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REVIEW

Efficacy and safety of dihydroartemisinin-piperaquine

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Summary Dihydroartemisinin-piperaquine, a fixed-dose combination antimalarial, is an inexpensive, safe and highly effective treatment for uncomplicated falciparum or vivax malaria. Efficacy assessed over 28–63 days has consistently exceeded 95% in the treatment of multidrug-resistant falciparum malaria. More than 2600 patients have been treated with this combination in prospective studies, mainly in Southeast Asia. Tolerability was uniformly good, and no serious adverse effects have been identified. The dosing regimen has been simplified from four doses to once daily over 3 days. More information on efficacy in Africa, and more pharmacokinetic and efficacy data in children are needed.

1. Introduction

It is widely accepted that artemisinin-based combination therapies (ACTs) provide the best available treatment for uncomplicated multidrug-resistant falciparum malaria (WHO, 2006). They give reliably rapid therapeutic responses, provide high cure rates with 3-day treatment regimens, are well tolerated, reduce gametocyte carriage and provide mutual protection for the partner drugs against the emergence of resistance (White, 1999).

Artesunate-mefloquine and artemether-lumefantrine, are both effective against multidrug-resistant strains of falciparum malaria (Nosten et al., 1994; van Vugt et al., 1999) and, like all ACTs, reduce post-treatment gametocyte carriage (Price et al., 1996). Widespread deployment has been associated with a reduction in the incidence of falciparum malaria both on the northwestern border of Thailand and in Kwa-Zulu Natal province, South Africa (Barnes et al., 2005; Muheki et al., 2004; Nosten et al., 2000). However, these drugs are relatively expensive (approximately 3US$ for artesunate-mefloquine and, until recently, 2.4US$ for artemether-lumefantrine per adult treatment course). The price of artemether-lumefantrine was reduced in September 2006 to 1US$ per average treatment course. Mefloquine-containing regimens are reliably effective, but early vomiting, particularly in young children, and later central nervous system adverse effects are relatively common (ter Kuile et al., 1995). For lumefantrine, which is a

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hydrophobic lipophilic compound, absorption is variable and may be inadequate when taken without food (White et al., 1999). Both mefloquine and lumefantrine share the same resistance mechanism, although the corresponding ACT cure rates exceed 90% everywhere they are used, except in western Cambodia. In Africa, artemisinin derivatives have also been combined with sulfadoxine-pyrimethamine (SP), chloroquine, and amodiaquine with varying success, dependent, predictably, on the prevalence of resistance to the partner drug in the areas where they have been evaluated (Abacassamo et al., 2004). Amodiaquine and SP containing ACTs are widely used, although increasing resistance to these partner drugs compromises their future.

The combination of dihydroartemisinin + piperaquine (DHA-PIP) is relatively inexpensive, costing as little as 1US$ for an adult treatment. Piperaquine (PIP), a bisquinoline antimalarial (1,3-bis [1-(7-chloro-4′quinolyl)- 4′piperazinyl]-propane), has a similar mode of action to other quinoline antimalarials: interference with haem detoxification (Davis et al., 2005). It has pharmacokinetic properties similar to chloroquine with a very large apparent volume of distribution and a very long terminal elimination half-life (Hung et al., 2004; Tarning et al., 2005). Piperaquine has been used extensively only in China, where it replaced chloroquine as first-line treatment in 1978. Over the next 16 years more than 200 metric tonnes were used. Mass treatments and mass prophylaxis were employed, and resistance reportedly developed (Changxiong et al., 1989; Chen et al., 1982). However, piperaquine was never used to treat malaria elsewhere. Although structurally similar to chloroquine, in vitro experiments have shown piperaquine to be active against highly chloroquine-resistant *Plasmodium falciparum* (Raynes, 1999; Vennerstrom et al., 1992), and the DHA-PIP combination certainly retains both high efficacy and a prolonged post-treatment prophylactic effect in areas where highly chloroquine-resistant *P. falciparum* is prevalent.

