Antimalarial Drug Studies in Cameroon Reveal Deteriorating Fansidar and Amodiaquine Cure Rates

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Abstract

The public health burden of malaria in Cameroon is worsened by the spread of resistance. In Cameroon since 1985 when this phenomenon was first described, resistance of the parasite to common antimalarial drugs has grown tremendously in the past 20 years. Resistance has developed with significant ecological facet variations. Chloroquine resistance for example varies between 25% in the northern Sahel savannah regions to a record 87% in the forest south of Cameroon. This resistance to chloroquine has stayed high since then and its further increase in other regions led the government in 2000 to temporarily switch to Amodiaquine as first line treatment. Fansidar resistance was reported to be at 43% in 1996, in Yaoundé, was 43% and 46.6% in Nkambe and Limbe respectively in 2002. The analysis of genes responsible for the transport or metabolism of drugs in *P. falciparum* show the high prevalence of mutations to *dhfr*, *dhps* and *Pfcrt*. Amodiaquine that was efficacious at 94% in 2002, recently was determined to have dropped to 80-82% in 2005 in Garoua, Yaoundé and Limbe. Amodiaquine and Fansidar have therefore rapidly deteriorated as monotherapies and their use as part of any treatment may lead to increased unresponsiveness, given that established mutations make it easy to propagate resistant parasites.

Résumé

Le fardeau qu'amène le paludisme au Cameroun est aggravé davantage par la propagation de la chimiorésistance. Depuis 1985 lorsque ce phénomène a été décrit pour la première fois, la chimiorésistance du parasite aux antipaludéens a augmenté énormément. C'est ainsi que la résistance s'est développée avec des variabilités par faciès écologiques. La chloroquino-résistance par exemple varie de 25% au nord du pays dans la région de la savane sahélienne à 87% dans la forêt au sud du pays. Cette résistance est restée élevée et a augmenté dans d'autres régions; ceci a amené le gouvernement à changer sa politique médicamenteuse en faveur de l'Amodiaquine comme médicament de première intention. Le taux de résistance du parasite au Fansidar reporté en 1996 à Yaoundé était de 43%. Ce taux en 2002 était aussi élevé à Limbe et Nkambe avec des valeurs de 43 et 46,6% respectivement. Les analyses des gènes responsables du transport ou du métabolisme des médicaments dans *P. falciparum* tels que le *dhps, dhfr* ou la *Pfcrt* montrent un taux de mutations élevé. L'efficacité de l'Amodiaquine qui était de 94% en 2002, est diminuée à 80-82% en 2005 dans les villes de Garoua, Yaoundé et Limbe. L'Amodiaquine et le Fansidar ont perdu leur efficacité en traitement mono thérapeutique. Leur utilisation en combinaison avec d'autres antipaludéens pourrait augmenter cette inefficacité, étant donnée que les mutations une fois établies sont faciles à être propagées.

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Antimalaria drug studies were conducted in the early 1980s to assess the efficacy of a range of anti-malaria drugs in Cameroon. These studies demonstrated various levels of resistance in Limbe where chloroquine resistance was first detected (Sansonetti *et al*, 1985). Following that discovery, a series of studies were done in other towns and varying levels of resistances were noted. Mefloquine resistance was higher in the north of Cameroon (Garoua- 20% clinical failure(CF) whilst chloroquine resistance was lowest (25%). The opposite situation was observed in Limbe where mefloquine failure was low (2%) and chloroquine failure was 86%. (Table 1, Fig 1). No further studies have been carried out to understand the dichotomy in responses to chloroquine and mefloquine between the two biotopes.

Recent studies reported a 43% pyrimethamine resistance in clinical isolates in Yaounde using the *in vitro* semi-microtest (Ringwald *et al*, 1996). Two years later, the same laboratory confirmed their own results as they found 43 % of the samples to be carrying mutation 108N of the *dhps* gene (Basco and Ringwald (1998), using the restriction fragment length polymorphism (RFLP) technique. Two studies still placed SP as efficacious with a 13.6% failure rate in children aged between 5 and 14 years. (Ringwald et

