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MINIREVIEW

Clindamycin as an Antimalarial Drug: Review of Clinical Trials

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Clinical trials from the 1970s and 1980s have shown the efficacy, safety, and practicability of the treatment of *Plasmodium falciparum* malaria with clindamycin. Two reviews from the early 1990s have summarized these studies in detail (24, 25). Since then, interest in clindamycin as an antimalarial has renewed and a number of recent clinical trials have evaluated clindamycin, both alone and as a partner in a combination, as a treatment for malaria.

This minireview summarizes the data on the drug, with special attention given to developments during the last 10 years. Since no studies with animals and few in vitro studies have been published since publication of the last review, this minireview will concentrate on human clinical trials.

PROPERTIES OF CLINDAMYCIN

Clindamycin (7-chloro-lincomycin) is a semisynthetic derivative of lincomycin and was introduced in the 1960s as an antibiotic.

It is available as clindamycin hydrochloride for oral administration in capsules, as clindamycin phosphate for intramuscular or intravenous injection, and as clindamycin palmitate for oral suspensions.

When given orally, clindamycin is well absorbed and peak concentrations are found after about 45 min. It is metabolized into three major, biologically active derivatives and is mainly excreted into the bile, with about 20% excreted by the kidneys (64). The normal elimination half-life of about 2 to 4 h is not altered in patients with severe renal disease, but impaired liver function leads to a prolongation of elimination (13).

The activity of clindamycin against anaerobic bacteria makes it an important agent in clinical practice (13). Furthermore, it is active against organisms such as *Plasmodium*, *Toxoplasma*, *Babesia*, and *Pneumocystis* spp. Clindamycin is the drug of choice for prophylaxis of *Toxoplasma* chorioretinitis in newborn infants (59) and is part of recommended regimens against both *Babesia microti* and *Babesia divergens* (23). In combination with pyrimethamine or primaquine, it is an alternative regimen for the treatment of toxoplasmosis and pneumocystosis, respectively (17, 59).

In vitro, clindamycin and its three major metabolites show strong inhibitory effects on *P. falciparum* (57), possibly by targeting the apicoplast (16). The drug accumulates slowly in the parasite (18). This is reflected in dose-response curves that show a plateau effect at concentrations above 0.01 μg/ml and demonstrates that a relevant inhibition can be achieved only through an exposure over more than 3 days (57). This could explain the slow onset of clinical action seen in vivo.

CLINDAMYCIN MONOTHERAPY

Since the first report of the successful treatment of falciparum malaria with clindamycin in 1975 (11), a total of more than 500 patients have been reported to have received antimalarial treatment with clindamycin alone. These studies, conducted in Africa, South America, and Southeast Asia, are summarized in Table 1. The study populations include semi-immune and nonimmune adults as well as a small number of children.

The following properties of clindamycin monotherapy for falciparum malaria are apparent from these trials. (i) Clindamycin monotherapy is an effective treatment. It must, however, be given for at least 5 days and at least twice daily. Analysis of all published studies that have used this regimen shows that clindamycin monotherapy has a mean efficacy of 98%. (ii) Clindamycin is well tolerated, and adverse events are mild and self-limiting. The adverse events encountered in all published trials correspond to the adverse event profile of clindamycin when it is used for the treatment of bacterial infections. Gastrointestinal side effects like diarrhea are most frequent, with perioral rashes reported as well. In all patients who have received the drug as an antimalarial, two cases of diarrhea probably due to *Clostridium difficile* toxin were reported (28). (iii) Clindamycin is a slowly acting drug. In the trials mentioned above, the overall mean parasite clearance time was in the range of 4 to 6 days. This compares unfavorably with the parasite clearance times of other antimalarials, which lie between 2 and 3 days (19) or which are even about 1 day in the case of artesunate (21). Correspondingly, with clindamycin treatment the rate of clinical cure is slow, with fever clearance times in the range of 3 to 5 days.

Clindamycin monotherapy for falciparum malaria cannot be recommended. The slow onset of action makes it potentially dangerous in cases in which fast parasite clearance is necessary, such as in children and nonimmune adults. Since clinical cure is delayed as well, it should also not be given to semi-immune individuals when other options are available. The combination of clindamycin with a fast-acting drug is necessary to take advantage of its full antimalarial potential.