Dihydroartemisinin (DHA) is the active metabolite of the more widely used artesunate and artemether and is manufactured as an oral antimalarial drug in China. Given alone, the artemisinin derivatives must be given for 7 days for optimum cure rates. Five-day regimens give lower cure rates and 3-day regimens of artemisinin monotherapy are associated with very high failure rates (40—80%) in non-immune patients, (Hien, 1994; McIntosh and Olliaro, 2000). Combining an artemisinin derivative with another antimalarial drug which is more slowly eliminated allows complete treatment to be given in 3 days and is now considered the treatment of choice for falciparum malaria (WHO, 2001, 2006).

Earlier formulations containing DHA and PIP also contained trimethoprim, and sometimes primaquine in a four-drug combination. Current formulations contain only DHA 40 mg and PIP 320 mg per tablet. DHA-PIP has been evaluated in large clinical trials in Southeast Asia, China and Rwanda (Ashley et al., 2004, 2005; Denis et al., 2002; Giao et al., 2004; Hien et al., 2004; Hung et al., 2004; Karema et al., 2006; Karunajeewa et al., 2004; Mayxay et al., 2006; Smithuis et al., 2006; Tangpukdee et al., 2005; Wilairatana et al., 2002; Ying et al., 2003). Further studies in Africa, Asia Oceania and South America have been conducted but not yet reported. Because of its relatively low cost, high efficacy and good tolerability, DHA-PIP has become national policy for first-line treatment in Vietnam. Where DHA-PIP is available in the private sector it is being used increasingly in Southeast Asia. The drug is not registered internationally, and manufacture is being upgraded to internationally accepted Good Manufacturing Practices (GMP) standards. Lack of a GMP formulation has limited its deployment outside Southeast Asia. This review summarizes the available data of efficacy and safety data from published trials.

2. Methods

Relevant trials were identified by a search of MEDLINE (1966—October 2006) and The Cochrane Library. Search terms used included dihydroartemisinin, piperaquine, Artekin and malaria. All published randomized trials that compared DHA-PIP with another antimalarial drug were included, as were non-randomized, non-controlled trials, including a study evaluating safety only. Unpublished data were not sought for this review. Our methods combine a narrative review approach to include more detailed information on safety and a meta-analysis of individual study efficacy results. Data were extracted, tabulated by study, and entered on to a computer database using Microsoft Office Excel 2003 (Microsoft Corp., Redmond, WA, USA). Meta-analysis of DHA-PIP efficacy in comparative studies was done using Stata version 8 (Stata Corp., College Station, TX, USA).

3. Results

Fourteen studies on combinations containing DHA-PIP were published in 13 articles between 2002 and October 2006 (Table 1). There was a total of 2636 patients (22 treatment arms) exposed to DHA-PIP for the treatment of multidrug-resistant uncomplicated *P. falciparum* malaria. Eleven studies were conducted in Southeast Asia (Thailand, Cambodia, Laos and Myanmar), one study was conducted in China and one study in Rwanda. Trials were conducted in patients of all age groups (the Rwandan study included only children aged 12—59 months). Six studies included patients with uncomplicated falciparum malaria only, and two covered falciparum or vivax malaria monoinfections. In six studies mixed infections were included; there were 186 patients with mixed falciparum and vivax malaria.

Eleven trials were randomized ($n = 2383$), and the remaining three trials ($n = 253$) were non-randomized uncontrolled trials. Eight trials were conducted with 28-day follow-up, two trials with 42-day, two trials with 56-day and two trials with 63-day follow-up. PCR genotyping to distinguish recrudescence from reinfections was done in seven of the studies (Table 1). In one study in Myanmar there was an effectiveness arm as well as an efficacy arm in which patients received DHA-PIP unsupervised. The comparator drug was the 3-day artesunate-mefloquine (MAS3) combination in eight studies.

Cure rates were calculated as proportions in most studies ($n = 8$). Five studies assessed efficacy using Kaplan-Meier survival analysis (Ashley et al., 2004, 2005; Giao et al., 2004; Mayxay et al., 2006; Smithuis et al., 2006).

