Drugs of the Future 1999, 24(11): 1203-1211

CCC: 0377-8282/99

Riamet™

Antimalarial

Co-Artemether
CGP-56697
Coartem™

1:6 fixed combination of artemether and lumefantrine (benflumetol)

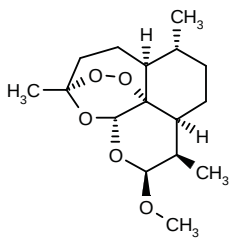
CAS: 141204-94-6

EN: 215966

Artemether+

Rec INN

(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepine



$C_{16}H_{26}O_5$ Mol wt: 298.3830

CAS: 071963-77-4

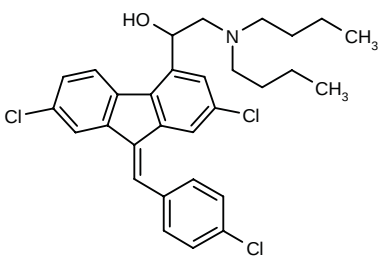
EN: 090712

Lumefantrine

Prop INN

Benflumetol

(±)-(*Z*)-2-(Dibutylamino)-1-[2,7-dichloro-9-(4-chlorbenzylidene)fluoren-4-yl]ethanol



$C_{30}H_{32}Cl_3NO$ Mol wt: 528.9478

CAS: 082186-77-4

EN: 269095

Introduction

Malaria continues to be the most important parasitic infection in humans, causing 300-500 million new cases each year and killing 1 person every 12 seconds (most often a child under 5 years of age). Malaria is an endemic disease in more than 100 countries, where almost 50% of the world population lives, including sub-Saharan Africa, India, Brazil, Sri Lanka, Vietnam, Columbia, Solomon Islands, Southeast Asia and other tropical and subtropical countries. It is caused by several species of *Plasmodium* spread by the bite of an infected female Anopheles mosquito. The parasite incubates in the liver for many months and eventually enters the bloodstream, triggering the disease. The symptoms of malaria include fever, chills, headache, muscle ache and malaise. The diagnosis should be considered in any patient who has been exposed to an endemic area, whatever the presentation. The diagnosis relies on a blood slide, which also indicates the type of malaria.

There are four main species of plasmodia causing malaria: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae*. *P. falciparum* is the most dangerous and is responsible for the highest number of deaths worldwide. It develops rapidly and symptoms appear usually within 2 weeks. Malaria caused by *P. falciparum* is not prone to long-term relapse, whereas *P. vivax* and *P. ovale* can remain quiescent in the liver for months and cause relapses for up to 4 years after exposure.

The current treatment of malaria relies on drugs such as chloroquine, pyrimethamine-sulfadoxine, quinine, mefloquine, halofantrine, amodiaquine or artemisinin. However, the development of resistance of plasmodia to established therapies such as chloroquine, quinine or mefloquine has hindered the control of malaria, making treatment very difficult. Also, mefloquine is contraindicated in patients with severe psychiatric conditions, epilepsy,

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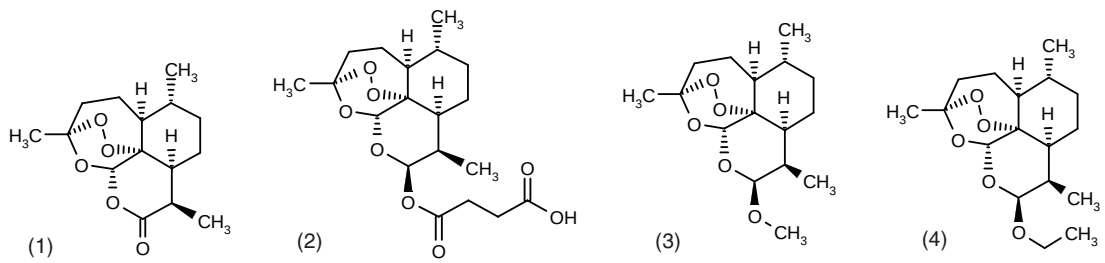
Table I: Chemical structures of antimalarial compounds derived from Artemisa annua.