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TABLE 1. Clinical trials[a] of clindamycin monotherapy against *P. falciparum* malaria

Study details					Regimen					Efficacy (%)	Reference
Yr	Place	Design[c]	Population[d]	*N*[e]	Dosage, form[b]	No. of doses/day	No. of days	Route[f]	Dosing[g]		
1975	United States	WHO	A	3	450 mg, salt	3	3	p.o.	No	100	11
1975	Thailand	WHO	A	10	450 mg, salt	3	3	p.o.	No	50	20
1981	Brazil	WHO	A	17	10 mg/kg, salt	2	3	i.v.	No	65	1
1981	Brazil	WHO	A	14	10 mg/kg, salt	2	7	i.v. + p.o.	Yes	100	1
1982	Brazil	WHO	A	26	10 mg/kg, salt	2	5	i.v., p.o.	Yes	100	2
1982	Philippines	WHO	A	24	300 mg, salt	2	7	i.v. + p.o.	Yes	100	53
1982	Philippines	WHO	A	12	600 mg, salt	2	7	i.v. + p.o.	Yes	100	53
1982	Philippines	WHO	A	12	10 mg/kg, salt	2	7	i.v. + p.o.	Yes	100	7
1982	Philippines	WHO	A	19	20 mg/kg, salt	2	3	i.v.	No	89	7
1984	Columbia	WHO	A	6	20 mg/kg, salt	2	3	i.v.	No	100	52
1984	Columbia	WHO	A	9	10 mg/kg, salt	2	7	i.v. + p.o.	Yes	100	52
1984	Columbia	WHO	A	5	20 mg/kg, salt	2	7	i.v.	Yes	100	52
1984	Columbia	WHO	A	10	20 mg/kg, salt	1	7	i.v.	No	100	52
1985	Sudan	WHO	A	20	5 mg/kg, salt	2	5	p.o.	Yes	90	15
1988	Brazil	WHO[h]	A, C	129	10 mg/kg, salt	2	5–7	p.o., i.v. + p.o., i.m.	Yes	97	40
1988	Brazil	WHO[h]	A, C	16	10 mg/kg, salt	1	5–7	p.o., i.v. + p.o.	No	50	40
1988	Brazil	WHO[h]	A, C	35	2.5 mg/kg, salt	1	5	p.o.	No	80	40
1989	Brazil	WHO	A	35	5 mg/kg, base	2	5	p.o.	Yes	100	27
1990	Philippines	WHO, RCT	A	31	300 mg, salt	2	5	p.o.	Yes	100	56
1990	Philippines	WHO, RCT	A	10	600 mg, salt	2	5	p.o.	Yes	100	56
1993	Gabon	WHO, RCT	A	38	5 mg/kg, base	2	5	p.o.	Yes	97	56
1994	East Timor	WHO	A	30	300 mg, salt	2	5	p.o.	Yes	100	44

[a] Data from two reports (30, 43) of studies with single subjects are not included.
[b] Eight milligrams of clindamycin hydrochloride salt is equivalent to 5 mg of base.
[c] WHO, study conducted according to World Health Organization guidelines (67). RCT, randomized controlled trial.
[d] Pop., study population; A, adults; C, children.
[e] *N*, number of subjects.
[f] i.v., intravenous; p.o., oral; i.v. + p.o., intravenous followed by oral administration; i.m., intramuscular.
[g] Adaequate dosing (i.e., given at least twice daily and more than 3 days).
[h] Short follow-up period (1 to 3 weeks) in most subjects.

QUININE-CLINDAMYCIN COMBINATIONS

Quinine, with its fast action and short elimination half-life, makes an ideal partner for clindamycin. In addition, in vitro studies have shown a synergistic or additive effect when the two drugs are used in combination, depending on the strain investigated (51, 57). The levels of both drugs in plasma are unchanged by coadministration (43). The combination was first evaluated clinically in small trials conducted in the United States and Thailand during the 1970s (11, 20, 43). Interest renewed only 20 years later with a series of studies conducted in Gabon.

To date, a total of eight clinical trials which include follow-up with an appropriate number of patients have been published. The study subjects included children, pregnant women, and both semi-immune and nonimmune adults. Table 2 summarizes the trials that were conducted according to World Health Organization guidelines. According to these guidelines, follow-up is done daily until the disappearance of the parasitemia and weekly for a total of 4 weeks or until the reappearance of parasitemia (67). In addition to these trials, several reports of studies that evaluated the treatment of malaria with clindamycin in combination with quinine or quinidine but that did not include a follow-up period have been published (5, 6, 8, 36, 38, 55). Even though efficacy cannot be assessed from these reports, they do show the wide acceptance that the combination has found for routine treatment. The largest of the studies described in these reports summarizes data for 69 travelers with severe *P. falciparum* malaria treated with quinine plus clindamycin (35).

