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Insights into the pharmacokinetic interactions between antimicrobial and antimalarial drugs following concurrent administration

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ABSTRACT

Background: The co-administration of different drugs is imperative to achieve a desired therapeutic objective or treat coexisting diseases. For example, the concurrent use of antimicrobial and antimalarial drugs is common in the tropics because malaria is frequently associated with other infections such as those of the respiratory tract, urinary tract, or ear, sexually transmitted infections (STIs), and diarrhea, among other infections. Although numerous benefits can be derived from co-administration of different drugs, the expected therapeutic outcome is sometimes affected by drug-drug interactions.

Objective: The study of antimicrobial and antimalarial drug interactions is of great significance to both treatment and research. It is therefore worrying that the analysis of drug-interaction data is often inadequate, leading in some cases to false conclusions about synergism or antagonism. This review aimed to discuss recent findings on antimicrobial and antimalarial drug-drug interactions and some pitfalls in their analysis and interpretation.

Methods: Important literature databases such as Elsevier, IEEExplore, Pubmed, Scopus, Web of Science, Google Scholar, ProQuest, ScienceDirect, and BioMed Central were selected based on the quality, extant content, and broad area of the discipline. The specific keywords related to the study were identified and used for the study purposely to identify related works.

Results: Co-administration of two or more drugs is considered rational when trying to achieve a desired therapeutic objective or treat co-morbidities but the possibility of drug-drug interactions could offset these benefits by bringing about sub-therapeutic drug concentrations that could ultimately lead to treatment failure.

Conclusion: Patients, physicians, pharmacists, and other healthcare providers may be unaware of the possible interactions between antibiotics and antimalarials as well as the mechanisms involved. It is therefore common practice to co-administer antimalarial and antibiotic drugs. Caution is required with the co-administration of these medicines. It is also of public health concern, as the interactions can contribute towards observed antibiotic resistance and treatment failure being experienced in recommended antibiotic treatment regimens.

Key words: Antimicrobial, Antimalarial, Drug-Drug Interaction, Concurrent Administration

Aperçu des interactions pharmacocinétiques entre les médicaments antimicrobiens et antipaludiques en cas d'administration concomitante.

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RÉSUMÉ

Contexte: La co-administration de différents médicaments est impérative pour atteindre un objectif thérapeutique souhaité ou traiter des maladies co-existantes. Par exemple, l'utilisation simultanée d'antimicrobiens et d'antipaludiques est courante sous les tropiques car le paludisme est fréquemment associé à d'autres infections telles que celles des voies respiratoires, des voies urinaires ou de l'oreille, aux infections sexuellement transmissibles (IST) et à la diarrhée, entre autres infections. Bien que de nombreux avantages puissent être tirés de la co-administration de différents médicaments, les résultats thérapeutiques attendus sont parfois affectés par les interactions médicamenteuses.

Objectif: L'étude des interactions entre les médicaments antimicrobiens et antipaludiques revêt une grande importance tant pour le traitement que pour la recherche. Il est donc préoccupant de constater que l'analyse des données sur les interactions médicamenteuses est souvent inadéquate, ce qui conduit dans certains cas à des conclusions erronées sur la synergie ou l'antagonisme. Cette étude a pour but d'examiner les résultats récents concernant les interactions entre les médicaments antimicrobiens et antipaludiques et certains pièges dans leur analyse et leur interprétation.

Méthodes: Des bases de données documentaires importantes telles que Elsevier, IEEExplore, Pubmed, Scopus, Web of Science, Google Scholar, ProQuest, ScienceDirect et BioMed Central ont été sélectionnées en fonction de la qualité, de leur contenu et du vaste domaine que couvre la discipline. Les mots-clés spécifiques liés à l'étude ont été identifiés et utilisés pour l'étude afin d'identifier les travaux connexes.

Résultats: La co-administration de deux médicaments ou plus est considérée comme rationnelle lorsqu'il s'agit d'atteindre un objectif thérapeutique souhaité ou de traiter des comorbidités, mais la possibilité d'interactions médicamenteuses pourrait contrebalancer ces avantages en provoquant des concentrations de médicaments sous-thérapeutiques qui pourraient finalement conduire à l'échec du traitement.