1. Artemisinin
2. Artesunate
3. Artemether
4. Arteether



arrhythmia or conduction anomalies. Resistant strains of *P. falciparum* are prevalent in Southeast Asia and are increasing elsewhere. Chloroquine-resistant strains of *P. vivax* are also emerging. Furthermore, malaria is prevalent in poor regions where people cannot afford expensive therapies, although cost is less of a problem for travelers and soldiers going to developed countries. These factors have been the impetus for the development of new preventive and curative therapies for malaria, which are urgently needed

New drugs and drug combinations have emerged, including pyronaridine, chlorproguanil-dapsone, atovaquone-proguanil, rectal artesunate and artemether-lumefantrine (1). Most of these new drugs and drug combinations contain artemisinin derivatives. Artemisinin is a naturally occurring compound extracted from Artemisia annua, a traditional Chinese herbal remedy for malaria, from which artesunate, artemether and arteether are derived (Table I). Co-artemether is a 1:6 fixed combination of artemether (20 mg) and lumefantrine (120 mg) (2). Lumefantrine is a highly lipophilic, synthetic racemic fluorene mixture that acts similarly to quinine, mefloquine and halofantrine and has schizontocide activity.

Lumefantrine and its combination with artemether was discovered by the Institute of Microbiology and Epidemiology of the Academy of Military Medical Sciences (AMMS) in Beijing and has been registered in China since 1992. Co-artemether is being codeveloped by Novartis Pharma AG for international registration and marketing as a joint venture with AMMS. Kunming Pharmaceutical Corporation manufactures artemether and is another partner in the joint venture.

Pharmacological Actions

Artemisinin derivatives are endoperoxide serquiterpene drugs derived from artemisinin that exert their antimalarial activity against the blood stage of the parasite through the formation of alkylating free radicals generated in the presence of the heme group in the digestive vacuole of the malaria parasites, the organelle wherein hemoglobin is degraded. This induces parasite death by preventing polymerization of the toxic heme moiety into inert polymeric hemoglobin (3-7).

Artemisinin derivatives are rapidly acting drugs which are effective against chloroquine-resistant plasmodia. When used as a single drug, artemether rapidly reduces parasitemia, although the recrudescence rate is high.

Lumefantrine exerts its antimalarial activity by interacting with the heme group, the degradation product of hemoglobin metabolism. Its structural similarities with mefloquine and halofantrine suggest potential cross-resistance.

The combination of the two drugs with different but complementary modes of action represents a major advance in the management of malaria, including prophylaxis and treatment of established cases while reducing the risk for parasite resistance development. The efficacy of co-artemether against plasmodia is due to its ability to break the reproductive cycle of the parasite by means of a gametocidal effect that halts disease progression and reduces transmission.

Pharmacokinetics and Metabolism

Artemether is absorbed rapidly with a fairly low bioavailability (~30%) which can be somewhat enhanced when taken with a fat-rich meal. Upon absorption, artemether is rapidly converted to dihydroartemisinin through the cytochrome CYP3A4. Peak concentrations of artemether and the active metabolite are reached at 1.8 and 1.2 h after ingestion, respectively, and are eliminated with a half-life of 0.84 and 0.43, respectively. Lumefantrine has a variable oral bioavailability that increases considerably when administered with a fatty meal. Peak plasma concentrations are reached slowly, at 6-10 h, and the drug is eliminated slowly with a half-life of approximately 4-5 days (8).

The multiple-dose pharmacokinetics of co-artemether administered alone and in combination with lumefantrine were investigated in Chinese patients with uncomplicated *P. falciparum* malaria. In this randomized, double-blind trial, artemether was administered as 20-mg tablets at 0, 8, 24 and 48 h and co-artemether as tablets containing 20 mg artemether plus 120 mg lumefantrine, administered at the same times. In both groups, the peak plasma levels (C_{max}) and AUC of artemether decreased over time, whereas the values for the active metabolite

Table II: Pharmacokinetic properties of co-artemether's individual components when given in fasting or fed state in healthy Asian volunteers (8-10) [Prous Science PKline database].

	Artemether (dihydroartemisinin)		Lumefantrine	
Parameter	Fasting	Fed	Fasting	Fed
Dose (mg)	80	80	480	480
K_a (h^{-1})	0.1 (0.4)		0.4	
$t_{½abs}$	1.9		5.3	
C_{max} (ng/ml)	157 (161)	85 (260)	380	5100
t_{max} (h)	1.7-1.8 (1.2-1.9)		6-10	6
AUC (ng·h/l)	1834 (2926)		6.8	108
t½ (h)	0.8-1.2 (0.4-0.9)		108	
Cl (l/h)	15 (169)		180	

dihydroartemisinin increased over time. In addition, there was evidence of a time-dependent decrease in the bioavailability of artemether. These findings indicate a time-dependent increase in first-pass metabolism of artemether via autoinduction. However, as dihydroartemisinin is also parasiticidal and is more potent than artemether against plasmodia, this change in the drug/metabolite ratio is expected to be clinically irrelevant as regards parasite clearance and cure rates. Finally, lumefantrine had little effect on the pharmacokinetics of artemether, the only difference being a 0.5-h delay in time to peak plasma levels in the presence of lumefantrine, which is also unlikely to have clinical impact (9).