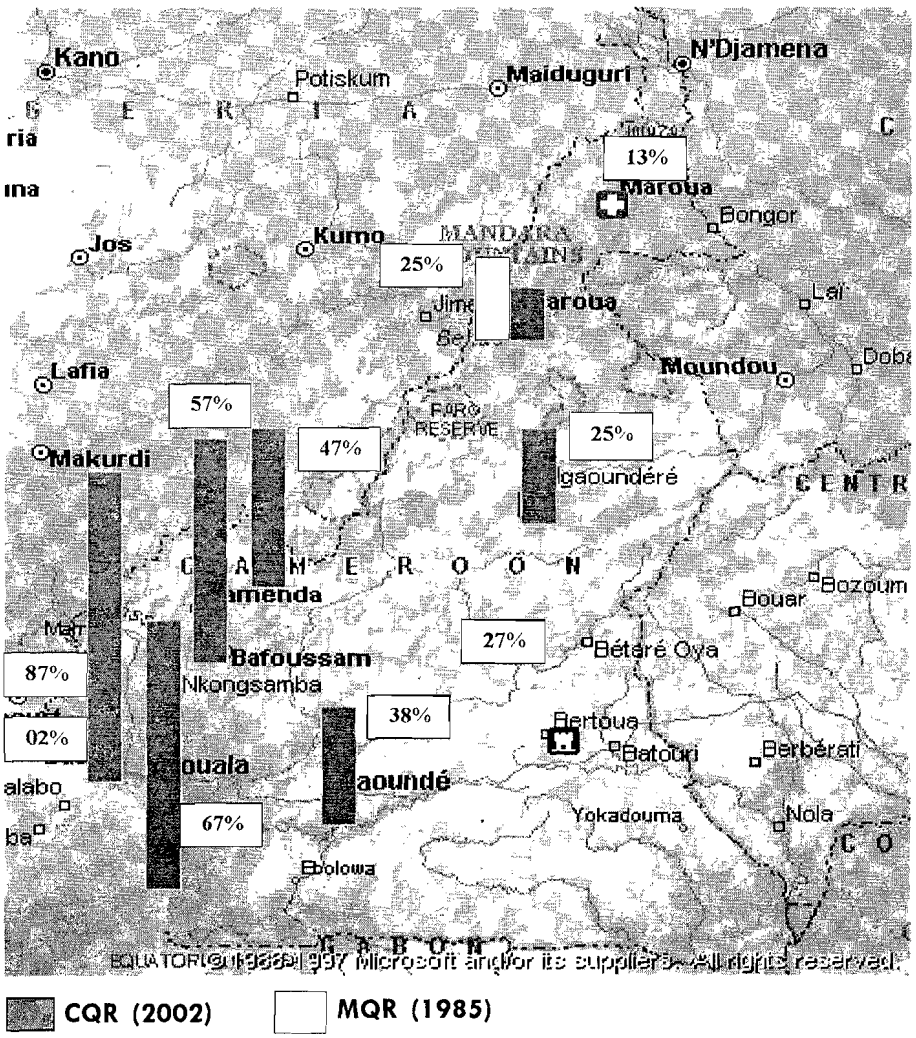

Fig 1 -Sites for *in vivo* Therapeutic Efficacy Trials Chloroquine and Mefloquine Failure Rates - Cameroon

Table 1 : Anti-Malaria drug resistance studies in Cameroon

Study Date	Study Drug	Age Group	Town	Failure	Author
1986	CQ	0.5 - 70	Kumba, Douala, Yaounde	DSA - 0.0% DSA - 0.0% DSA - 0.0%	Brasseur *et al*, 1986
1986	CQ	0.5 - 70	Limbe	Clin.Failure|CFI - 86%	Brasseur *et al*, 1986
1988	CQ	0.5 - 70	Garoua	CF – 25%	Brasseur *et al*, 1988
1988	Q	0.5 - 70	Limbe	CF – 33%	Brasseur *et al*, 1988
1988	Q	0.5 - 70	Nationwide	CF – 06%	Brasseur *et al*, 1988
1992	MQ	0.5 - 70	Garoua	CF – 20%	Brasseur *et al*, 1992a
1992	MQ	0.5 - 70	Limbe	CF – 02%	Brasseur *et al*, 1992b
1992	CQ	0.5 - 70	Bamenda	CF – 56%	Ndiffor *et al*, 1992
1994	CQ	>5 years	Yaounde	CF - / PF - 46% DSA – 53%	Ringwald *et al*, 1996
1996	Pyr, Cyclog.	>5 years	Yaounde	DSA - 42% MM(dhfr) – 43%	Ringwald *et al*, 1996
1998	CQ	>5 years	Yaounde	CF - 51%	Basco & Ringwald, 1998
1998	Pyr	>5 years	Yaounde	MM (dhfr) - 43%	Basco & Ringwald, 1998
1998	AQ	> 5years	Yaounde	CF – 0.0%	Ringwald *et al*, 1998
1998	Sulf	>5 years	Yaounde	MM (dhps) – 03%	Basco & Ringwald, 1998
1999	Pyr	> 5 years	Yaounde	DSA - 63%	Basco & Ringwald, 1999
2000	CQ	>5 years	Yaounde	CF – 40% PF – 49%	Ringwald *et al*, 2000
2000	Pyr/Sulf	>5 years	Yaounde	CF – 12%	Ringwald *et al*, 2000
2002	CQ	0.5-70 years	Limbe Molyko Bolifamba	CF – 15%	Titanji *et al*, 2001
2002	CQ	<5 years	Garoua Maroua Yaounde Eseka Douala Bafousam Bertoua Ngoundere Ndop	CF - 18% CF – 13% CF - 38% CF – 56% CF – 67% CF – 57% CF – 27% CF - 25% CF – 47%	Soula *et al*, 2002
2002	SP	<5 years	Yaounde Djoum	CF - 6% CF – 7%	Soula *et al*, 2002
2002	CQ AQ	2-10 years	Kribi	DSA – 61% DSA- 13.5%	Angamey *et al*, 2002
2002	SP AQ	< 10years	Kribi	CF- 13.6% CF- 10.2%	Basco *et al*, 2002
2003	SP	<10 years	Nkambe Limbe	CF-46.0% CF-43.5%	Mbacham et *al*, 2005a
2004	SP AQ AQ+SP	<5 years	Garoua	CF-40.5% CF-18.8% CF-14.5%	Mbacham *et al*, 2005b
	SP AQ AQ+SP	<5 years	Limbe	CF-40.0% CF-20.0% CF-13.6%	
	SP AQ AQ+SP	<5 years	Yaounde	CF-30.4% CF-28.2% CF-18.4%	