Conclusions: Les patients, les médecins, les pharmaciens et autres prestataires de soins de santé peuvent ne pas être conscients des interactions possibles entre les antibiotiques et les antipaludiques ainsi que les mécanismes impliqués. C'est pourquoi il est courant de coadministrer des médicaments antipaludiques et antibiotiques. La prudence est de rigueur lors de la co-administration de ces médicaments. Il s'agit également d'un problème de santé publique, car les interactions peuvent contribuer à l'observation d'une résistance aux antibiotiques et à l'échec du traitement dans les schémas thérapeutiques antibiotiques recommandés.

Mots-clés: antimicrobien, antipaludéen, interaction médicamenteuse, administration concomitante

INTRODUCTION

Treatment response of *P. falciparum* malaria is influenced by many factors. Such factors include drug quality, pharmacokinetic characteristics of individual drugs, parasite sensitivity, host genetics, drug-drug interactions and food-drug interactions. Inter-individual variability with respect to extent and rate of absorption, metabolism, distribution, plasma protein binding and elimination has been shown to influence the plasma concentration of drugs, hence affecting treatment outcomes in return.[1] Antimicrobials are one of the most commonly prescribed classes of medications all over the world,[2] and these drugs are associated with many significant drug interaction activities as both inducers and inhibitors of enzymes.[3] Coexistence of malarial and bacterial infections is common in tropical regions, particularly in Africa.[4] As a result of this, antimalarials and antibiotics are usually prescribed together, and coadministration of these 2 classes of anti-infective is inevitable in most instances.[3,4] Antimicrobial and antimalarial drugs manifest a wide variety of drug interactions, which can differ greatly in their extent of severity and clinical relevance. Not only co-medication, but also food and herbal medicine can interact with these drugs and vice versa. The nature of these interactions can be of pharmacodynamic (PD) and/or pharmacokinetic (PK) origin.

A PD interaction consists of an alteration of a pharmacological response, through either agonism or antagonism, without affecting the kinetics of the drug. In cases of PD interactions, physicians are advised to re-evaluate the benefit-risk ratio of the co-prescribed drug for each individual patient.[5] Pharmacokinetic drug-drug interactions occur when one drug alters the absorption, distribution, metabolism or excretion of another drug, leading to alterations in the plasma concentrations of the latter and subsequently at the site of action. Drug-drug interactions that lead to altered drug absorption can influence the rate and/or the extent of absorption. Interactions affecting absorption can result from the formation of insoluble drug complexes, or from changes to gastric pH or gastrointestinal motility. Displacement of highly protein-bound drugs from their plasma protein binding sites can alter drug distribution. However, theoretically, this will not affect the average unbound concentration (Cu) of drug at steady state for most drugs, with the exception of highly extracted, intravenously administered drugs, which are quite rare.[6] Drug-drug interactions affecting the renal excretion of drugs can arise from alterations to the transporters involved in the efflux of drug molecules into the urine by secretion. Alterations to the pH or flow of urine can also result in drug-drug interactions. Drug metabolism occurs mainly in the liver, although other sites such as the gastrointestinal tract, kidneys, skin and lungs can be involved. In phase I of drug metabolism, the drug undergoes reactions such as oxidation, reduction or hydrolysis, which introduce a chemically reactive group to the drug molecule or expose such a group. Cytochrome P-450 (CYP) enzymes are the main enzymes responsible for drug metabolism; the CYP1, CYP2 and CYP3 families provide the principal enzymes responsible for the metabolism of 80% of currently known drugs.[7] Historically, the relevance of drug distribution, particularly of protein binding, has been over-emphasized in the assessment of drug interactions, and nowadays the main cause of drug-drug interactions has been recognized to be modulation of the activity, i.e., inhibition or induction, of cytochrome P450 (CYP) enzymes and transporters. Clinicians, prescribing the drug and pharmacists often involved in medication review, therapeutic drug monitoring (TDM), or consultation on drug choice or dose, should be aware of clinically relevant interactions between antimicrobial-antimalarial drugs co-medication, in order to avoid toxicity, side effects, or inadequate treatment. PK interactions are in most cases manageable by adjusting the dose and by monitoring of drug levels (TDM) or vital signs.

This review article will address PK interactions between antimicrobial and antimalarial drugs. The scope is to present an overview of PK studies on drug-drug interactions of commonly prescribed antimicrobial and antimalarial drugs in daily clinical practice.