Thus, the main drawback of artemisinin derivatives, including artemether, is the short half-life of the active metabolite (dihydroartemisinin), which favors high recrudescence rates when used alone. Lumefantrine, on the other hand, is a slowly eliminated drug for which antimalarial efficacy is a function of the time during which blood levels exceed inhibitory concentrations. These two factors allow artemether and lumefantrine to act in a synergistic manner against plasmodia.

The pharmacological properties of artemether and lumefantrine when given as co-artemether are summarized in Table II.

Toxicity

Artemisinin derivatives are much less toxic than quinoline antimalarials. Neurotoxicity has been observed in large animals only after high doses. In clinical trials, co-artemether has been well tolerated, with no treatment discontinuations due to adverse events or laboratory abnormalities.

Clinical Studies

Clinical data for co-artemether show that at adequate doses, typical malaria symptoms (parasite count, fever) clear within 36-52 h, with a 28-day cure rate of more than 90% even in areas where malaria parasites have developed resistance to other antimalarial drugs. Co-artemether is well tolerated and can be administered even to small children. This is important as children comprise the largest population at risk of malaria. Co-artemether is indicated for the treatment of malaria, including the emergency treatment of adults and children with malaria due to *P. falciparum* or mixed infections including *P. falciparum* resistant or not to other drugs. Evidence shows that co-artemether is effective even in areas with multidrug resistant malaria.

In a randomized, dose-finding clinical study in Thailand in 260 patients with drug-resistant, microscopically confirmed acute uncomplicated *P. falciparum* malaria or mixed malaria including *P. falciparum*, treatment with co-artemether (4 tablets of 20/120 mg given at 0, 8, 24 and 48 h) gave cure rates of 71.3% at 28 days, with a parasite clearance time of 32 h. This regimen was superior to regimens consisting of 2 tablets at the same time periods or 4 tablets at 0, 8 and 24 h (8) (Box 1).

In an open study in 60 African children with acute uncomplicated malaria due to *P. falciparum*, co-artemether given in 4 doses within 2 days cleared all parasites within 72 h with no neurologic, cardiac or other adverse events. However, second malaria episodes were recorded in 27% of the children by 4 weeks, which in most cases were due to new infections (11) (Box 2).

In another open phase II study, 102 previously untreated patients with *P. falciparum* malaria from an area in China where chloroquine resistance is highly prevalent received treatment with co-artemether for 2 days while being kept for 28 days in a transmission-free hospital. Co-artemether rapidly cleared parasites and fever from most patients within 30 and 18 h, respectively, with a cure rate of 96.1% at 28 days. Only four patients (3.9%) developed recrudescence within 4 weeks (12) (Box 3).

These noncomparative studies demonstrated that co-artemether was safe and effective in the treatment of acute malaria, although it had a lower prophylactic effect at the doses and regimens used. Comparative studies also demonstrated the high efficacy of co-artemether as a therapy for acute uncomplicated *P. falciparum* malaria.

When compared with chloroquine in children from Tanzania, a region with high levels of chloroquine resistance, co-artemether was much more effective and induced resolution of signs and symptoms faster than the reference drug, with no serious drug-related adverse

Box 1: Population pharmacokinetics of co-artemether in malaria patients (8) [Prous Science CSline database].

Design	Randomized, double-blind, dose-finding clinical study
Population	Thailand patients aged over 15 years with microscopically confirmed acute uncomplicated *P. falciparum* malaria or mixed malaria including *P. falciparum* (n = 260)
Treatments	(A) Co-artemether, 80/480 mg p.o. at 0, 8, 24 and 48 h (n = 87) (B) Co-artemether, 40/240 mg p.o. at 0, 8, 24 and 48 h (n = 87) (C) Co-artemether, 80/480 mg p.o. at 0, 8 and 24 h (n = 86)
Withdrawals	A: 6/87; B: 11/87; C: 7/86
Results	Cure rate (%) at 28 days: A (71.3) > C (48.8) ≅ B (47.1) Parasite clearance time (h): B (36) ≥ A (32) = C (32)
Conclusions	Artemether and lumefantrine had complementary pharmacodynamic properties resulting in high efficacy rates

Box 2: Co-artemether in the treatment of children with uncomplicated malaria (11) [Prous Science CSline database].

