Dihydroartemisinin–piperaquine resistance in *Plasmodium falciparum* malaria in Cambodia: a multisite prospective cohort study

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Summary

Background Artemisinin resistance in *Plasmodium falciparum* threatens to reduce the efficacy of artemisinin combination therapies (ACTs), thus compromising global efforts to eliminate malaria. Recent treatment failures with dihydroartemisinin-piperaquine, the current first-line ACT in Cambodia, suggest that piperaquine resistance may be emerging in this country. We explored the relation between artemisinin resistance and dihydroartemisinin–piperaquine failures, and sought to confirm the presence of piperaquine-resistant *P falciparum* infections in Cambodia.

Methods In this prospective cohort study, we enrolled patients aged 2–65 years with uncomplicated *P falciparum* malaria in three Cambodian provinces: Pursat, Preah Vihear, and Ratanakiri. Participants were given standard 3-day courses of dihydroartemisinin–piperaquine. Peripheral blood parasite densities were measured until parasites cleared and then weekly to 63 days. The primary outcome was recrudescent *P falciparum* parasitaemia within 63 days. We measured piperaquine plasma concentrations at baseline, 7 days, and day of recrudescence. We assessed phenotypic and genotypic markers of drug resistance in parasite isolates. The study is registered with ClinicalTrials.gov, number NCT01736319.

Findings Between Sept 4, 2012, and Dec 31, 2013, we enrolled 241 participants. In Pursat, where artemisinin resistance is entrenched, 37 (46%) of 81 patients had parasite recrudescence. In Preah Vihear, where artemisinin resistance is emerging, ten (16%) of 63 patients had recrudescence and in Ratanakiri, where artemisinin resistance is rare, one (2%) of 60 patients did. Patients with recrudescent *P falciparum* infections were more likely to have detectable piperaquine plasma concentrations at baseline compared with non-recrudescent patients, but did not differ significantly in age, initial parasite density, or piperaquine plasma concentrations at 7 days. Recrudescent parasites had a higher prevalence of *kelch13* mutations, higher piperaquine 50% inhibitory concentration (IC_{50}) values, and lower mefloquine IC_{50} values; none had multiple *pfmdr1* copies, a genetic marker of mefloquine resistance.

Interpretation Dihydroartemisinin–piperaquine failures are caused by both artemisinin and piperaquine resistance, and commonly occur in places where dihydroartemisinin–piperaquine has been used in the private sector. In Cambodia, artesunate plus mefloquine may be a viable option to treat dihydroartemisinin–piperaquine failures, and a more effective first-line ACT in areas where dihydroartemisinin–piperaquine failures are common. The use of single low-dose primaquine to eliminate circulating gametocytes is needed in areas where artemisinin and ACT resistance is prevalent.

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Introduction

Artemisinin combination therapy—the use of a potent, short-acting artemisinin and a less-potent, long-acting partner drug—is recommended worldwide for the treatment of *Plasmodium falciparum* malaria.[1] Dihydroartemisinin–piperaquine, one of the few artemisinin combination therapies still effective against multidrug-resistant *P falciparum* in southeast Asia, was adopted as the first-line antimalarial treatment in Cambodia in 2008. Several earlier studies[2–4] documented the excellent safety and tolerability of dihydroartemisinin–piperaquine in Cambodia, as well as efficacy of 96–98% after 28 days or 63 days in the Cambodian provinces of Oddar Meancheay, Siem Reap, Pursat, and Kratie.[3–6] However, the rapid spread of artemisinin resistance in Cambodia[7–11] and throughout mainland southeast Asia[10–12] threatens the efficacy of dihydroartemisinin–piperaquine and all other artemisinin combination therapies.[13] This danger arises because as more parasites become resistant to artemisinin, more parasites need to be eliminated by the lone partner drug; therefore, they are more likely to spontaneously develop genetic resistance to piperaquine and other partner drugs.

Preliminary evidence for this development has been provided by three studies that show declining efficacy of dihydroartemisinin–piperaquine shortly after its widespread deployment in western Cambodia. In a 2008–10 study,[14] the efficacy of dihydroartemisinin–piperaquine after 42 days was 75% in Pailin and 89% in

Panel: Research in context

Evidence before this study

We searched PubMed using the terms "dihydroartemisinin", "piperaquine", "efficacy", and "Cambodia" without any date or language restrictions on June 5, 2015. We identified 13 articles, six of which were original clinical trials of the efficacy of dihydroartemisinin–piperaquine for treatment of uncomplicated *Plasmodium falciparum* malaria in Cambodia. Three studies from 2001–05 showed that efficacy was 96–98% before dihydroartemisinin–piperaquine was widely used. Three later studies reported reduced efficacy (46–89%) in 2008–13, after dihydroartemisinin–piperaquine became widely used. Treatment failure has been linked to parasite *kelch13* mutations, which are associated with artemisinin resistance. All three of the later studies found no association between treatment failures and high piperaquine in-vitro IC_{50} values (a measure of parasite susceptibility to piperaquine). The role of in-vivo piperaquine resistance in treatment failures has not been adequately assessed.

