Progress in the development of piperaquine combinations for the treatment of malaria

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Purpose of review

Dihydroartemisinin–piperaquine is a new and extremely promising artemisinin-containing fixed-combination antimalarial, about to be registered with international regulatory authorities such as the European Medicines Agency. A formulation produced according to good manufacturing practices should be available soon.

Recent findings

Piperaquine is characterized by a slow absorption, long mean terminal elimination half-life and large mean volume distribution. However, children, compared to the population mean profile, tend to have a smaller central volume of distribution, a shorter distribution half-life and a more rapid fall in early piperaquine plasma concentrations, suggesting that an increase of the weight-adjusted dosage in children may be required. In addition, the oral bioavailability of piperaquine improves when given with a high-fat meal, though this does not necessarily translate into a higher efficacy. Several clinical trials have repeatedly shown that dihydroartemisinin–piperaquine is well tolerated and efficacious, with the only exception of one trial recently carried out in Papua New Guinea. Patients treated with dihydroartemisinin–piperaquine may have a higher rate of person-gametocyte-weeks, though it is unclear whether this translates into a higher infectiousness to biting anophelines.

Summary

The dosage recommended for children may need to be reviewed and the usefulness of the coadministration with food should be determined. Establishing safety and efficacy of this treatment in pregnancy remains a priority.

Keywords

antimalarials, combinations, dihydroartemisinin–piperaquine, malaria

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Introduction

Piperaquine is a bisquinoline antimalarial drug related to chloroquine and other 4-aminoquinolines that was synthesized independently in France and China in the 1960s [1]. After the adoption in 1978 of piperaquine instead of chloroquine as the antimalarial recommended by the Chinese Malaria Control Programme, the equivalent of 140 million adult treatment doses or over 200 metric tons were manufactured and distributed in China [2], where it was also used for human chemoprophylaxis. The administration of piperaquine to more than 20 000 people in six Chinese provinces was associated with a decrease in malaria incidence [1]. Nevertheless, with the emergence of *Plasmodium falciparum* piperaquine-resistant strains, piperaquine use in the late 1980s decreased.

In the 1990s, piperaquine was reconsidered as one of the components of short-course artemisinin-based combination treatments [1]. The first combination tested, China-Vietnam 4 (CV4), containing dihydroartemisinin, piperaquine phosphate, trimethoprim and primaquine phosphate, was reformulated, following few small-scale, nonrandomized trials, as China-Vietnam 8 (CV8), the same combination with different quantities of the single components [1]. In 2000, after a few clinical trials, the Vietnamese Malaria Control Programme decided to introduce CV8 as first-line treatment for *P. falciparum* malaria. Nevertheless, the unclear role of the trimethoprim in the treatment, the risk of haemolysis in G6PD-deficient patients and the low dose of dihydroartemisinin, determined the evolution of CV8 towards dihydroartemisinin–piperaquine [1].

Both the mechanism of action and of resistance of piperaquine have not been well characterized but are likely to be similar to those described for drugs of the same class [2]. Cross-resistance between piperaquine and chloroquine has been reported [1]. However, piperaquine has

also been shown to be active against highly chloroquine-resistant *P. falciparum* [3].

Pharmacokinetics

Piperaquine's pharmacokinetic properties are similar to those of chloroquine, that is, a very large apparent volume of distribution and a very long terminal elimination half-life [3]. The first pharmacokinetic data obtained from Cambodian malaria patients (*P. falciparum* or *P. vivax*) treated with dihydroartemisinin–piperaquine showed, both in adults and children, slow absorption, long mean terminal elimination half-life and large mean volume distribution [4]. Similar results have recently been obtained in Melanesian children (5–10-year-old) with uncomplicated *P. falciparum* or nonfalciparum malaria [5]. Two pharmacokinetic studies were conducted in the framework of the international registration of dihydroartemisinin–piperaquine, one in Thailand involving intense sampling in adult men and the other in Burkina Faso involving sparse sample analysis in young children. In these two studies, the model best describing the kinetics of piperaquine in adult patients was a three-compartment model with first-order elimination and two first-order absorption processes [6]. The plasma concentration vs. time profiles were characterized by one slow absorption process that started within 1 h of dosing (process 1) and one very quick input (almost bolus like) that arose about 3–4 h after dosing (process 2). The extremely large volume of distribution of piperaquine led to very long half-life values, with median values of 531 h (22 days) and 468 h (20 days) in adults and children, respectively.