Infectious diseases account for most of the major public-health issues all over the world. They are caused by virulent microorganisms which are spread through direct contact or vectors. Four major microorganisms responsible for the common diseases of public health importance are bacteria, fungi, protozoan and viruses; they are the causative organisms for such diseases as tuberculosis, aspergillosis, malaria and HIV/AIDs respectively. Some other infections classified as neglected infectious diseases e.g. leprosy, filariasis and onchocerciasis are also caused by microorganisms. Malaria, tuberculosis, HIV/AIDS and some form of fungal infections are the main cause of mortality globally.[8] Malaria a protozoan infection is prominent amongst infections in the tropics. It is spread by mosquitoes and has been recognized as a grave and critical illness for many years.[9] It causes most of the deaths chiefly among all other infection around the world with heaviest toll in

Africa with reported cases elsewhere in other parts of the world such as Europe, Asia, Central and South America.[10]

Human population is rarely exposed to one pathogen alone. In malaria endemic zones there is manifestation of concurrent infections with malaria. In such instances malaria patients may be exposed to bacterial, viral, parasitic, or other microbial infections resulting in co-morbidities. These co-infections could arise due to susceptibility of human host to different pathogenic organisms. In other instances, malaria may increase the risk of other infections or vice versa. While HIV infection can increase severity of malaria infection, conversely malaria infection is also associated with strong CD4+ cell activation and ideal microenvironment for the spread of the virus among the CD4+ cells and for rapid HIV-1 replication.[11] Similar clinical features in these co-infections pose serious diagnostic challenges, especially in impoverished areas where the capacity for laboratory testing is limited.[12] Concurrent illnesses may be consequentially severe than mono infection. Co-existence of malaria and invasive bacterial infections or other pathogens can become life-threatening necessitating more complicated therapy. For example, it was reported that coexistence of malaria and invasive bacterial infections is a frequent and life-threatening condition in many endemic African settings,[13] with further report that concluded that invasive bacterial disease can contribute to the clinical severity of malaria in children necessitating the choice of broad-spectrum antibiotics in addition to malaria chemotherapeutics.[14]

The presence of concurrent infections can militate against containment of individual infections. For instance, malaria can impair or complicate the management of tuberculosis and increase mortality in the patients. The prevention of malaria in TB patients appears to be an effective strategy to reduce overall mortality,[14] because it was reported that more than a third of the TB patients were co-infected with malaria during hospital stay.[14] An evaluation of the epidemiological, clinical, immunological interaction as well as interactions of the drugs in the two diseases are yet to be reported.[15] While malaria alone account for high mortality in the sub Saharan parts of the world, concurrence with other infectious diseases may enhance morbidity and deaths.

Co-infections in humans needs structural and molecular similarities between the host and pathogens.[15,16] For example, Burkitt's lymphoma is a common infection that is found in areas with malaria transmission. Malaria can cause induction of immune activation which can be responsible for the growth some forms of lymphomas; it can also induce immunoregulatory responses and reduce neutrophils that cause reduction of reactive oxygen species (ROS) and cytokine production to the risk of invasive non typhoidal salmonella infections.[17]

Multitudinous of infections require multiple medications to prevent mortality. Various drugs such antimalarials, antibiotics, antifungals, antihelminthes, antiretrovirals e.t.c. are frequently prescribed alone or in combination when managing co-infectious cases. These polychemotherapeutics provide sufficient ground for drug-drug interactions which may either be beneficial or detrimental. The majority of observed drug- drug interactions are mediated by mixed function oxidases known as Cytochrome P450 (CYP) enzymes. These are membrane associated proteins found in the endoplasmic reticulum of the liver.[18] These enzymes contain a haem prosthetic group, where haem group is the iron-porphyrin unit.[17,18] CYP are a major source of variability in drug pharmacokinetics and response. Out of about 57 putatively functional human CYPs, only about a dozen enzymes, belonging to the CYP1, 2, and 3 families, are responsible for the biotransformation of most foreign substances including 70-80% of all drugs in clinical use. Alteration of pharmacokinetic parameters are the hallmark of CYP enzymes mediated metabolism of drugs. Pharmacokinetic parameters such as Tmax, AUC, Cmax were reviewed in some reports involving co-administration of some antimicrobial agents with the view of providing additional base line information on drug- drug interaction involving antimicrobial agents when concurrently administered.

