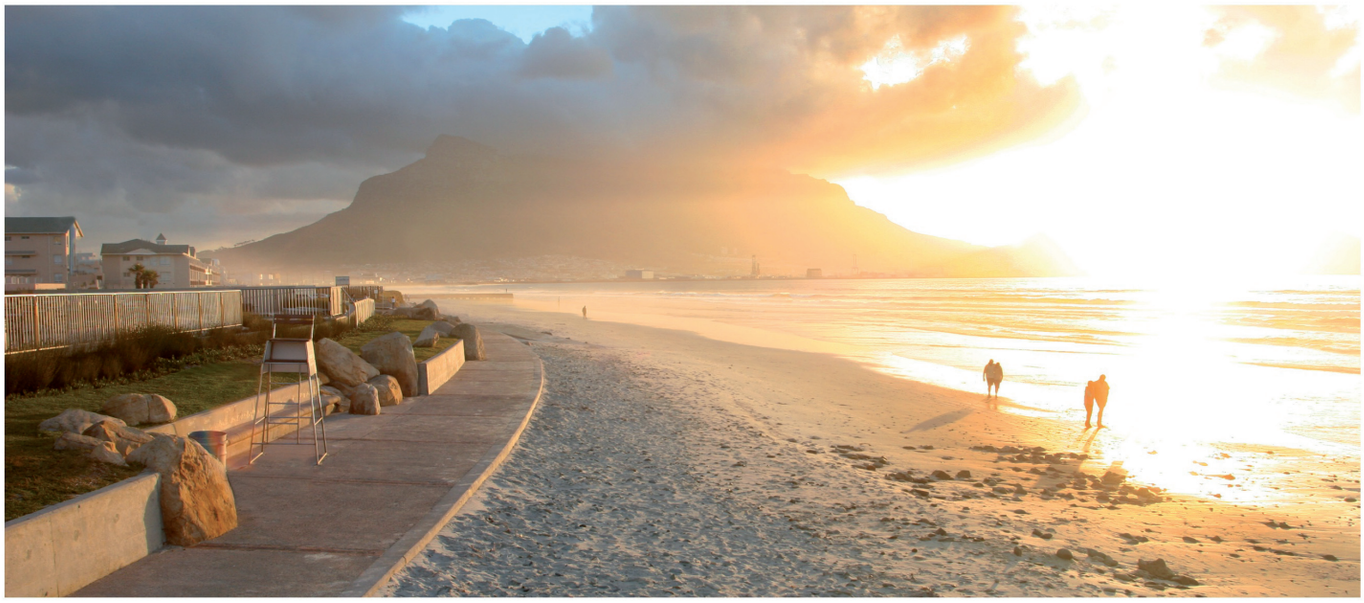
Table I. Potential drug interactions with chemoprophylaxis currently recommended to prevent *P. falciparum* malaria

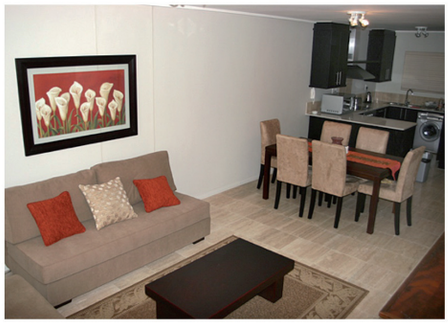
Antimalarial	Other drug	Interaction	Clinical management
Atovaquone/ proguanil (Malanil)	Chloroquine	The combination of chloroquine and proguanil increases the risk of developing mouth ulcers[1]	**Monitor.** If ulcers are severe, consider discontinuing one of the drugs[1]
	Indinavir	Concomitant administration of atovaquone and indinavir resulted in a 23% (8 - 35%) decrease in indinavir trough level (Cmin)[1]	**Monitor** for decreased indinavir efficacy[1]
	Lopinavir/ritonavir (Kaletra)	May decrease plasma concentrations of atovaquone[2,3]	Clinical significance **uncertain**, although increases in atovaquone dosage may be needed[2,3]
	Metoclopramide	Reduction of atovaquone bioavailability[1]	Preferably **avoid** combination. When this combination has to be used, carefully monitor for decreased atovaquone efficacy (breakthrough malaria)[1]
	Rifabutin	In one study of 24 volunteers, atovaquone plasma levels were reduced by 34%[1]	**Avoid** combination[1]
	Rifampicin	Atovaquone levels reduced by approximately 50%[1]	**Avoid** combination[1]
	Tetracycline	Associated with a 40% reduced serum concentration of atovaquone[1]	If concomitant use is necessary, carefully **monitor** for decreased atovaquone efficacy (breakthrough malaria)[1]
	Typhoid vaccine	Proguanil significantly decreases the immune response to typhoid vaccine[1]	**Separate dosages.** Allow 10 days to elapse between the last dose of live typhoid vaccine and the administration of proguanil[1]
	Warfarin	Proguanil may potentiate the anticoagulant effect of warfarin, increasing the risk of bleeding[1]	**Monitor** INR with addition or withdrawal of proguanil therapy. Reassess periodically during proguanil therapy. Adjustments of warfarin dose may be necessary