A population pharmacokinetic study nested in a large randomized clinical trial on the safety and efficacy of dihydroartemisinin–piperaquine included 98 Burmese or Karen patients aged 3–55 years with *P. falciparum* uncomplicated malaria and reported similar pharmacokinetic parameters, with a very large steady-state volume of distribution and a long estimated terminal half-life [7•]. In this study, the mean posttreatment prophylactic period was estimated at about 20 days. Nevertheless, children, compared to the population mean profile, tended to have a smaller central volume of distribution, a shorter distribution half-life and a more rapid fall in early piperaquine plasma concentrations, suggesting a higher risk of recrudescence and earlier reinfection. In Papua, Indonesia, piperaquine plasma concentration at day 7 was the major determinant of the therapeutic response and children had a higher risk of having lower levels [8]. Similarly, in Papua New Guinea, a trend towards a lower risk of treatment failure (PCR-uncorrected) and plasma piperaquine levels at day 7 has been reported [9•]. These data suggest that an increase of the weight-adjusted dosage in children may be required.

Piperaquine is highly lipid-soluble and its oral bioavailability may be lower when given without any food. A study on eight healthy white adults (randomized cross-over of piperaquine administration in the fasting and fed states, 56-day interval) reported that, relative to the fasting state, the oral bioavailability of piperaquine is approximately doubled by a high-fat meal [10]. The enhanced bioavailability of piperaquine with a moderate fat meal has been confirmed in 26 healthy Vietnamese individuals [11]. Although this does not necessarily mean that piperaquine or the corresponding combinations should be given with fat, a recent study in Papua New Guinea reported an efficacy of less than 90% at day 42 in children treated with dihydroartemisinin–piperaquine, whereas that of artemether–lumefantrine (administered with fat) was 99% [9•]. However, a reanalysis of data from 981 children (<5-year-old) treated with dihydroartemisinin–piperaquine administered with either milk or a biscuit in seven clinical trials both in Africa and Asia reported a 3.1% (range 0–7.1%) recrudescence rate at day 42, with a significantly lower risk of recurrent malaria as compared with those treated with artemether–lumefantrine [12•]. Nevertheless, an additional study on Vietnamese healthy volunteers reports no influence of food intake (standardized Vietnamese meal) on the pharmacokinetics of piperaquine [13]. The issue of whether to recommend the administration of dihydroartemisinin–piperaquine with a biscuit or a glass of milk remains. Though coadministration with food may improve the drug's bioavailability, its implementation at peripheral health facilities is not obvious. A similar recommendation exists already for artemether–lumefantrine, but it is rarely implemented, at least in sub-Saharan African countries. High cure rates at day 28 with unsupervised artemether–lumefantrine have been reported [14], though the plasma lumefantrine concentrations at day 3 and day 7 after treatment were significantly lower, with the children less than 5 years of age having the lowest values [15]. Considering that this result was obtained after careful explanation to the caregiver on the need of administering the treatment with food, what will occur at busy health clinics will probably be less than optimal.

Efficacy

A recent review identified 14 studies published in 13 articles between 2002 and October 2006 and involving 2636 patients exposed to dihydroartemisinin–piperaquine, most of them conducted in south-east Asia, one in China and one in Rwanda [3]. Dihydroartemisinin–piperaquine efficacy was excellent, with overall 28-day cure rates or Kaplan–Meier-derived estimates of 97–98% in China, Cambodia, Myanmar, Laos PDR, Thailand and Vietnam. In Rwanda, dihydroartemisinin–piperaquine