Taken together, these studies have established the combination as an efficient and practicable option for the treatment of malaria. The most important feature of the combination is that it allows a reduction in the treatment time. Whereas quinine must be given for at least 7 days and clindamycin must be given for at least 5 days to achieve a reasonably high cure rate, the combination is effective, at least in the African trials, when it is administered for only 3 days. Since any treatment that lasts longer than the clinical symptoms of malaria is associated with poor compliance, a short duration of treatment is an important condition for general acceptance of the drug. In addition, frequent adverse effects of quinine (cinchonism) make a short course of quinine necessary. The addition of tetracycline or doxycycline to quinine can effectively reduce the treatment time as well. However, in contrast to clindamycin, the use of both drugs is contraindicated in children and pregnant women. For children with severe malaria a 4-day regimen (31) is preferable to a 3-day regimen, since the time to parasite clearance is correlated to the initial parasite load and over 60% of the subjects in the study with African children initially had hyperparasitemia (31, 65). In two studies conducted in Thailand, the drugs were administered three or four times daily for 7 days. Further clinical trials in this region should evaluate if shorter and simpler regimens are equally effective.

The question of whether the combination can improve par-

TABLE 2. Clinical trials of clindamycin plus quinine against *P. falciparum* malaria

Study details					Regimen							Efficacy (%)	Reference
					Clindamycin		Quinine						
Yr	Place	Design[b]	Pop.[c]	*N*[d]	Dosage, form[a]	No. of doses/day	Dosage	No. of doses/day	Route[e]	Days	Dosing[f]		
1974	United States	WHO	A	5	450 mg, salt	4	540 mg	3	p.o.	3	Yes	100	43
1975	United States	WHO	A	5	450 mg, salt	3	560 mg	3	p.o.	3	Yes	60	11
1975	United States	WHO	A	2	600 mg, salt	1	560 mg	3	p.o.	3	No	50	11
1975	Thailand	WHO	A	4	450 mg, salt	3	540 mg	3	p.o.	3	Yes	100	20
1975	Thailand	WHO	A	5	150 mg, salt	3	270 mg	3	p.o.	3	No	60	20
1988	Brazil	WHO, RCT	A	40	10 mg/kg, base	2	12 mg/kg	2	p.o.	3	Yes	90	28
1994	Gabon	WHO, RCT	C	34	5 mg/kg, base	2	12 mg/kg	2	p.o.	3	Yes	88	32
1995	Gabon	WHO, RCT	C[g]	50	5 mg/kg, base	3	8 mg/kg	3	i.v.	4	Yes	96	31
1995	Gabon	WHO, RCT	A	40	5 mg/kg, base	2	12 mg/kg	2	p.o.	3[h]	Yes	92	41
1997	Gabon	WHO[i]	C	161	8 mg/kg, salt	2	8 mg/kg	2	p.o.	3	Yes	97	62
2000	Thailand	WHO, RCT	A	68	5 mg/kg, base	4	8 mg/kg	3	p.o.	7	Yes	100	50
2001	France	WHO, RCT	A	53	5 mg/kg, salt	3	8 mg/kg	3	i.v.	3	Yes	100	45
2001	Thailand	WHO, RCT	P	65	5 mg/kg, NS[j]	3	8 mg/kg	3	p.o.	7	Yes	100	37

[a] Eight milligrams of clindamycin hydrochloride salt is equivalent to 5 mg of base.
[b] WHO, study conducted according to World Health Organization guidelines (67); RCT, randomized controlled trial.
[c] Pop., study population; A, adults; C, children; P, pregnant women.
[d] *N*, number of subjects.
[e] i.v., intravenous; p.o., oral.
[f] Adaequate dosing (i.e., clindamycin given at least twice daily and more than 3 days).
[g] Severe malaria.
[h] Quinine was administered for only 1.5 days.
[i] Short follow-up (3 weeks).
[j] NS, not specified.

asite and fever clearance times cannot be answered with certainty. Two of the randomized controlled trials have found a faster parasite clearance with the combination in comparison to that with quinine monotherapy, whereas three of the randomized controlled trials could not find a difference. Similarly, two of the studies reported a faster clearance of fever from the combination group and two found no difference. Faster parasite clearance times by use of the combination might be a phenomenon found primarily in patients with high initial parasitemias (65), as seen in the children with severe malaria in the Gabonese study (31). However, a faster parasite clearance time does not necessarily lead to lower rates of mortality, and it is not known whether the addition of clindamycin to quinine may reduce the rate of mortality.