There were differences between studies in the formulation of the drug given (Table 1), and the dosing schedule,

Table 1 Evaluated studies of the antimalarial efficacy of dihydroartemisinin-piperaquine combinations ($n = 2636$)

Author and year published	Study site	Design[a]	Drug[b]	Malaria species[c]	No. of patients	Follow-up (days)	28-day cure rates (%)	PCR-adjusted cure rates (%)
Denis et al. (2002)	Cambodia	SAT	DHA-PIP	P.f	106	56	96.9	95.5
Wilairatana et al. (2002)	Thailand	RCT	DHA-PIP + TMP	P.f	234	28	97	No genotyping
			MAS3		118		97	
Ying et al. (2003)	China	RCT	DHA-PIP	P.f	30	28	96.7	No genotyping
			DHA-PIP + TMP		30		96.7	
Hien et al. (2004)	Vietnam	Pilot	DHA-PIP + TMP	P.f or mixed	76	56	ND[d]	97.4
			MAS3		38			100
		RCT	DHA-PIP + TMP		157			97.4
			DHA-PIP		166			98.7
			MAS3		77			98.7
Karunajeewa et al. (2004)	Cambodia	SAT	DHA-PIP	P.f or P.v	62	28	100	No genotyping
Hung et al. (2004)	Cambodia	SAT	DHA-PIP	P.f or P.v	38 (adults)	28	97	No genotyping
					47 (children)		98	
Giao et al. (2004)	Vietnam	RCT	DHA-PIP + TMP + primaquine	P.f	82	28	94	No genotyping
			AP		79		95	
Ashley et al. (2004)	Thailand	2 RCTs	DHA-PIP	P.f or mixed	59	28	98	No genotyping
			DHA-PIP + AS		59		100	
			MAS3		59		100	
			DHA-PIP		179	63		96.1
			DHA-PIP + DHA		174			98.3
			MAS3		176			94.9
Ashley et al. (2005)	Thailand	RCT	DHA-PIP (DP3)	P.f or mixed	170	63	100	99.4
			DHA-PIP (DP4)		163		100	100
			MAS3		166		98.8	95.7
Tangpukdee et al. (2005)	Thailand	RCT	MAS3	P.f	60	28	100	No genotyping
			DHA-PIP (DP3)		120		99	
Smithuis et al. (2006)	Myanmar	RCT	DHA-PIP (supervised)	P.f or mixed	156	42	99	99
			DHA-PIP (unsupervised)		171		99	99
			MAS3 (supervised)		162		100	99
			MAS3 (unsupervised)		163		100	100
Mayxay et al. (2006)	Lao PDR	RCT	MAS3	P.f or mixed	110	42		99
			DHA-PIP (DP3)		110			100
Karema et al. (2006)	Rwanda	RCT	DHA-PIP (DP3)	P.f	252	28	90.4	95.2
			AS + AMO		252		82.1	92
			SP + AMO		258 (children)		74.1	84.7

[a] SAT: single-arm trial; RCT: randomized controlled trial.
[b] DHA-PIP: dihydroartemisinin-piperaquine; DHA-PIP + TMP: DHA-PIP + trimethoprim (Artecom®); MAS3: artesunate + mefloquine; DHA-PIP + TMP + primaquine: DHA-PIP + TMP + primaquine (CV8); AP: atovaquone-proguanil (Malarone); DHA-PIP + AS: DHA-PIP + artesunate; DHA-PIP + DHA: DHA-PIP + dihydroartemisinin; AS + AMO: artesunate + amodiaquine; SP + AMO: sulfadoxine-pyrimethamine + amodiaquine; DP3: three-dose regimen; DP4: four-dose regimen.
[c] P.f: *Plasmodium falciparum*; P.v: *Plasmodium vivax*.
[d] Not done.

with a four-dose regimen being used in nine studies and a three-dose regimen in five studies (Ashley et al., 2005 compared the three-dose and four-dose regimens). In addition four studies dosed by age rather than weight (Denis et al., 2002; Hien et al., 2004; Hung et al., 2004; Karunajeewa et al., 2004). Two Thai studies gave extra DHA or artesunate to some of the patients receiving DHA-PIP to investigate whether the cure rate could be enhanced with more artemisinin derivative. The methods used to obtain information on tolerability and safety, i.e. active detection versus