MATERIALS AND METHODS

Review strategy and study selection

This review is designed to study the insights and perspectives of pharmacokinetic interactions between antimicrobial and antimalarial drugs. Studies show that unstructured literature review (ULR) has been popularized in medical studies. As a result, ULR as a method is adopted in this study to summarize research findings. Key literature databases were selected based on the quality, extant content, and broad area of the discipline. These include Elsevier, IEEExplore, Pubmed, Scopus, Web of Science, Google Scholar, ProQuest, ScienceDirect, and BioMed Central. The Pubmed database was searched for PK interaction studies on drug-drug interactions of antimicrobial and antimalarial drugs. The keywords related to the study were identified and

used for the study, purposely to identify related works. The search terms "NOT in vitro" was added since this review focuses on original articles of studies with human subjects. Summaries of product characteristics or package leaflets were not consulted since these sources will only present a snapshot of the available information and will therefore not give a good overall impression of their use in clinical practice.

Data extraction

To identify eligible papers, 5 criteria were put in place:

1. The paper must be peer-reviewed.
2. The paper must be written in the English language.
3. The paper must be in the pharmacogenomics/pharmacokinetics discipline.
4. The paper is investigating the interaction of antimicrobial and antimalarial drugs
5. The paper described the basis for the interaction between the antimicrobial and antimalarial drugs.

After performing the search query, each paper's abstract and keywords were manually sieved to exclude papers not related to the study.

RESULTS AND DISCUSSION

1. AMODIAQUINE INTERACTIONS

Amodiaquine (ADQ), [4-(7-chloro-4-quinolylamino)-2-(diethylaminomethyl) phenol dihydrochloride] is a 4-aminoquinoline antimalarial which act by inhibiting the degradation of hemoglobin in the food vacuole of plasmodium parasit[19]. After oral administration, ADQ undergoes rapid and extensive hepatic metabolism by N-dealkylation to the active metabolite, N-desethylamodiaquine (DEAQ) with CYP2C8 as the main CYP isoform responsible for the biotransformation[20, 21]. It has been widely used for treatment of malaria over the past 50 years and is more active than chloroquine (also a 4-aminoquinoline) against Plasmodium falciparum parasites which are moderately chloroquine resistant[20]. Due to widespread chloroquine resistance, ADQ is being considered as a replacement for chloroquine as a first line drug in Africa but severe side effects such as agranulocytosis and hepatoxicity are restricting its clinical use[22].

1.1 Amodiaquine and Rifampicin

Tuberculosis frequently co-exists with malaria in the tropical countries of sub Saharan Africa where the diseases are endemic. Tuberculosis increases the burden of *Plasmodium falciparum* mortality in these areas with lower socio-economic indices. A research study in Nigeria in 2018[23] discovered that coadministration of ADQ and RIF resulted in significant decreases in the critical pharmacokinetic parameters of ADQ, such as area under the curve (AUC0–∞) of about 66%, time to peak plasma concentration (Tmax) of about 10%, maximum plasma concentration of about 44%, and elimination half-life of about 55%, while the AUC0–∞ and Tmax of the main metabolite desethylamodiaquine increased about 2-fold and 3-fold respectively during the coadministration of RIF with ADQ. The metabolic ratio increased significantly, from 1.55 to 2.68. The AUC0–∞ and Tmax of the drug ADQ, as well as the maximum concentration of both the drug and its metabolite fell outside the point of estimates of the test/reference ratio of the geometric means of 80-125% of bioequivalence range[23]. Drug-drug interactions may worsen malaria infection when the body is exposed to sub-therapeutic concentrations of antimalarials or even result in untoward adverse effects exacerbating malaria symptoms when plasma concentrations are raised beyond therapeutic levels.

1.2 Amodiaquine and Co-trimoxazole

Co-trimoxazole, [(CTZ) a combination of sulfamethoxazole and trimethoprim] is an inhibitor of bacterial purine biosynthesis and is commonly used to treat HIV-associated Pneumocystis jiroveci infections[24]. A study evaluated for the first time the effect of CTZ co-administration on the pharmacokinetics of ADQ in healthy adult volunteers, and observed that CTZ significantly increased ADQ exposure and decreased plasma levels of the active metabolite DEAQ[25]. Co-administration of ADQ and CTZ resulted in significant increases in the total area under the concentration-time curve (AUCT), maximum plasma concentration (Cmax) and terminal elimination half-life ($T_{½}$) of ADQ compared with values with ADQ dosing alone (AUC_T: 234.36±57.21 vs 366.42±62.48 h ng/ml; C_{max}: 24.86±7.28 vs 40.28±11.15 ng/ml; $T_{½}$: 6.49±3.56 vs 9.24±2.97 h), while the oral plasma clearance markedly decreased (3862.66±756.38 vs 2654.28±650.12 L/h). Co-administration also led to a pronounced decrease in the ratio of $AUC_{(metabolite)}/AUC_{(unchanged\ drug)}$ and highly significant decreases in $C_{max.}$[25].