In summary, a regimen of 5 mg of clindamycin kg of body weight plus 10 mg of quinine base per kg every 12 h for 3 days may be an excellent option for the treatment of uncomplicated malaria in Africa and other areas with low-grade resistance to antimalarial drugs. A 4-day treatment with a loading dose and subsequent administration every 8 h is appropriate for patients with very high initial levels of parasitemia and severe malaria. In areas with multiresistant parasites, such as Thailand, the duration possibly needs to be prolonged to 5 or even 7 days; however, further studies need to address this question.

CHLOROQUINE-CLINDAMYCIN COMBINATIONS

P. falciparum is highly resistant to chloroquine in most areas of the world. Despite this, it is still widely used and often remains the recommended first-line treatment in areas of Africa where malaria is endemic. The question of whether the addition of clindamycin to chloroquine would substantially improve the cure rate was addressed in a series of studies conducted in Gabon, an area where the rate of chloroquine resistance is high (32). Clindamycin was given at a dosage of 5 mg of base per kg every 12 h for 3 days in all three trials.

Sixty-five children were included in the first trial (32). The addition of clindamycin to a standard regimen of chloroquine (total dose of 25 mg/kg) achieved a cure rate of only 70%, which was nevertheless a considerable improvement over the 9% cure rate achieved with chloroquine alone. In semi-immune adults, the same chloroquine-clindamycin regimen led to a cure rate of 97% (26).

To improve the efficacy of the combination for children, the addition of clindamycin to a high dosage of chloroquine (total dose of 45 mg/kg) was evaluated in 76 patients (42). The high dosage of chloroquine with clindamycin was able to improve the cure rate to 94%, whereas the cure rate was 32% with high-dose chloroquine monotherapy.

In summary, the clindamycin-chloroquine combination is effective and a reasonable treatment option for semi-immune adults in areas with high rates of chloroquine resistance. In nonimmune individuals, a 3-day treatment is effective only together with a dosage of chloroquine that is too high for common use. In practice, therefore, the usefulness of the chloroquine-clindamycin combination is limited.

OTHER COMBINATIONS

No clinical studies have evaluated clindamycin combinations other than those with quinine or chloroquine. Artemisinin derivates such as artesunate seem to be good candidates for combination therapy with clindamycin. Preclinical studies have shown that artemisinin and clindamycin have a weak synergis-

tic effect against an artemisinin-resistant parasite strain but not against a sensitive strain (9). Similar to quinine, artemisinins have short elimination half-lives, act rapidly, and must be given for at least 5 days when administered alone. Clinical studies with a clindamycin-artemisinin combination are warranted.

CLINDAMYCIN AGAINST *P. VIVAX* MALARIA

One study conducted in Brazil has investigated the efficacy of 5 days of clindamycin treatment against vivax malaria (29). The clearance of *Plasmodium vivax* was prolonged compared to that of *P. falciparum*, and recrudescence of *P. vivax* but not of *P. falciparum* was observed in all patients. Similar results were found in another study from Brazil (1). Seven patients with mixed infections were treated with clindamycin, and in comparison to the clearance of *P. falciparum*, the clearance of *P. vivax* was prolonged in four patients and recrudescences were observed in five patients.

A recent study in Thailand investigated the effect of a regimen of 300 mg of clindamycin given four times daily for 7 days. Despite the long treatment time of 7 days, only 7 of 12 subjects (58%) were cured (49).

The antirelapse activity of clindamycin in patients with *P. vivax* malaria was investigated by Clyde et al. (11). Four volunteers were infected with *P. vivax*, treated with chloroquine, and subsequently given a 14-day course of clindamycin. Relapses were observed in all patients.

A study from Thailand reported on 24 patients in whom *P. vivax* reappeared within 28 days of treatment with either quinine (12 patients) or quinine-clindamycin (12 patients) (50). The addition of clindamycin therefore does not improve the effect of quinine against *P. vivax* malaria.