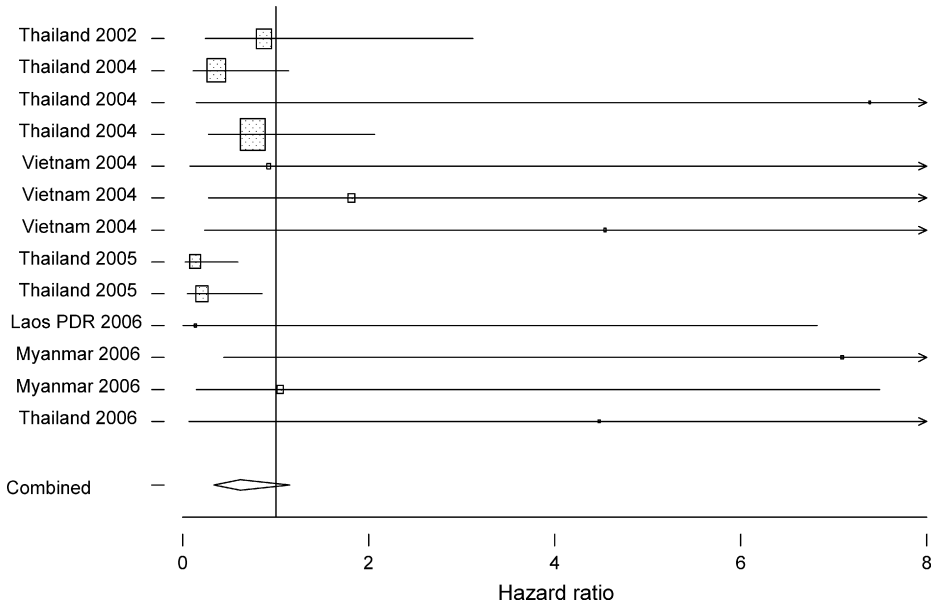

Figure 1 Cure rates of dihydroartemisinin-piperaquine (DHA-PIP) versus mefloquine-artesunate (MAS3) in comparative studies. The size of boxes is proportional to number of events in individual treatment arms and thus contribution to overall effect. The diamond represents overall odds ratio and 95% CI.

passive reporting were not obvious in the majority of the publications. There were no studies in pregnant women.

3.1. Efficacy

The efficacy in these studies of DHA-PIP in multidrug-resistant falciparum malaria was excellent, with overall 28-day cure rates or Kaplan-Meier derived estimates of ~97—98% ($n = 2636$) in China, Cambodia, Myanmar, Laos PDR, Thailand and Vietnam (Table 1). In the comparative studies the efficacy of DHA-PIP was as good as MAS3 (Figure 1) and it was better than artesunate + amodiaquine and sulfadoxine-pyrimethamine + amodiaquine in Rwanda.

With such high cure rates it has not been possible to show superiority against the artesunate-mefloquine comparator arm, or to identify or characterize the determinants of treatment failure (Stepniewska and White, 2006). PCR-corrected efficacy exceeded 96% in the studies with longer follow-up, i.e. with 56 days in Vietnam and 63 days in Thailand. There was concern that the dose of DHA might not be optimal but efficacy was not improved by the addition of more DHA or artesunate in two Thai studies (Ashley et al., 2004). The *P. falciparum* recrudescences and new infections all occurred between days 28 and 35 in one Vietnamese study, whereas in the Thai studies the majority of patients' recrudescences appeared between days 43 and 63 with a median (range) time to recrudescence of 56 (28—63) days (Ashley et al., 2004, 2005; Hien et al., 2004). The lowest efficacy of DHA-PIP reported was 88.6% (80.3—93.7) at 28 days, observed in Rukara, one of the Rwandan sites (Karema et al., 2006). This is a site of high seasonal transmission and thus difficulty in genotype assessment (i.e., reinfections may have been called recrudescence).