1.3. Amodiaquine and Efavirenz

In countries with high prevalence of malaria and HIV infections, co-infection is common. Thus, in these regions, there is a very high possibility of a patient taking an antimalarial and an antiretroviral drug concurrently. Efavirenz, a nonnucleoside reverse transcriptase inhibitor (NNRTI), is metabolized principally by CYP2B6 and to a lesser degree by CYP3A4[26].

In a study[27], co-administration of amodiaquine and efavirenz resulted in significant increases ($p < 0.05$) in Cmax, Tmax, AUCT and elimination half-life ($T_{1/2}$) of amodiaquine compared with values for amodiaquine alone. Also, efavirenz caused a pronounced decrease in the AUC (metabolite)/AUC (unchanged drug) ratio of amodiaquine along with a significant decrease ($p < 0.05$) in Cmax and AUC of the metabolite[27]. The study concluded that efavirenz significantly alters the pharmacokinetics of amodiaquine, exposure to amodiaquine is increased leading to toxic effect, and reduction in the antimalarial activity since amodiaquine is a prodrug that relies on its active metabolite against malaria parasites.

2. QUININE INTERACTIONS

Quinine remains an important antimalarial drug almost 400 years after its effectiveness was first documented, but its continued use is challenged by its poor tolerability, poor compliance with complex dosing regimens, and the availability of more efficacious antimalarial drugs[28]. However, with increasing resistance to chloroquine, quinine again played a key role, particularly in the treatment of severe malaria, and to date, quinine continues to play a significant role in the management of malaria[28]. The occurrence of resistance to chloroquine and sulfadoxine-pyrimethamine by the malaria parasite in Southern Asia, Africa, and South America has stimulated renewed interest in quinine as an alternative drug for treating multidrug-resistant Plasmodium falciparum malaria[29,30]. Quinine is available as oral, rectal, and injectable formulations, and it has tolerable side effects if used correctly and at the normal therapeutic doses[30]. Quinine is mainly metabolized to its major metabolite, 3-hydroxyquinine (3-HQN), by cytochrome P450 (CYP) 3A4, whereas CYP 1A2 also plays a minor role in quinine biotransformation[30].

2.1 Quinine and ciprofloxacin

Among the antibiotics, quinolones are a group that enjoy wide acceptability because of their broad spectrum of action. Quinolones, such as nalixidic acid, ciprofloxacin, ofloxacin, levofloxacin, gemifloxacin, and sparfloxacin, are available for clinical purposes. Among this class of antibiotics, ciprofloxacin is frequently prescribed to treat bacterial infections and may be most of the time prescribed along with antimalarial in the tropics[31]. Ciprofloxacin is a synthetic fluoroquinolone with a broad antimicrobial spectrum[31], and has been reported as a potent inhibitor of CYP 3A4 and 1A[.32]. A study by Adegbola *et al*., 2016.[33], reported that administration of quinine plus ciprofloxacin resulted in significant increases in the total area under the concentration-time curve, maximum plasma concentration (Cmax), and terminal elimination half-life (T1/2b) of quinine compared with values with quinine dosing alone (AUC: 27.93 6 8.04 vs. 41.62 6 13.98 h.mg/L; Cmax: 1.37 6 0.24 vs. 1.64 6 0.38 mg/L; T1/2b: 16.28 6 2.66 vs. 21.43 6 3.22 hours), whereas the oral plasma clearance markedly decreased (23.17 6 6.49 vs. 16.00 6 5.27 L/h). In the presence of ciprofloxacin, there was a pronounced decrease in the ratio of AUC (metabolite)/AUC (unchanged drug) and highly significant decreases in Cmax and AUC of the metabolite. Ciprofloxacin may increase the adverse effects of concomitantly administered quinine, which can have serious consequences on the patient. It was recommended that a downward dosage adjustment of quinine might be necessary when concurrently administered with ciprofloxacin[33].