In summary, clindamycin, either alone or in combination with quinine, should not be used for the treatment of *P. vivax* malaria.

CLINDAMYCIN DURING PREGNANCY

Clindamycin is generally considered safe for use by pregnant women (10, 12). The pharmacokinetic properties of clindamycin remain unchanged during pregnancy (47). The drug readily crosses the placenta (46) and is secreted in small amounts into human milk (58).

A recent study with pregnant women compared a quinine-clindamycin regimen against an artesunate regimen and showed high cure rates and the safety of the regimen for both the mothers and the children (37). In addition, three case reports that did not include a follow-up of the mothers or the children have described the use of clindamycin alone (39), quinine-clindamycin (54), or quinidine-clindamycin (48) in pregnant women.

Even though great caution should be used when any drug is given during pregnancy, the risk must be compared to the risk of malaria to the mother and the child during pregnancy. Not only do pregnant women have an increased risk for malaria and malaria attacks are more severe in pregnant women than in nonpregnant women (14), but the child is also at an increased risk for preterm birth and low birth weight (60). Given the low level of efficacy of chloroquine, the frequent side effects of chloroquine therapy, and the low rate of compliance associated with quinine therapy, alternatives are urgently needed. Further clinical trials to assess the efficacy and safety of a simple and short clindamycin-quinine regimen during pregnancy are urgently needed.

SAFETY

Although clindamycin is generally well tolerated, it can lead to the development of *C. difficile*-associated diarrhea, a common complication of antibiotic treatment (66). The risk of developing colitis with clindamycin treatment is similar to the risks with treatment with expanded-spectrum cephalosporins and broad-spectrum penicillins, and the rate of colitis is about 5% among hospitalized patients (4). The risk increases by use of combinations of any of these drugs. The strongest risk factor for the disease is hospitalization, with outpatients having a fraction of the risk compared to that for inpatients (22). Other important factors are concomitant disease, advanced age, and the duration of treatment (3).

C. difficile-associated colitis is rare in subjects taking clindamycin for 3 days or less (61). If clindamycin is discontinued immediately after the appearance of diarrhea, the disease is often self-limiting, and with appropriate treatment, severe morbidity or mortality is extremely rare (34). Children are at far lower risk, and mortality was reported only during the era before identification of the cause of the disease and the introduction of an effective treatment (69).

Few data are available on the prevalence of *C. difficile* in hospitals in regions where malaria is endemic. A study from Zambia suggests that it might be considerably less of a problem than it is in industrialized countries (68).

A 3-day outpatient treatment for malaria would be unlikely to cause severe *C. difficile*-associated colitis, since the majority of patients would be young, otherwise healthy subjects receiving treatment for a short duration as outpatients. However, health professionals and patients should be aware of the risk and know the proper means of management of the disease.

CONCLUSIONS

Chloroquine, the first and last good antimalarial, has become ineffective in most regions of the world. The problem is most serious in Africa, where the rates of mortality and morbidity from this disease are highest. Chloroquine is slowly being replaced by sulfonamide-pyrimethamine combinations in many parts of Africa. While they are effective, inexpensive, and easily administered, it is known that resistance develops rapidly, and high-grade resistance is already observed in parts of East Africa (63). Thus, the search for the next antimalarial for first-line treatment is on, and given the current scarcity of options, the quinine-clindamycin combination is a contender in the race.

Clindamycin plus quinine is not an ideal antimalarial regimen: the need for twice-daily dosing is an obstacle for its general use in areas where malaria is endemic. Given the short half-lives of both clindamycin and quinine and the short treatment course, complete and accurate administration is essential. Assurance that the correct dose has been taken and that dosing has been for the correct duration is thus more important with clindamycin and quinine than with drugs with long

elimination half-lives, such as amodiaquine, sulfadoxine-pyrimethamine, and mefloquine.

The cost of clindamycin limits its usefulness in areas where malaria is endemic. Although several generic formulations are available, a 3-day treatment course would still cost more than sulfadoxine-pyrimethamine, but its cost would compare favorably to that of atovaquone-proguanil or halofantrine. In adults who can safely take doxycycline, its substitution for clindamycin offers no clear advantage or disadvantage. However, for the target population (children and pregnant women), quinine plus clindamycin is an extremely useful antimalarial combination. In recent years, enough clinical data have emerged to advocate wider use of the combination for the treatment of malaria.

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