efficacy was slightly lower (95.2%) but better than that of amodiaquine–artesunate and sulfadoxine–pyrimethamine + amodiaquine [16]. Nevertheless, its efficacy was particularly low (88.6%) in one site, Rukara, situated in the eastern part of the country, towards the Ugandan border, whereas in the two other sites the efficacy was almost 100%. The reason for such difference is unclear, but the efficacy estimation of several other treatments has been consistently lower in Rukara than in the other Rwandan sites. Several other studies were published after October 2006. In Papua, Indonesia, 754 patients with either *P. falciparum* or *P. vivax* or both infections were treated with either artemether–lumefantrine (375) or dihydroartemisinin–piperaquine (379) and followed up until day 42 [8]. Both treatments were given with food (biscuit or milk) and the administration directly observed for dihydroartemisinin–piperaquine, whereas for artemether–lumefantrine, only the morning dose was supervised. The risk of failure (PCR-corrected) was 4.4%, with no difference between the two treatments. However, the cumulative risk of any parasitological failure was greater after artemether–lumefantrine than after dihydroartemisinin–piperaquine, reflecting the longer elimination of piperaquine as compared with lumefantrine. *P. vivax* recurrence occurred significantly more often in the artemether–lumefantrine (38%) as compared with the dihydroartemisinin–piperaquine group (10%). The risk of anaemia at the end of the study was also significantly lower for patients having received dihydroartemisinin–piperaquine than for those on artemether–lumefantrine. A study comparing amodiaquine–artesunate with dihydroartemisinin–piperaquine was carried out in the same location, though food was not coadministered with treatment [17]. Dihydroartemisinin–piperaquine performed significantly better than amodiaquine–artesunate in terms of overall parasitological failure rate at day 42 (13 vs. 45%), true recrudescence of *P. falciparum* infection (4.8 vs. 16%) and parasitological failure with *P. vivax* [initial infection with any species: 9.1 vs. 33%; initial infection with *P. vivax* (alone or mixed): 16 vs. 48%]. As in the previous study, the risk of anaemia at the end of the study was significantly lower in the dihydroartemisinin–piperaquine group. In Cambodia, 464 patients (adults and children) were treated with either mefloquine–artesunate or dihydroartemisinin–piperaquine [18]. Both treatments were extremely efficacious, with a PCR-corrected efficacy at day 63 of 97.5%. Similar results were obtained in Peru with the PCR-corrected efficacy at day 63 of 98.4% for dihydroartemisinin–piperaquine and 99.6% for mefloquine–artesunate [19].

In Uganda, dihydroartemisinin–piperaquine was compared with artemether–lumefantrine in two sites, Aduku Health Centre, Apac District [20] and Kihihi Health Centre, Kanungu District [21]. In both studies, children 6-month-old to 10-year-old were recruited and the treatment was administered with a glass of milk. The follow-up lasted until day 42. In both studies, the unadjusted risk of recurrent falciparum parasitaemia was significantly lower in the dihydroartemisinin–piperaquine group. Nevertheless, the risk of recurrent parasitaemia due to possible recrudescence was significantly lower in the dihydroartemisinin–piperaquine group in Aduku Health Centre (day 42: 6.9 vs. 16%) [20] but not in Kihihi Health Centre, where the efficacy of artemether–lumefantrine was also high (at day 42: 2.0 vs. 5.8%) [21]. In Burkina Faso, children aged at least 6 months were treated with either dihydroartemisinin–piperaquine, artemether–lumefantrine or amodiaquine–sulfadoxine–pyrimethamine and followed up until day 42 [22]. It is unclear whether the treatment was coadministered with food as this information is not specifically reported. The risk of recurrent parasitaemia, unadjusted by genotyping, was significantly higher for patients receiving artemether–lumefantrine than for patients receiving amodiaquine and sulfadoxine–pyrimethamine or dihydroartemisinin–piperaquine, both at day 28 and day 42. However, there was no difference between treatment groups when the failure rate was adjusted by genotyping, which for the dihydroartemisinin–piperaquine was as low as 2.2% at day 42.

An additional study carried out in Papua New Guinea, at the Alexishafen and Kunjingini Health Centres in Madang and East Sepik Provinces, reported surprisingly low estimate of dihydroartemisinin–piperaquine efficacy, that is, 88% at day 42, significantly lower than artemether–lumefantrine. However, it should be noted that the study had not been powered for comparing the different treatments tested, rather to estimate the treatment efficacy with 5% precision and 95% confidence [9•]. Indeed, this was a four-arm study, with around 100 patients per arm, a relatively small sample size compared with other published studies. In any case, the reasons for such disappointing results are unclear, though the authors mention the cross-resistance between chloroquine and piperaquine [9•]. However, as mentioned above, piperaquine, though structurally related to chloroquine, has been shown to be effective *in vitro* against chloroquine-resistant strains [1,3,23]. In addition, the results of a multicentre trial, comparing dihydroartemisinin–piperaquine with artemether–lumefantrine in 1553 6–59-month-old children with uncomplicated malaria, carried out in five African sites (Burkina Faso, Kenya, Mozambique, Uganda and Zambia) showed that both treatments were highly efficacious at day 28 and day 42, with a estimated efficacy (PCR-corrected) above 90% [24•], despite the high chloroquine resistance previously observed in some of the sites. This study has been carried out for the international registration of Good Manufacturing Practice (GMP) dihydroartemisinin–piperaquine. A study with