Added value of this study

Our findings suggest that dihydroartemisinin–piperaquine treatment is failing in Pursat and Preah Vihear, where artemisinin resistance is prevalent, but remains highly efficacious in Ratanakiri where artemisinin resistance is uncommon. Treatment failures were not associated with older patient age, higher initial parasite density, or high piperaquine plasma concentration at 7 days. Instead, recrudescent parasites had more *kelch13* mutations and high piperaquine IC_{50} values, indicating that dihydroartemisinin–piperaquine failures are due to both artemisinin and piperaquine resistance. These recrudescent parasites also have reduced mefloquine IC_{50} values and lack multiple copies of *pfmdr1*, a genetic marker for mefloquine resistance.

Implications of all the available evidence

Dihydroartemisinin–piperaquine is failing quickly in four western Cambodian provinces (Pailin, Pursat, Oddar Meanchey, and Preah Vihear), and is associated with parasite resistance to both artemisinin derivatives and piperaquine. Evidence of piperaquine resistance in *P falciparum* should prompt efforts to map this phenotype in Cambodia and other southeast Asian countries, to elucidate its molecular mechanism, and to discover new drugs that circumvent piperaquine resistance. Artesunate plus mefloquine should be tested as a first-line therapy where dihydroartemisinin–piperaquine failures have been documented, and also as a salvage treatment for dihydroartemisinin–piperaquine failures in Cambodia. Clinical trials should be done of a triple-drug regimen of dihydroartemisinin–piperaquine plus mefloquine.

Pursat, but 100% in Preah Vihear and Ratanakiri in northern and eastern Cambodia. Because dihydroartemisinin–piperaquine failures were found not to be associated with piperaquine 50% inhibitory concentration (IC_{50}) in this study, and piperaquine plasma concentrations at 7 days were not measured, piperaquine resistance in Pailin and Pursat could not be confirmed. The emergence of piperaquine resistance is also difficult to reconcile with concomitant decreases in piperaquine IC_{50} values in Pailin and Pursat.[14] In a 2013 study,[15,16] the efficacy of dihydroartemisinin–piperaquine after 42 days in Oddar Meancheay was 46%. Although patients with recrudescence or cure had similar exposures to piperaquine in this study, the piperaquine IC_{50} values for recrudescent parasites were not higher than those for non-recrudescent parasites. Given this result, piperaquine resistance in this province also could not be confirmed. In a 2011–13 study,[17] the proportion of recrudescent infections by 42 days after dihydroartemisinin–piperaquine treatment was higher in western Cambodia (15%) than in eastern Cambodia (3%). Patients with recrudescence or cure in this study had similar exposures to piperaquine and carried parasites with similar piperaquine IC_{50} values. In view of these findings and the lack of a genetic marker, piperaquine resistance in western Cambodia has not been confirmed, although increasing piperaquine IC_{50} values in northern Cambodia suggest that it may be emerging.[18]

The lack of clear evidence of piperaquine resistance in Cambodia hinders efforts to define its role in dihydroartemisinin–piperaquine failures, identify and validate genetic markers for use in large surveillance programmes, and study its molecular mechanism. We did a cohort study to identify piperaquine-resistant *P falciparum* infections in Cambodia. We postulated that such infections would be associated with artemisinin resistance,[19] dihydroartemisinin–piperaquine failures, adequate piperaquine exposure, and decreased susceptibility of *P falciparum* isolates to piperaquine in vitro. We also postulated that dihydroartemisinin–piperaquine would fail more often in areas where artemisinin resistance is prevalent than where it is emerging. We therefore compared the efficacy of dihydroartemisinin–piperaquine for the treatment of uncomplicated *P falciparum* malaria in Pursat, Preah Vihear, and Ratanakiri, where the prevalences of *kelch13* mutations—a genetic marker for artemisinin resistance in Cambodia and elsewhere in southeast Asia[9,10]—were 76%, 21%, and 4%, respectively, in 2011–12.[10] We also compared the prevalence of *kelch13* mutations, plasma piperaquine concentrations after 7 days, and in-vitro piperaquine IC_{50} values between non-recrudescent and recrudescent infections to investigate the presence of piperaquine-resistant parasites.

Methods

Study design and participants

For this prospective cohort study, we recruited patients from provincial referral hospitals and district health

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