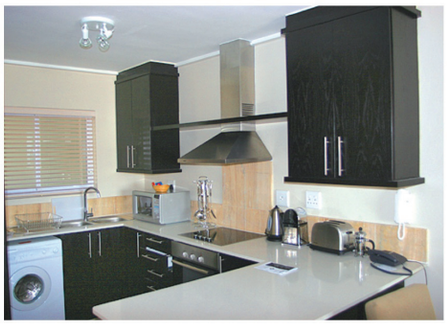
Antimalarial	Other drug	Interaction	Clinical management
	Zidovudine	Atovaquone may elevate the plasma concentration of zidovudine. The changes are unlikely to result in any clinically significant interactions unless the patient is also receiving other drugs that potentially have haematological toxicity[1]	**Monitor** patient for bone marrow toxicity[1]
Doxycycline	Alcohol	With chronic alcohol abuse the serum levels of doxycycline may fall below minimum therapeutic concentrations; this effect does not occur with acute intake of alcohol[4,5]	**Preferably avoid;** if no alternative prophylaxis suitable, consider doubling the dose of doxycycline[5]
	Antacids containing: calcium, bismuth, aluminium, and magnesium	Reduces the absorption and serum concentrations of doxycycline significantly, compromising therapeutic efficacy[1]	**Preferably avoid,** or if combination essential **separate dosages:** administer doxycycline at least 2 hours before, or 4 - 6 hours after antacids[4,6]
	Carbamazepine	Reduces the plasma half-life of doxycycline by approximately 50% and may result in decreased prophylactic efficacy[4,6,7]	Consider **increasing (possibly doubling) dose** of doxycycline[1]
	Digoxin	Increased digoxin levels and digoxin toxicity[1]	**Monitor closely** for digoxin toxicity. Dosage adjustment of digoxin may be required[1]
	Hormonal/oral contraception, e.g. ethinyl oestradiol, norethisterone, norgestrel	Decreased contraceptive effect[1,4]	**Additional** form of **non-hormonal birth control** should be used[1]
	Iron	Decreased absorption of doxycycline and iron salts. Efficacy may be reduced[4,6]	**Separate dosages** by as much as possible. Give iron at least 3 hours before or 2 hours after the doxycycline dose[4,6]
	Methotrexate	Increased risk of methotrexate toxicity[1]	**Preferably avoid**. If combination essential, **monitor closely** for evidence of methotrexate toxicity, especially when methotrexate is administered in high doses[1]
	Milk and dairy products	Absorption of doxycycline may be reduced by up to 30% because of the calcium ions found in milk	**Separate doses**. Avoid dairy for at least 1 hour before or 2 hours after taking doxycycline. The small amounts of milk used in coffee and tea appear not to interact significantly[4,6]
	Phenobarbitone	Decreased doxycycline effectiveness[1]	If used concurrently, consider a **dosage increase** of doxycycline[1]
	Phenytoin	Decreased doxycycline effectiveness[1]	If used concurrently, consider a **dosage increase** of doxycycline[1]
	Retinoids, e.g. acitretin, isotretinoin	Increased risk of increased intracranial pressure/pseudotumour cerebri[1,6]	Combination **contraindicated**[1]
	Rifampicin	Increased doxycycline clearance. Potential loss of doxycycline efficacy	**Avoid combination**
	Warfarin	Potentiation of anticoagulant effect possible. Increased risk of bleeding[1]	**Monitor** INR with addition or withdrawal of doxycycline therapy. Reassess periodically during doxycycline therapy. Adjustments of warfarin dose may be necessary in order to maintain the desired level of anticoagulation[1]
Mefloquine	Antiarrhythmics, e.g. amiodarone, disopyramide	Both drugs may increase QT interval. Increased risk of torsades de pointes[7] and cardiac arrest[1]	Mefloquine is **not recommended** for patients with cardiac conduction abnormalities. Concurrent use of mefloquine and antiarrhythmics, or other agents that prolong the QT interval, is not recommended[1]
	Anticonvulsants	Seizures have been reported, even in patients without a history of seizure disorder[1]	Mefloquine is **contraindicated** in patients with a history of convulsions[1]