Design	Open clinical study
Population	Gambian children aged 1-6 years with uncomplicated *P. falciparum* malaria (n = 60)
Treatments	Co-artemether, 10/60 mg p.o. if 5-10 kg, 20/120 mg p.o. if 10-15 kg, 30/180 mg p.o. if 15-20 kg, 40/240 mg p.o. if 20-25 kg at 0, 8, 24 and 48 h
Adverse Events	QTc prolongation 30/60 (50%)
Results	Parasite clearance time (h): 36 Parasite clearance rate (%) at 72 h: 100% Cure rate (%) at 28 days: 71 Recurrence/new infection rate at 4 weeks: 16/60 (27%)
Conclusions	Co-artemether was a safe and effective combination for the treatment of acute *P. falciparum* malaria

Box 3: Efficacy of co-artemether in the treatment of malaria (12) [Prous Science CSline database].

Design	Open clinical study
Population	Chinese patients with previously untreated *P. falciparum* malaria kept for 28 days in a transmission-free hospital (n = 105)
Treatments	Co-artemether, 80/480 mg p.o. at 0, 8, 24 and 48 h
Withdrawals [causes]	3/105 [noncompliance]
Results	Parasite clearance time (h): 30 Parasite clearance rate (%) at 24 h: 99.4 Fever clearance time (h): 18 Cure rate at 28 days: 98/102 (96.1%) Recrudescence rate: 4/102 (3.9%)
Conclusions	Co-artemether was a highly effective and well-tolerated treatment for acute uncomplicated *P. falciparum* malaria in an area in which chloroquine resistance was prevalent

events. Assessment with PCR-RFLP allowed discriminating between recrudescences and new infections. In both arms of the study, patients with subsequent recrudescence had higher initial mean parasite densities. Of interest, the initial values in patients treated with co-artemether were even higher, thus confirming the greater efficacy of this drug combination. The rate of reinfection, which increased over time as expected in an endemic area, was also higher in chloroquine-treated patients. The estimated percentages of patients with new infections at 28 days were 30.1% with co-artemether and 56.1% with chloroquine; the estimated percentages of patients with recrudescences at the same time period were 15.8% and 79.9% (13, 14) (Box 4).

Box 4: Efficacy and safety of co-artemether compared with chloroqine in the treatment of malaria in young children (14) [Prous Science CSline database].

Design	Randomized, open, comparative clinical study
Population	Tanzanian children aged 1-5 years with previously untreated acute *P. falciparum* malaria (n = 260)
Treatments	Co-artemether (Co), 10/60 mg p.o. if 5-10 kg, 20/120 mg p.o. if 10-15 kg, 30/180 mg p.o. if 15-20 kg, 40/240 mg p.o. if 20-25 kg (n = 130) Chloroquine (Ch), 2.5 mg/kg over 3 days (n = 130)
Withdrawals [causes]	118/260 [lack of efficacy 96/260, adverse events 8/260, lost to follow-up 6/260, consent withdrawal 3/260, protocol violation 5/260]; Co: 24/130 (18.5%), Ch: 94/130 (72.3%)
Results	Parasite clearance rate (%) at 1 day: Co (97.8) > Ch (59) [p <0.001], at 2 days: Co (100) > Ch (81.8) [p <0.001], at 3 days: Co (100) > Ch (95.9) [p <0.001] Gametocytes cleared (%) at 6 h: Co (98.5) ≥ Ch (93.1) Hemoglobinopenia (<8.0 g/dl), % change at 14 days: Co (–49.1) > Ch (–27.8) (<6.5 g/dl): Co (–85.5) > Ch (–58.8) Cure rate at 7 days: Co (109/116 [94%]) > Ch (34/96 [35.4%]), at 14 days: Co (95/110 [86.4%]) > Ch (10/97 [10.3%]), at 28 days: Co (63.6%) > Ch (5%) Estimated recrudescence rate (%) at 7 days: Co (2.5) < Ch (68.2), at 14 days: Co (6.8) < Ch (82.6), at 28 days: Co (15.8) < Ch (79.9) Estimated new infection rate (%) at 7 days: Co (1.3) < Ch (24.2), at 14 days: Co (11.4) < Ch (56.2), at 28 days: Co (30.1) < Ch (56.1)
Conclusions	Co-artemether was a highly effective combination against acute *P. falciparum* malaria in children from an area of high malaria transmission rates and very high levels of chloroquine resistance

Box 5: Co-artemether versus quinine in the treatment of malaria in children (15) [Prous Science CSline database].