2.2 Quinine and Nevirapine

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) which interrupts the reverse transcription of viral RNA to DNA, a crucial step for HIV replication[34]. Each of the NNRTIs is metabolised to some degree by the cytochrome P450 system of enzymes, making them prone to clinically significant drug interactions34. In addition, they elicit variable effects on other drugs, acting as either inducers or inhibitors of the metabolising enzymes. Data from *in-vitro* and *in-vivo* studies indicate that nevirapine is principally metabolised by CYP3A4, and to a minor extent by CYP2B6. It also induces both enzymes but has little potential to be involved in inhibitory drug interactions[34,35].

A study demonstrated that concurrent administration of nevirapine, a known inducer of CYP3A4, with quinine, a substrate of the isoenzyme, results in a significant reduction in the plasma levels of the antimalarial[36]. Plasma levels of 3-hydroxyquinine, the major metabolite of quinine, are elevated in the presence of nevirapine, and recommended that adjustment of the quinine dose may be necessary when the drug is co-administered with nevirapine, which should be balanced against the potential increase in toxicity that may be associated with

elevated plasma levels of the metabolite36. Administration of quinine plus nevirapine resulted in significant decreases (P < 0.01) in the total area under the concentration-time curve (AUCT), maximum plasma concentration (Cmax) and terminal elimination half-life ($T_{½b}$) of quinine compared with values with quinine dosing alone (AUC: 53.29 ± 4.01 vs 35.48 ± 2.01 h mg/l; Cmax: 2.83 ± 0.16 vs 1.81 ± 0.06 mg/l; $T_{½b}$: 11.35 ± 0.72 vs 8.54 ± 0.76 h), while the oral plasma clearance markedly increased (11.32 ± 0.84 vs 16.97 ± 0.98 l/h). In the presence of nevirapine there was a pronounced increase in the ratio of AUC (metabolite)/AUC (unchanged drug) and highly significant increases in Cmax and AUC of the metabolite (P < 0.01).

2.3 Quinine and Ritonavir

Protease inhibitors such as ritonavir contribute to the improved health of HIV+ individuals, and their inclusion in antiretroviral regimens is commonplace. However, protease inhibitors are often involved in clinically important drug interactions resulting from alteration of cytochrome P450 metabolism[37]. Ritonavir is primarily metabolized by the CYP3A4 isoenzyme and it has a high binding affinity to P-glycoprotein (P-gp)[37]. The drug is also a potent inhibitor of CYP3A4- mediated metabolism and a modest agent for blocking P-gp binding [37,38].

Soyinka *et a*l., in 2009.[39], demonstrated that concurrent administration of ritonavir, a known inhibitor of CYP3A4, with quinine, a substrate of the same isoenzyme, results in marked increases in plasma levels of the antimalarial, whereas the plasma concentrations of 3-hydroxyquinine, the major metabolite of quinine, are remarkably diminished. The high magnitude of elevation of the plasma concentrations of quinine, with its potential adverse effects, suggests the need for downward adjustment of the dosage of the drug when given concurrently with ritonavir[39]. Similarly, quinine caused modest but statistically significant increases in ritonavir plasma levels that might not warrant dosage adjustment of the protease inhibitor when used at a booster dose. Concurrent ritonavir administration resulted in about fourfold increases in both the Cmax and AUCT [Cmax 2.79 _ 0.22 vs. 10.72 _ 0.32 mg l-1, 95% confidence interval (CI) 7.81, 8.04; AUC 50.06 _ 2.52 vs. 220.47 _6.68 mg h-1 l-1, 95% CI 166.3, 175.3], a significant increase (P < 0.01) in the elimination half-life (11.15 _ 0.80 vs. 13.37 _ 0.33 h, 95% CI 1.64, 2.77) and about a 4.5-fold decrease in CL/F (12.01 _ 0.61 vs. 2.71 _ 0.09 l h-1) of quinine. Also, with ritonavir, there was a pronounced reduction of AUC (metabolite)/AUC(unchanged drug) ratio of quinine (1.35 _ 0.10 vs. 0.13 _ 0.02) along with a marked decrease in Cmax (1.80 _ 0.12 vs. 0.96 _ 0.09 mg l-1) and AUC0-48h (62.80 _ 6.30 vs. 25.61 _ 2.44 mg h-1 l-1) of the metabolite. Similarly, quinine caused modest but significant increases (*P* < 0.01) in the Cmax, AUC and elimination $T_{½}$ of ritonavir [39].