3.1.1. *Plasmodium vivax* malaria

In two studies (Hung et al., 2004; Karunajeewa et al., 2004) where DHA-PIP was used to treat 20 patients with vivax malaria monoinfections, and in other studies reporting the treatment of 186 patients with mixed falciparum and vivax infections, it was highly efficacious, suppressing the first vivax relapse at around 3 weeks (as does chloroquine) but not providing radical cure. Thus relapse usually appeared 6 or more weeks after treatment.

3.2. Effectiveness

One study (in Myanmar) assessed effectiveness by comparing observed with non-observed (on the second and third days) treatment. Efficacy and effectiveness were identical with an overall PCR-corrected failure rate on day 42 of 0.6% (95% CI 0.2—2.5) for DHA-PIP and 0% (0—1.2) for MAS3 ($P = 0.16$) (Smithuis et al., 2006). Capillary blood concentrations of piperaquine taken on day 7 were also similar in the two groups supporting the good adherence inferred from the study results (Smithuis et al., 2006).

3.3. Safety

The safety of DHA-PIP was reported in all 14 clinical trials. DHA-PIP was well tolerated in adults and children. Just as efficacy was similarly high in all trials, reported adverse events were similarly low. From 2002 to October 2006, a total of 2636 patients in 13 studies were exposed to DHA-PIP for the treatment of multidrug-resistant uncomplicated *P. falciparum* (and *P. vivax*) malaria in whom safety endpoints were reported. The main adverse events reported are shown in detail in Table 2.

Adverse events were defined conventionally as symptoms, not present at baseline, which appeared after treatment started. Some papers mentioned 'possible drug adverse effects' which may have been malaria-related. Dizziness was the most frequently reported adverse event occurring in between 0.4% and 31.8% patients in (1/252

Table 2 Summary of adverse events following treatment with dihydroartemisinin-piperaquine

Study/site	Nausea	Vomiting	Anorexia	Dizziness	Headache	Diarrhoea	Abdominal pain	Sleep disturbance	Neuropsychiatric adverse events	Cardiovascular dysfunction	Haematological dysfunction	Hepatological dysfunction	Dermatological adverse events	Total no. of evaluated patients
Denis et al. (2002) Cambodia	5 (4.7)	NR	4 (3.8)	5 (4.7)	0 (0)	5 (4.7)	5 (4.7)	NR	NR	NR	NR	NR	1 (0.9)	106
Wilairatana et al. (2002) Thailand	8 (3.4)	0 (0)	NR	11 (4.7)	9 (3.8)	NR	NR	0 (0)	0 (0)	NR	NR	NR	NR	234
Ying et al. (2003) China	3 (5)	1 (1.6)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	60
Hien et al. (2004) Vietnam	8 (2)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	399
Karunajeewa et al. (2004) Cambodia	NR	NR	NR	NR	NR	NR	NR	NR	NR	0 (0)	0 (0)	0 (0)	NR	62
Hung et al. (2004) Cambodia	3 (4)	NR	1 (1)	12 (14)	30 (36)	NR	9 (11)	1 (1)	NR	NR	NR	NR	NR	80
Giao et al. (2004) Vietnam	NR	NR	NR	NR	1 (1.2)	NR	NR	NR	NR	NR	NR	NR	1 (1.2)	82
Ashley et al. (2004) Bangkok, Thailand	11 (9.3)	NR	NR	9 (7.6)	12 (10.2)	NR	NR	NR	NR	NR	NR	NR	NR	118
Ashley et al. (2004) Mae Sot, Thailand	30 (8.5)	18 (1.7)	NR	51 (14.5)	NR	20 (5.7)	35 (9.9)	20 (7.4)	NR	0 (0)	0 (0)	0 (0)	1 (0.3)	353
Ashley et al. (2005) Thailand	37 (11.1)	23 (6.9)	NR	37 (11.1)	NR	33 (9.9)	28 (8.4)	42 (12.6)	NR	NR	NR	NR	3 (0.9)	333
Tangpukdee et al. (2005) Thailand	5 (4.2)	0 (0)	0 (0)	4 (3.3)	4 (3.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	120
Smithuis et al. (2006) Myanmar	39 (11.9)	6 (1.8)	10 (8.3)	104 (31.8)	0 (0)	11 (9.2)	3 (0.9)	0 (0)	NR	NR	0 (0)	NR	0 (0)	327
Mayxay et al. (2006) Lao PDR	6 (5.5)	3 (3)	10 (9)	12 (11)	11 (10)	8 (7)	12 (11)	17 (15.5)	0 (0)	NR	NR	NR	0 (0)	110
Karema et al. (2006) Rwanda	2 (0.8)	5 (2)	3 (1.2)	1 (0.4)	2 (0.8)	8 (3.2)	6 (2.4)	0 (0)	0 (0)	NR	NR	NR	0 (0)	252