Design	Multicenter, open, comparative clinical study
Population	Thailand children with uncomplicated *P. falciparum* malaria (n = 219)
Treatments	Co-artemether (Co) for 48 h (n = 111) Quinine (Q) for 8 days (n = 108)
Withdrawals	Co: 37/111, Q: 37/108
Results	Parasite clearing time (h): Co (40) < Q (77) [p <0.001] Gametocytes (%) remaining at 1-3 days: Co (14) < Q (27), at 14 days: Co (1) < Q (13) Cure rate (%) at 28 days: Co (51-87) ≅ Q (56-83)
Conclusions	Co-artemether was similar to quinine as a therapy for acute *P. falciparum* malaria but acted faster on both gametocytes and symptoms

Co-artemether administered for 2 days was similar to an 8-day quinine treatment in the 28-day cure rate in patients with acute *P. falciparum* malaria included in an open clinical study. However, co-artemether not only offered a shorter therapeutic regimen but also acted faster, as demonstrated by the anti-gametocyte activity of both treatments on days 1-3 (15) (Box 5).

In a randomized, double-blind clinical study, co-artemether was compared with mefloquine in the treatment of patients with acute *P. falciparum malaria* from Thailand, a region with a high prevalence of drug resistance. Patients treated with co-artemether showed significantly shorter parasite, gametocyte and fever clearance times than patients treated with mefloquine. However, 28-day cure rates were higher among patients treated with mefloquine (16) (Box 6).

Co-artemether was also compared to halofantrine in the treatment of uncomplicated *P. falciparum* malaria in Dutch and French travelers returning from the tropics. Co-artemether was initially more effective than halofantrine, as determined by measuring the parasite reduction at 24 h and the parasite and fever clearance times (17) (Box 7).

An extension of the same study essentially gave the same results. However, when assessing the 28-day cure rate, which took into account the initial cure and any recrudescence or new infection, the results showed a

Box 6: Co-artemether versus mefloquine in the treatment of malaria (16) [Prous Science CSline database].

Design	Randomized, double-blind, comparative clinical study
Population	Patients over 12 years of age from Thailand with uncomplicated *P. falciparum* malaria (n = 252)
Treatments	Co-artemether (Co), 80/480 mg p.o. at 0, 8, 24 and 48 h (n = 126) Mefloquine (M), 750 mg at 0 h → 500 mg at 8 h (n = 126)
Withdrawals [social reasons]	Co: 12/126, M: 7/126
Results	Parasite clearance time (h): Co (43) < M (66) [p <0.001] Gametocytes: Co (152) < M (331) [p <0.001] Fever clearance time (h): Co (32) < M (54) [p <0.005] Cure rate (%) at 28 days: Co (69.3) < M (82.4) [p = 0.002]
Conclusions	Co-artemether was effective against multidrug-resistant *P. falciparum* malaria; however, higher doses may be required to improve long-term cure rates

Box 7: Co-artemether versus halofantrine in the treatment of malaria (17) [Prous Science CSline database].

Design	Comparative, randomized, double-blind clinical study
Population	French and Dutch subjects aged over 18 years with uncomplicated microscopically confirmed *P. falciparum* malaria (n = 59)
Treatments	Co-artemether (Co), 80/480 mg p.o. at 0, 6-8, 24 and 48 h (n = 27) Halofantrine (H), 500 mg p.o. at 0, 6-8 and 12 h (n = 32)
Adverse Events	Co: QTc prolongation 8%, H: QTc prolongation 31%
Results	Parasite clearance time (h): Co (32) < H (48) [p <0.001] Fever resolution time (h): Co (24) ≤ H (32) Cure rate (%) at 28 days: Co (88) < H (100)
Conclusions	Co-artemether was an effective and well-tolerated treatment for uncomplicated *P. falciparum* malaria

Box 8: Efficacy and tolerability of co-artemether versus halofantrine in the treatment of malaria (18) [Prous Science CSline database].