3. ARTEMETHER-LUMEFANTRINE INTERACTIONS

Artemether and lumefantrine have different modes of action and act at different points in the parasite life cycle. Oral formulations of AL are available as tablet and dispersible formulations with similar pharmacokinetic properties[40]. A six-dose regimen of artemether (20 mg) co-formulated with lumefantrine (120 mg) is recommended; with first and second doses taken eight hours apart, the third dose is taken 24 hours after the first and the remaining doses 12 hours apart[40]. Artemether-lumefantrine is a highly effective fixed-dose artemisinin-based combination therapy, and the most widely used of the World Health Organization recommended first-line treatments for uncomplicated Plasmodium falciparum malaria[40]. While artemether is primarily metabolized by CYP3A4/5 and 2B6 to the biologically active main metabolite dihydroartemisinin, which is further converted to inactive metabolites through UDP-glucuronosyltransferases catalyzed glucuronidation by UGT1A9 and UGT2B7 with minor contribution from UGT1A1 and UGT1A8[41]. Lumefantrine is primarily N-debutylated to desbutyl-lumefantrine by CYP3A4/5[41].

3.1 Artemether-lumefantrine and Nevirapine

Nevirapine significantly reduced artemether Cmax and AUC (median 28 versus 11 ng/mL, *P*<0.01, and 123 versus 34 ng · h/mL, *P*<0.01) and dihydroartemisinin Cmax and AUC (median 107 versus 59 ng/mL, *P*<0.01, and 364 versus 228 ng - h/mL, *P*<0.01)[42]. Lumefantrine Cmax and AUC were non-significantly reduced by nevirapine[42]. Artemether/lumefantrine reduced nevirapine Cmax and AUC (median 8620 versus 4958 ng/mL, *P*<0.01, and 66 329 versus 35 728 ng - h/mL, P<0.01). Co-administration of artemether/lumefantrine with nevirapine resulted in a reduction in artemether, dihydroartemisinin, lumefantrine and nevirapine exposure[42]. These drug interactions may increase the risk of malaria treatment failure and development of resistance to artemether/lumefantrine and nevirapine.

3.2 Artemether-lumefantrine and dolutegravir

A study evaluated the dolutegravir/artemether-lumefantrine interaction in a two-way crossover study and measured artemether, dihydroartemisinin, lumefantrine, and desbutyl-lumefantrine over 264 h[43]. Dolutegravir did not significantly change the maximum

concentration in plasma, the time to maximum concentration, and the area under the concentration-time curve (AUC) for artemether, dihydroartemisinin, lumefantrine, and desbutyl-lumefantrine. However, coadministration of dolutegravir with artemether-lumefantrine resulted in a 37% decrease in DTG trough concentrations[43]. When given with dolutegravir, artemether's Cmax decreased by 13% (geometric mean ratio [GMR], 0.87; 90% confidence interval [CI], 0.67 to 1.14) after approximately 2 h, with a 5% increase in the area under the concentration-time curve from time 0 to the last measurable concentration (AUC0-t ; GMR, 1.05; 90% CI, 0.84 to 1.32). The active metabolite dihydroartemisinin peak concentrations decreased by 19% (GMR, 0.81; 90% CI, 0.64 to 1.03) after 2.3 h, with a decrease of 8% in AUC0-t (GMR, 0.92; 90% CI, 0.79 to 1.07). Artemether and dihydroartemisinin were eliminated from plasma with average half-lives of 5 and 2.5 h, respectively[43].

Similarly, lumefantrine showed peak concentrations approximately 4 h after drug administration, with a 12% increase in Cmax (GMR, 1.12; 90% CI, 0.97 to 1.29) and 10% increase in AUC0-t (GMR, 1.10; 90% CI, 0.96 to 1.27)[43]. The lumefantrine metabolite desbutyl-lumefantrine had a 3% decrease in Cmax (GMR, 0.97; 90% CI, 0.79 to 1.18) and a 4% decrease in AUC0-t (GMR, 0.96; 90% CI, 0.80 to 1.15), representing approximately 1.7% of the total circulating lumefantrine. Both lumefantrine and desbutyl-lumefantrine had prolonged mean elimination half-lives of approximately 83 and 142 h, respectively.