NR: not reported.
Data are given as *n* (%).

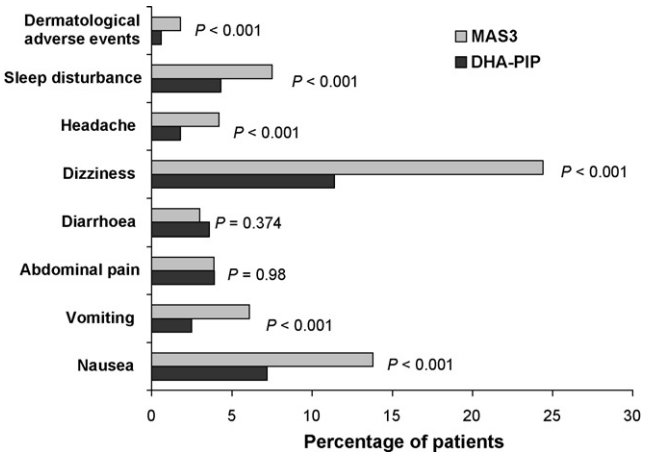

Figure 2 Adverse events in dihydroartemisinin-piperaquine (DHA-PIP) treatment groups versus artesunate-mefloquine (MAS3) treatment groups in eight studies.

children in Rwanda and 104/327 in Myanmar) respectively. Gastrointestinal adverse events were also relatively commonly reported adverse events in the DHA-PIP treatment groups (see below). No patients reported neuropsychiatric problems (Table 2). This suggested an upper 95% CI for the actual incidence of neuropsychiatric reactions, if indeed they occur at all, of <1 in 600.

As treatment, DHA-PIP was generally better tolerated than the comparator groups, which in most studies were the MAS3 combination (Figure 2). For example in Vietnamese patients, only 2% (3/157) and 3% (5/166) reported adverse effects in the DHA-PIP-trimethoprim and DHA-PIP groups respectively compared with 16% (12/77) in the MAS3 group ($P = 0.002$) (Hien et al., 2004). In the study in Laos the proportion of patients with at least one adverse event was also higher in the MAS3 group (64/110; 58%) than in the DHA-PIP (48/110; 44%) group ($P = 0.03$) (Mayxay et al., 2006). The only potentially serious adverse effects of artemisinin derivatives reported to date are rare type 1 hypersensitivity reactions; two reports from Thailand reported urticaria occurring in four patients treated with DHA-PIP (Ashley et al., 2004, 2005).

3.4. Gastrointestinal adverse events

The frequency of early vomiting was reported in nine studies. This ranged from 1.6% to 6.9%, a rate similar or less than with mefloquine regimens. The only adverse events which were reported as occurring with a higher frequency following DHA-PIP treatment compared with MAS3 were abdominal pain and diarrhoea (Figure 2). In one study on the western border of Thailand, non-severe abdominal pain occurred more frequently in the DHA-PIP group than the MAS3 group; 12.3% (22/179) patients compared to 5% (8/176; $P = 0.025$) (Ashley et al., 2004). In other studies the median (range) proportion of patients reporting abdominal pain was 6.6% (4.7—11%) (Ashley et al., 2005; Denis et al., 2002; Hung et al., 2004). Diarrhoea within the first 28 days of follow-up was reported by 12% of patients in the four-dose DHA-PIP regimen compared with 5% in the MAS3 group, and 8% in a three-dose DHA-PIP regimen (equivalent total dose DHA-PIP in the two regimens). The difference between the MAS3 and a four-dose DHA-PIP regimen was statistically significant ($P = 0.026$) (Ashley et al., 2005). Diarrhoea occurred mainly on days 1—3 after treatment and was mild. The median (range) percentage of patients with post-treatment diarrhoea was 5.2% (4.7—9.9%) overall in these studies (Ashley et al., 2004, 2005; Denis et al., 2002).