Design	Comparative, randomized, double-blind clinical study
Population	French and Dutch subjects aged over 18 years with uncomplicated microscopically confirmed *P. falciparum* malaria (n = 103)
Treatments	Co-artemether (Co), 80/480 mg p.o. at 0, 6-8, 24 and 48 h (n = 51) Halofantrine (H), 500 mg p.o. at 0, 6-8 and 12 h (n = 52)
Withdrawals [causes]	Co: 12/51 [recrudescence 8/51, lost to follow-up 2/51, noncomplicance 1/51, protocol violation 2/51, other 1/51] H: 10/52 [adverse events 1/52, lost to follow-up 3/52, noncompliance 6/52, protocol violation 1/52]
Adverse Events	Co: 27/51 (53%) [headache 14%, fatigue 8%, myalgia 8%, sleep disorder 8%, vomiting 2%, diarrhea 6%] H: 30/52 (58%) [headache 8%, fatigue 4%, myalgia 2%, sleep disorder 12%, vomiting 14%, diarrhea 12%]
Results	Parasite clearance time (h): Co (32) < H (48) [p <0.001] Parasite reduction rate (%) at 24 h: Co (99.7) > H (89.6) [p <0.001] Fever resolution time (h): Co (24) ≤ H (32) Cure rate (%) at 28 days: Co (82) < H (100) [p = 0.006]
Conclusions	Co-artemether was effective and well tolerated for the treatment of uncomplicated *P. falciparum* malaria

Box 9: Co-artemether versus pyrimethamine/sulfadoxine in the treatment of malaria (19) [Prous Science CSline database].

Design	Comparative, randomized, double-blind clinical study
Population	African children under 5 years of age with *P. falciparum* malaria having > 5000 parasites/µl (n = 287)
Treatments	Co-artemether (Co), 20/120 mg p.o. (double dose in children above 15 kg) at 0, 8, 24 and 48 h (n = 144) Pyrimethamine-sulfadoxine (P/S), 12.5/250 mg p.o. (double dose in children above 15 kg) once (n = 143)
Withdrawals [causes]	Co: 11/144 at 4 days [no parasites 4/143, adverse events 1/144, noncompliance 1/144, consent withdrawal 1/144, lost to follow-up 4/144]; 14/133 at 15 days [consent withdrawal 1/133, lost to follow-up 13/133] P/S: 6/143 at 4 days [adverse events 1/143, lost to follow-up 4/143, concurrent treatment 1/143]; 9/137 at 15 days [noncompliance 2/137, consent withdrawal 2/137, lost to follow-up 3/137, concurrent treatment 2/137]
Results	Parasite clearance rate at 3 days: Co (133/133 [100%]) > P/S (128/137 [93.4%]) [$p = 0.003$], at 15 days: Co (111/119 [93.3%]) ≅ P/S (125/128 [97.7%]) Gametocyte carrying rate (%) at 2 weeks: Co (0) < P/S (28.9) Recrudescence/new infection rate at 3-4 weeks: Co (20/119) > P/S (1/128) Treatment for second malaria: Co (26/119) > P/S (8/128)
Conclusions	Co-artemether was a safe and rapidly acting treatment for acute uncomplicated *P. falciparum* malaria, although it had a short prophylactic effect against new infections

Box 10: Co-artemether versus artesunate-mefloquine in the treatment of multidrug-resistant malaria (20) [Prous Science CSline database].

Design	Randomized, open, comparative clinical study
Population	Patients with symptomatic microscopically confirmed *P. falciparum* malaria from western Thailand (n = 617)
Treatments	Co-artemether (Co), 1-2/6-12 mg/kg p.o. at 0, 8, 24 and 48 h (n = 309) Artesunate (A), 4 mg/kg p.o. o.d. for 3 days + Mefloquine (M), 15 mg/kg p.o. on day 2 → 10 mg/kg on day 3 (n = 308)
Withdrawals [causes]	139/617 [lost to follow-up 104/617, protocol violation 5/617, noncompliance 3/617, concomitant medications 16/617, adverse events 2/617, death 1/617]
Adverse Events	Co: 177/309 (57%) [dizziness 15%, sleep disorder 12%, vomiting 3.1%, nausea 6%, palpitations 10%, pruritus/rash 4%, neurological (abnormal gait, paresthesia, tremor, nystagmus, abnormal coordination, ataxia) 3%] A+M: 232/308 (75%) [dizziness 35%, sleep disorder 25%, vomiting 13%, nausea 17%, palpitations 19%, pruritus/rash 3%, neurological (abnormal gait, paresthesia, tremor, nystagmus, abnormal coordination, ataxia) 10%]
Results	Parasite clearance time (days): Co (4) ≅ A+M (3) Parasite clearance rate (%) at 3 days: Co (100) = A+M (100) Fever clearance time (days): Co (1) = A+M (1) Fever clearance rate (%) at 24 h: C (53) ≅ A+M (52), at 72 h: Co (>90) ≅ A+M (>90) Cure rate (%) at 28 days: Co (85.2) ≤ A+M (97.7), at 63 days: Co (81.3) ≤ A+M (94.4) Recrudescence/new infection rate at 63 days: Co (61/248 [24.6%]) ≥ A+M (28/230 [12.2%])
Conclusions	Co-artemether was as effective and better tolerated than artesunate-mefloquine in the acute treatment of multidrug-resistant malaria, although higher doses may be required to improve long-term efficacy

trend to a greater effect with halofantrine. Tolerability was better with co-artemether, as no patients withdrew for this reason (18) (Box 8).