4. PROGUANIL INTERACTIONS

Proguanil is a synthetic biguanide derivative of pyrimidine which is mainly considered as a prodrug of its major metabolite, cycloguanil, which is an inhibitor of dihydrofolate reductase. However, there are now reports that other mechanisms of action may also be involved since the action of proguanil but not cycloguanil with atovaquone is synergistic in antimalarial activity[44]. Currently, proguanil is used only for chemoprophylaxis as a combination with chloroquine in areas with a low prevalence of chloroquine resistant Plasmodium falciparum and for treatment of malaria in combination with atovaquone or dapsone[45]. Also, in some countries including Nigeria, proguanil is chronically administered for malaria prophylaxis in sickle cell anaemia patients[46]. The metabolism of proguanil is mediated partly by CYP 3A4 but mainly by CYP2C19[45,46]. Proguanil is slowly absorbed from the gastrointestinal tract and is metabolized to two major products, cycloguanil and 4-chlorophenyl-biguanide by CYP 3A4 and CYP 2C19. Although cycloguanil is the active form of the drug, the 4-chlorophenyl derivative is therapeutically inactive[45,46].

4.1 Interaction with Efavirenz

Co-administration of proguanil and efavirenz resulted in significant increases ($p < 0.05$) in Cmax, Tmax, AUCT and elimination half-life (T1/2”) of proguanil compared with values for proguanil alone [Cmax: 2.55±0.24 mg/l vs 3.75±0.48 mg/l; Tmax: 2.80±0.99 h vs 4.80±0.99 h; AUCT: 45.58±12.75mgh/l vs 97.00±23.33mgh/l; T1/2”: 16.50±4.55 h vs 23.24±4.08 h]47. Also, efavirenz caused a pronounced decrease in the AUC (metabolite)/AUC (unchanged drug) ratio of proguanil along with a significant decrease ($p < 0.05$) in Cmax and AUC of the metabolite. These results indicate that efavirenz significantly alters the pharmacokinetics of proguanil[47]. These suggest that the protection against malaria by proguanil may be decreased when the drug is co-administered with efavirenz and the antimalarial efficacy is dependent on cycloguanil plasma levels.

Table 1: Mechanism of pharmacokinetic interactions between antimalarial and antimicrobial drugs

S/N	Antimalarial	Antimicrobial	Mechanism of PK Interaction	References
1	Amodiaquine	Rifampicin	Induction of CYP2C8 by Rifampicin	Ademisoye *et. al.,* 2018
2	Amodiaquine	Cotrimoxazole	Inhibition of CYP 2C8 by Cotrimoxazole	Ademisoye *et. al.,* 2015.
3	Amodiaquine	Efavirenz	Inhibition of CYP 2C8 by Efavirenz	Soyinka *et. al.,* 2013
4	Quinine	Ritonavir	Inhibition of CYP 3A4 by Ritonavir	Soyinka *et. al.,* 2009.
5	Quinine	Nevirapine	Induction of CYP 3A4 by Nevirapine	Soyinka *et. al.,* 2009.
6	Quinine	Ciprofloxacin	Inhibition of CYP 3A4 by Ciprofloxacin	Adegbola *et. al.,* 2016.
7	Proguanil	Efavirenz	Inhibition of CYP 2C19 by Efavirenz	Soyinka *et. al.,* 2010.
8	Artemether-Lumefantrine	Nevirapine	Induction of CYP 3A4 by Nevirapine	Byakika-Kibwikia *et. al.,* 2012
9	Artemether-Lumefantrine	Dolutegravir	Inhibition of CYP 3A4 by Dolutegravir	Walimbwa *et. al.,* 2016.

CONCLUSION

In conclusion, the review revealed that there are pharmacokinetic interactions between antimalarial and antimicrobial agents when they were concurrently administered. The summary of the antimalarial and antimicrobial drugs discussed with the mechanism of their pharmacokinetic interactions are illustrated in Table 1. It is worthy to note that attention to dosage and dosage regimens be paid to when there is need to concurrently administer antimalarial and antimicrobial agents to prevent treatment failure and adverse drug reaction.

Interactions involving antimicrobials often result from alterations in the absorption of the antimicrobial from the gastrointestinal tract or changes in the hepatic metabolism or renal elimination of the drugs concurrently administered. While certain classes of antibacterial drugs are known to interact with many other drugs, the interaction potential of most classes of antimicrobials is not uniform among members of the class. This diversity in interaction potential provides the clinician with an opportunity to avoid potential interactions by means of appropriate drug selection. An understanding of the common, clinically significant drug interactions involving antimalarial and antimicrobial agents will enable the physician to avoid unnecessary adverse drug reactions. The authors report that there are no competing interests to declare.

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