3.5. Miscellaneous

In a Cambodian study, 46% of all patients reported one or more symptoms between day 1 and day 28 (Denis et al., 2002). In another Cambodian study, 18% of patients reported symptoms during the 32-h dosing period that were not reported on day 0. Headache, dizziness and nausea were reported on the first day of treatment (Hung et al., 2004). In a Vietnamese study dry mouth and itching without visible abnormalities were reported in one patient and headache in another patient in the DHA-PIP (with trimethoprim and primaquine) group (Giao et al., 2004).

3.6. Laboratory tests

Five studies (1195 patients) reported biochemical parameters. Changes in complete blood count, white cell count, plasma glucose and haematocrit between days 0 and 7 were reported in three studies ($n = 748$). In one Thai study, there was a decrease in haematocrit between days 0 and 7, followed by recovery (Ashley et al., 2005). This is the common pattern observed after malaria treatment in low transmission settings and was not different to observations following treatment with the comparator drugs. The large study in Myanmar reported a similar mean increase in haemoglobin between the DHA-PIP and artesunate-mefloquine groups ($P = 0.12$) (Smithuis et al., 2006). In the Cambodian study, the haematocrit remained unchanged throughout the period of monitoring (34.2% at baseline vs. 34.6% at 72 h: $P > 0.1$) (Karunajeewa et al., 2004). No changes in white blood cell counts were reported. Minor fluctuations in liver function tests following treatment in some patients ($n = 691$), which returned to normal by day 7.

3.7. Electrocardiographic findings

In the Cambodian study ($n = 62$; 30 adults, 32 children) there was significant lengthening of the mean QTc at 24 h compared with baseline status ($P = 0.003$) but non-significant lengthening at 48 h when piperaquine levels would have been higher ($P = 0.105$). However, in no patients at any time after treatment was started was the QTc increased to >60 ms and no other arrhythmias or ECG abnormalities were observed (Karunajeewa et al., 2004). On the western border of Thailand, a total of 32 patients in DHA-PIP group had serial ECGs performed. Five patients had a prolonged QTc calculated by the machine at any time point, with a median increase of 2 ms of the QTc, compared with that at baseline and at 52 h (i.e. 4 h after the final dose of treatment). Checking these values manually found only one to be slightly prolonged (Ashley et al., 2004). These data do not suggest any clinically significant effects on myocardial electrophysiology at therapeutic doses.

3.8. Pregnancy exposures

There were two inadvertent pregnancy exposures in the Thai studies, both in the first trimester. A 36-year-old woman at 11 weeks of gestation had a threatened abortion 9 weeks after drug exposure but went on to deliver a 2.5-kg healthy male infant (Ashley et al., 2004). The second was in a 26-year-old multiparous Burmese woman with a date of conception estimated from an 18-week ultrasound to be 1 day after the final dose of DHA-PIP. A 2.3 kg male infant was delivered at home at 41 weeks gestation. Findings of routine examination were normal, apart from the low birth-weight, a feature of malaria in pregnancy (Ashley et al., 2005).

3.9. Serious adverse events

A number of serious adverse events have been reported following treatment with DHA-PIP, although they were all considered to be unrelated to the drug toxicity. These include five deaths, three in studies from Thailand, one from a study in Myanmar, and one from a study in Cambodia. Of the two adult deaths one was considered to be from severe malaria, and therefore represents treatment failure, and one was from gunshot wounds. The other three were in children and considered to be from bacterial sepsis ($n = 2$) and bacterial meningitis.