Antimalarial	Other drug	Interaction	Clinical management
	Antipsychotics, e.g. pimozide, amisulpiride, chlorpromazine, haloperidol, quetiapine, risperidone and sertindole	An increased risk of cardiotoxicity, including ventricular arrhythmias, QT prolongation, torsades de pointes and cardiac arrest[1,7]	Mefloquine is **contraindicated** in patients with a history of a psychiatric illness. Caution is advised if mefloquine and antipsychotics (used for non-psychiatric indications) are used concomitantly[1]
	Artemether/lumefantrine	Plasma concentrations of lumefantrine were reduced by one-third when artemether-lumefantrine was given concurrently with mefloquine in healthy subjects[1]	Clinical significance of this interaction is **uncertain**. If combination used, it is particularly important that artemether-lumefantrine is given with fat-containing food to increase its bioavailability[1]
	Beta-blockers, e.g. atenolol, propranolol	Theoretically the combination might result in prolongation of the QT interval[5]	Mefloquine is **not recommended** for patients with cardiac conduction abnormalities. Mefloquine prophylaxis may be used with **caution** in individuals using beta-blockers who do not have arrhythmias.[8] Preferably use alternative chemoprophylaxis
	Calcium-channel blockers, e.g. nifedipine, verapamil, diltiazem	Theoretically the combination might result in prolongation of the QT interval[5]	Mefloquine is **not recommended** for patients with cardiac conduction abnormalities. Mefloquine prophylaxis may be used with **caution** in individuals using calcium-channel blockers who do not have arrhythmias.[8] Preferably use alternative chemoprophylaxis
	Chloral hydrate	Both drugs may increase QT interval. Increased risk of torsades de pointes[7] and cardiac arrest[1]	Concurrent use of mefloquine and agents that prolong the QT interval is **not recommended**[1]
	Chloroquine	Concurrent use may increase risk of seizures and possibly cause additive cardiac toxicity [4,6,9]	**Avoid combination**. If combination essential, mefloquine should not be given for at least 12 hours after the last chloroquine dose[7]
	Clarithromycin	Increased risk of cardiotoxicity including QT prolongation, torsades de pointes and cardiac arrest[1]	Concurrent administration of agents that prolong the QT interval is **not recommended**[1]
	Digoxin	Increased plasma levels of digoxin[7]	Use combination with **caution. Monitor** digoxin levels[7]
	Erythromycin	Increased risk of cardiotoxicity including QT prolongation, torsades de pointes and cardiac arrest[1]	Use combination with **caution. Monitor** QT interval at baseline and periodically during treatment[1]
	Fluconazole	Increased risk of cardiotoxicity including QT prolongation, torsades de pointes and cardiac arrest[1]	**Caution** is advised if fluconazole and mefloquine are used concomitantly[1]
	Fluoxetine	Increased risk of cardiotoxicty including QT prolongation, torsades de pointes and cardiac arrest[1]	Mefloquine is **contraindicated** in patients with a history of a psychiatric illness. Concurrent administration of fluoxetine and mefloquine is not recommended[1]
	Halofantrine	Concurrent use may result in serious cardiac abnormalities[7,9]	Treatment with halofantrine is **contraindicated** when mefloquine has been used for prophylaxis[7,9]
	Ketoconazole	Ketoconazole increases mefloquine plasma concentrations significantly[1]	**Avoid** combination
	Quinine or quinidine	Quinine may inhibit the metabolism of mefloquine, thereby increasing mefloquine levels.[4] The combination also increases risk of seizures and ECG abnormalities, cardiac arrest or potentially serious cardiac conduction abnormalities[4,6-8]	**Separate dosages.** Mefloquine should not be given for at least 12 hours after the last dose of quinine[6,7]
	Quinolones, e.g. ciprofloxacin, lomefloxacin, ofloxacin	Increased risk of convulsions[10]	**Avoid** combination

LAGOON BEACH APARTMENTS







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Antimalarial	Other drug	Interaction	Clinical management
	Rifampicin	Decreased plasma concentration of mefloquine via induction of mefloquine metabolism[1]	**Avoid** combination
	Tricyclic antidepressants, e.g. amitriptyline	Increased risk of ventricular arrhythmias[7]	Mefloquine is **contraindicated** in patients with a history of a psychiatric illness
	Valproic acid	Accelerated sodium valproate metabolism may result in lower concentrations and loss of seizure control[4,6,7,11]	Mefloquine is **contraindicated** in epileptics. If used for other indications, monitor valproic acid levels[4,6,7,11]

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Single Suture

Lessons from Cuba

A Canadian study that looked at Cuba concludes that if we all lost just 4 or 5 kilograms mortality rates would drop significantly. This lesson comes from the economic crisis that Cuba suffered between 1991 to 1995, resulting from the collapse of the Soviet empire in 1989. Between these dates people in Cuba were only getting around 1 800 calories a day and had to walk or cycle wherever they needed to go.

The result was an average drop in body mass index of 1.5 units and a halving of the obesity rate to just 7%. Deaths from potentially fatal diseases fell dramatically in the following years – diabetes by 51%, coronary artery disease by 35% and stroke by 20%.

And Cuba is now being lauded as it joins the West with Castro's release of power! A follow-up study in 20 years' time would be instructive.

Franco M, *et al. CMAJ* 2008; 178: 1032-1034.