Co-artemether was compared to pyrimethamine-sulfadoxine, another drug combination used in the treatment of acute malaria, in a clinical study in African children with acute uncomplicated *P. falciparum* malaria. Co-artemether acted more rapidly than the reference combination, as assessed by the parasite clearance rate at 3 days and the gametocyte-carrying rate at 2 weeks. However, more children treated with co-artemether required treatment for new infections within 4 weeks (19) (Box 9).

Co-artemether has also been compared to the antimalarial drug combination of artesunate-mefloquine. In an open trial in 617 patients from the western border of Thailand, with acute uncomplicated multidrug-resistant *P. falciparum* malaria, both combinations rapidly and reliably

cleared fever and parasitemia with no differences in the initial therapeutic response. However, the 63-day cure rate was significantly higher for artesunate-mefloquine (94%) than for co-artemether (81%). Co-artemether was also better tolerated (20) (Box 10).

In these studies, co-artemether was more effective that comparative drugs as initial treatment, with shorter clearance rates for both parasites and fever. However, lower cure rates at 28 days may indicate higher recrudescence and/or new infection rates, indicating that at the doses used, the combination has a short prophylactic effect and would be more useful as a treatment. However, recrudescences might be due to insufficient resorption of the drug or drug consumption by parasites and not to true genetic resistance to co-artemether, which has not been established. The initial clearance of parasites in patients with highly resistant malaria suggests the lack of resistance and reinforces the rapid action of co-artemether in the treatment of uncomplicated malaria. A possible explanation for the relatively poor long-term efficacy of co-artemether may be insufficient dosage. In fact, a clinical study (presented only in the form of a congress abstract) comparing standard versus higher doses of co-artemether concluded that higher dose schedules demonstrated substantial improvement in cure rate (21).

Manufacturers

Inst. Microbiol. Epidemiol. Acad. Military Med. Sci. (CN); Novartis Pharma AG (CH).

References

1. Winstanley, P., Olliaro, P. *Clinical trials of chemotherpy for falciparum malaria.* Exp Opin Invest Drugs 1998, 7: 261-71.

2. Zhou, Y., Ning, D., Wang, S., Ding, D., Li, G., Shan, C., Liu, G. (Ciba Geigy AG; Institute of Microbiology and Epidemiology). *Antimalarial compsns.* CA 2065285, CN 1058717, EP 500823, JP 92501568, US 5677331, WO 9202217.

3. Cumming, J.N., Ploypradith, P., Posner, G.H. *Antimalarial activity of artemisinin (qinghaosu) and related trioxanes: Mechanism(s) of action.* Adv Pharmacol 1997, 37: 253-97.

4. Cumming, J.N., Wang, D., Park, S.B., Shapiro, T.A., Posner, G.H. *Design, synthesis, derivatization, and structure-activity relationships of simplified tricyclic, 1,2,4-trioxane alcohol analogues of the antimalarial artemisinin.* J Med Chem 1998, 41: 952-64.

5. Posner, G.H., Cumming, J.N., Ploypradith, P., Oh, O.H. *Evidence for Fe(IV)=O in the molecular mechanism of action of the trioxane antimalarial artemisinin.* J Am Chem Soc 1995, 117: 5885-6.

6. Posner, G.H., Cumming, J.N., Woo, S.H., Ploypradith, P., Xie, S., Shapiro, T.A. *Orally active antimalarial 3-substituted trioxanes: New synthetic methodology and biological evaluation.* J Med Chem 1998, 41: 940-51.

7. Paitayatat, S., Tamchompoo, B., Thebtaranonth, Y., Yuthavong, Y. *Correlation of antimalarial activity of artemisinin derivatives with binding affinity with ferroprotoporphyrin IX.* J Med Chem 1997, 40: 633-8.

8. Ezzet, F., Mull, R., Karbwang, J. *Population pharmacokinetics and therapeutic response of CGP 56697 (artemether + benflumetol) in malaria patients.* Br J Clin Pharmacol 1998, 46: 553-61.