a similar design but using mefloquine–artesunate instead of artemether–lumefantrine and within the same programme was carried out in Asia [25]. Both treatments had similar and high efficacy. A large multicentre trial on dihydroartemisinin–piperaquine, artemether–lumefantrine and amodiaquine–artensunate in children of 6–59 months with uncomplicated malaria is ongoing in 10 sites distributed in seven African countries. Children are actively followed up until day 28 and then passively for the next 6 months. This study should estimate the frequency of retreatment and the safety of multiple treatments in this age group. Results are expected for mid-2010.

Gametocyte carriage

In some studies, patients treated with dihydroartemisinin–piperaquine had a higher production of gametocytes than those treated with mefloquine–artesunate [19,26], whereas in others gametocyte carriage for *P. falciparum* was either similar to the comparator drug [8] or significantly lower [21]. In Kenya, gametocyte carriage was assessed with the quantitative nucleic sequence-based amplification technique (QT-NASBA), a more sensitive method than microscopy, in patients treated with either dihydroartemisinin–piperaquine or artemether–lumefantrine [27]. Gametocyte clearance was significantly better in the artemether–lumefantrine group and the development of gametocytes was significantly higher and longer at days 3, 7 and 14 in the dihydroartemisinin–piperaquine group, though after 28 days no difference could be observed between treatment arms. Similarly, in the multicentre trial in Africa mentioned above, patients treated with dihydroartemisinin–piperaquine had a significantly higher rate of person-gametocyte-weeks compared with those having received artemether–lumefantrine [24•]. Such an effect has been attributed to the low dose of dihydroartemisinin in the combination treatment, though it is unclear whether this translates into higher infectiousness to biting anophelines and hence increased transmission potential [28•].

Safety

Dihydroartemisinin–piperaquine is well tolerated both in adults and in children, with low report of adverse events [3]. In Papua, Indonesia, patients treated with dihydroartemisinin–piperaquine had a significantly higher risk of diarrhoea on days 1 and 2 [8]. In Papua New Guinea, the incidence rate ratio for rash was significantly higher among patients treated with artesunate–sulfadoxine–pyrimethamine and dihydroartemisinin–piperaquine than those treated with chloroquine–sulfadoxine–pyrimethamine [9•]. Other studies did not show any difference in the occurrence of adverse events between dihydroartemisinin–piperaquine and the comparator drug(s).

Future perspectives

Dihydroartemisinin–piperaquine has been tested so far in adults and children with uncomplicated malaria, *P. falciparum* and *P. vivax*. Pregnant women are considered a high-risk group for malaria infection, but there are currently no data on the use of dihydroartemisinin–piperaquine in pregnancy [29]. Inadvertent exposure to dihydroartemisinin–piperaquine has been documented in two women (at 11 weeks and 18 weeks gestation) who delivered normal babies [30]. A large multicentre trial investigating the safety and the efficacy of dihydroartemisinin–piperaquine and other artemisinin-based combination treatments in pregnant women with malaria in the second and third trimester will soon start in four African countries (Burkina Faso, Ghana, Malawi and Zambia) with funding from the European and Developing Countries Clinical Trials Partnership (EDCTP) and the Gates Foundation. Such study will be carried out within the framework of the Malaria in Pregnancy Consortium. In addition, considering the long elimination half-life of piperaquine and if it is shown to be safe in pregnancy, this drug could be a good candidate for the intermittent preventive treatment during pregnancy, possibly with another drug with similar pharmacokinetic properties [31].

Conclusion

Dihydroartemisinin–piperaquine has consistently been shown to be well tolerated, safe and efficacious in Asia, Africa and South America, both in children and in adults with uncomplicated malaria due to *P. falciparum*, *P. vivax* or mixed infections. However, the recommended dose for children may need revision. Its administration with a fatty meal should enhance piperaquine bioavailability, though it is unclear whether this will translate into a higher efficacy. Advantages and disadvantages of this practice should be considered, keeping in mind that in several studies in which there was no coadministration with food, treatment efficacy was high. Its imminent registration with international drug authorities such as the European Medicines Agency should make the GMP product widely available. Establishing its safety and efficacy in pregnancy, both for treating clinical malaria and as intermittent preventive treatment, remains a priority.

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