al, 2000; Basco et al 2002b). Clinical evaluation of the efficacy for SP resistance has not been investigated properly in other parts of the country and there is no information on the correlation between molecular markers, resistance and therapeutic failure to SP.

Studies by Mbacham et al, (2005a) in Nkambe, demonstrated that adequate clinical and parasitological response for Fansidar stood at 46.6% while it was 43.5% in Limbe. Late parasitological failure (LPF) was higher in Limbe (30.6%) compared to Nkambe (10.3%). The prevalence of the 437-G mutation was lower in Nkambe, (57.6%), than in Limbe (70%). The serine to asparagine mutation at position 108 of *P. falciparum's DHFR* present in the investigated sites had varying occurrence rates of 4% in Dschang (Savanna), 14% in Fontem (Upland Forest), 44% in Limbe (Littoral-Forest) and 46% in Nkambe (Guinea-Savanna). Analyses demonstrate that all genotypes that carried the 108N mutation also carried the 51-Ile and 59-Arg mutations similar to the Dd2 resistant strain as opposed to the Thailand strain K1 with mutations 51-Asn and 59-Arg. All sensitive alleles (S108) were 51-Asn and 59-Cys. In Cameroon, SP is used for intermittent preventive therapy in pregnancy.

The next series of drug studies were conducted in Yaounde and involved patients attending a Catholic dispensary in the northern part of the town. In those studies reported by the Ringwald group from 1994-2001, aminoquinoline and anti-folate resistance was observed to increase with time (Table1 1). A multi-centre opened, randomised controlled study of amodiaquine and chloroquine conducted in Senegal Gabon, Cameroon and Burkina Faso demonstrated that amodiaquine (30mg/kg for three days) was significantly efficacious than chloroquine in West and Central Africa. Studies between 1997 and 2001 in Cameroon showed that amodiaquine remained efficacious in the treatment of uncomplicated malaria in West and Centre provinces with high chloroquine resistance (Brasseur *et al*, 1999; Ringwald *et al*, 1998; Agnamey, *et al*, 2002; Basco *et al*, 2002). Recently Titanji *et al*, (2002) published data suggesting that chloroquine resistance was declining in Limbe and attributed this to a drop in drug pressure. These authors used 7 day evaluations and assessed resistance in all age groups (children and adults) and the apparent decline may not be true because of the spontaneous rate of recovery in adults, with a more developed immunity.

In view of the high levels of chloroquine resistance noted in several parts of Cameroon, the Ministry of Health recommended that chloroquine be replaced by amodiaquine as first line treatment. However, there was limited data on the efficacy of amodiaquine and Fansidar nationwide and how well the latter could serve as an alternative. A few studies were however conducted that showed AQ was still efficacious in the late 1990s leading up to 2000. There is now evidence from a recently completed three arm, randomised, controlled, double blinded study of S-P, AQ, and S-P+AQ, that with the adequate clinical and parasitological responses on day 14 for S-P, AQ and S-P+AQ were 59.5%, 82.2%, 85.5% in Limbe, 60.0%, 86.4%, 80.0% in Yaounde and 69.6%, 71.8%, 82.6%, in Garoua respectively. Amodiaquine and Fansidar have rapidly deteriorated as

monotherapies and their inclusion in combinations is likely to fail as well (Mbacham *et al*, 2005b).

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