9. van Agtmael, M.A., Cheng-Qi, S., Qing, J.X., Mull, R., van Boxtel, C.J. *Multiple dose pharmacokinetics of artemether in Chinese patients with uncomplicated falciparum malaria.* Int J Antimicrob Agents 1999, 12: 151-8.

10. Bindschedler, Degen, L., Lu, Z.L., Liu, G.Y., Fan, F. *Comparative bioavailability of benflumetol after administration of single oral doses of co-artemether under fed and fasted conditions to healthy subjects.* 14th Int Cong Trop Med Malar (Nov 17-22, Nagasaki) 1996, Abst P-01-96.

11. von Seidlein, L., Jaffar, S., Pinder, M., Haywood, M., Snounou, G., Gemperli, B., Gathmann, I., Royce, C., Greenwood, B. *Treatment of African children with unomplicated falciparum malaria with a new antimalaria drug, CGP 56697.* J Infect Dis 1997, 176: 1113-6.

12. Jiao, X., Liu, G.Y., Shan, C.O., Zhao, X., Li, X.W., Gathmann, I., Royce, C. *Phase II trial in China of a new, rapidly-acting and effective oral antimalarial, CGP 56697, for the treatment of Plasmodium falciparum malaria.* Southeast Asian J Trop Med Public Health 1997, 28: 476-81.

13. Hatz, C., Abdulla, S., Mull, R., Gathmann, I., Royce, C. *Efficacy of CGP 56697 vs. chloroquine for treatment of P. falciparum malaria in young symptomatic children in Tanzania.* Clin Microbiol Infect 1997, 3 (Suppl. 2): Abst P753b.

14. Hatz, C., Abdulla, S., Mull, R., Schellenberg, D., Gathmann, I., Kibatala, P., Beck, H.P., Tanner, M., Royce, C.*Efficacy and safety of CGP 56697 (artemether and benflumetol) compared with chloroquine to treat acute falciparum malaria in Tanzanian children aged 1-5 years.* Trop Med Int Health 1998, 3: 498-504.

15. Sabchareon, A., Attanath, P., Gathmann, I. et al. *An open comparative 28 day trial of CGP 56697 (2 days) versus oral quinine (8 days) in the treatment of acute P. falciparum malaria in Thai children.* J Clin Microbiol Infect 1997, 3 (Suppl. 2): Abst P752.

16. Looareesuwan, S., Wilairatana, P., Chokejindachai, W., Chalermrut, K., Wernsdorfer, W., Gemperli, B., Gathmann, I., Royce, C. *A randomized, double-blind, comparative trial of a new oral combination of artemether and benflumetol (CGP 56697) with mefloquine in the treatment of acute Plasmodium falciparum malaria in Thailand.* Am J Trop Med Hyg 1999, 60: 238-43.

17. van Agtmael, M., Bouchaud, O., Malvy, D. et al. *A randomised, double-blind trial of CGP 56697 versus halofantrine in the treatment of Plasmodium falciparum malaria in Europe.* Clin Microbiol Infect 1997, 3 (Suppl. 2): Abst P754.

18. van Agtmael, M., Bouchaud, O., Malvy, D. et al. *The comparative efficacy and tolerability of CGP 56697 (artemether + lumefantrine) versus halofantrine in the treatment of uncomplicated falciparum malaria in travellers returning from the tropics to the Netherlands and France.* Int J Antimicrob Agents 1999, 12: 159-69.

19. von Seidlein, L., Bojang, K., Jones, P. et al. *A randomized controlled trial of artemether/benflumetol, a new antimalarial and pyrimethamine/sulfadoxine in the treatment of uncomplicated falciparum malaria in African children.* Am J Trop Med Hyg 1998, 58: 638-44.

20. van Vugt, M., Brockman, A., Gemperli, B., Luxemburger, C., Gathmann, I., Royce, C., Slight, T., Looareesuwan, S., White, N.J., Nosten, F. *Randomized comparison of artemether-benflumetol and artesunate-mefloquine in treatment of multidrug-resistant falciparum malaria.* Antimicrob Agents Chemother 1998, 42: 135-9.

21. van Vugt, M., Wilairatama, P., Gemperli, B., Gathmann, I., Royce, C., Nosten, F., White, N., Looareesuwan, S. *Double-blind, randomised trial of standard and high dose regimens of CGP 56697, a new oral antimalarial combination in the treatment of multi-drug resistant Plasmodium falciparum malaria in Thailand.* Clin Microbiol Infect 1997, 3 (Suppl. 2): Abst. P753a.