4. Discussion

This review summarized the findings of 14 studies which enrolled more than 2600 adults and children (including 252 children aged 12—59 months). Only published trials were reviewed, although we consider publication bias in favour of the drug to be unlikely given the limited availability of the combination for trial use and its relative novelty. We think it is very unlikely that trials were conducted during the period of review which were not reported. The studies were conducted mainly in Southeast Asia ($n = 11$), but also in China ($n = 1$) and Africa (Rwanda) ($n = 1$). The DHA-PIP combinations were consistently found to be highly efficacious and well tolerated. Notably, DHA-PIP was highly effective against multidrug-resistant falciparum malaria in Asia. The lowest efficacy reported was in Rwandan children. Clearly more information on efficacy is needed from Africa in children and in high transmission settings to define both the efficacy and period of post-treatment prophylaxis. More information on the pharmacokinetics of piperaquine in children is also needed to ensure optimum dose regimens are advised in this important group.

DHA-PIP has some advantages over MAS3, which is the standard drug of choice for treatment of uncomplicated multidrug-resistant falciparum malaria in many parts of Asia. It is a fixed-dose coformulation (although a fixed-dose formulation of MAS3 will soon be available), which improves adherence. It is better tolerated, and it is currently considerably less expensive. The safety profile of the artemisinin derivatives is now well characterized. Rare type 1 hypersensitivity reactions are well recognized, and patients with urticarial reactions should not receive these drugs again. Concerns over central nervous system and haematological toxicity have receded. Indeed their excellent safety and efficacy profiles have made them a prime target for counterfeiters. The therapeutic index of piperaquine still remains poorly defined. The most common possibly drug-related side effects of DHA-PIP found in clinical trials were gastrointestinal reactions. Abdominal discomfort was known in China as a dose-limiting adverse effect, and is therefore not unexpected, although it is also a feature of acute malaria. The reported incidence ranged from 1 to 11%. The incidence of nausea and vomiting were about 6% and 2% respectively. Similar rates are reported with other antimalarials. Quinoline antimalarial drugs are potentially cardiotoxic; specifically some members of this class cause prolongation of the electrographic QRS and QT intervals (Hien and White, 1993; Touze et al., 2002). Although piperaquine is structurally related to chloroquine and quinine, no clinically significant electrocardiographic, cardiovascular or metabolic effects (especially on plasma glucose) have been observed (Karunajeewa et al., 2004).

As has been observed in other reviews of antimalarials, safety reporting varied considerably and was not standardized. WHO-endorsed guidelines could improve this, judging by the widespread adoption of their standard efficacy protocols. There have been no prospective assessments of DHA-PIP in pregnant women. There are concerns over the safety of artemisinin derivatives in the first trimester of pregnancy, although increasing confidence of safety in the second and third trimesters (McGready et al., 2001; WHO, 2003). Preclinical testing with piperaquine has raised no specific concerns for pregnancy so DHA-PIP may be a potential antimalarial for pregnant women, but clearly prospective studies of pharmacokinetics, efficacy, and safety are needed.

This review presents available evidence from prospective studies in over 2600 patients which suggests that DHA-PIP is a safe, well tolerated, highly efficacious fixed-dose antimalarial combination treatment that could make an important contribution to the control of multidrug-resistant falciparum malaria. Its current low price makes it an attractive proposition for antimalarial treatment and its prolonged suppression of reinfections, whilst making it vulnerable to the spread of resistance, does make it a promising candidate for intermittent presumptive/preventive therapy. Despite accumulating evidence of efficacy and safety, countries relying on external funding to change their antimalarial treatment policy to an ACT are not able to consider DHA-PIP as an option. This is because manufacturing processes have not been recognized as meeting international GMP standards. This is being rectified, and GMP formulations are likely to be available in the near future. Resistance to piperaquine developed in China before and prospective monitoring of efficacy of the combination in areas where it is deployed is strongly recommended. Further efficacy studies are needed from high transmission settings and pharmacokinetic studies are needed especially in children and pregnant women, and detailed large scale adverse event reporting (phase 4 assessment) are recommended to confirm that rare adverse effects do not arise.

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Ethical approval: Not required.

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