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Chloroquine Resistance in *Plasmodium vivax*

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Emerging resistance to chloroquine (CQ) by *Plasmodium vivax* threatens the health of the hundreds of millions of people routinely exposed to the risk of infection with this organism. CQ has been the first-line therapy for vivax malaria since 1946 (32, 115). *Plasmodium falciparum* developed resistance to CQ in the 1950s (110), and today it occurs globally (91). Resistance by *P. vivax* was unknown until 1989, when Australians repatriated from Papua New Guinea failed routine treatment (94). Subsequent reports affirmed that finding, and CQ-resistant *P. vivax* (CRPV) was reported from Indonesia (8, 35, 99, 100, 111). Reports from Myanmar (76, 82) and India (56, 107) followed. CRPV appeared in travelers from Guyana, South America (88). However, studies in Thailand (38, 72, 103), the Philippines (10), and Vietnam (105) revealed only CQ-sensitive *P. vivax*. Surveys in Indonesia revealed a low frequency of CRPV in the west (~10%) (15, 16, 49, 50, 51, 53, 75) and a higher risk in the east (~45%) (9, 18, 52, 81, 102, 106). This minireview summarizes the present state of knowledge of CRPV as a scientific, clinical, and public health problem. It examines the genesis of CQ therapy for *P. vivax* and the laboratory and clinical data underpinning the diagnosis of CRPV. The available data showing the global distribution of CRPV are listed. Finally, the clinical data on alternative therapies against CRPV are reviewed.

**VIVAX MALARIA AND ANTIMALARIAL THERAPY**

Four species in the genus *Plasmodium* routinely infect humans. *P. vivax* infects 80 million people annually and accounts for most cases of malaria occurring outside Africa (79). It rarely causes death but inflicts debilitating fever, chills, nausea, vomiting, and myalgia. The prevalence of *P. vivax* typically ranges from <1 to 25% in areas of Asia and the Americas where the organism is endemic, but it is resurging and now threatens to reencroach on anachroch where it had been eradicated (7, 28, 31). The chemotherapeutic management of vivax malaria therefore represents an issue of importance to global health.

The life cycle of plasmodia defines the chemotherapeutic strategies. These parasites pass through a complex life cycle marked by forms of distinct morphology, function, location, clinical consequence, and susceptibility to antimalarial agents. Figure 1 illustrates the four families of antimalarial drugs defined on the basis of their activities against specific stages in the life cycle. CQ is a blood schizonticide against both *P. vivax* and *P. falciparum*. Its activity as a gametocytocide within therapeutic ranges is nonexistent against *P. falciparum* gametocytes but is potent against *P. vivax* gametocytes. CQ alone exerts no known sporonticidal or tissue schizonticidal activity.

Relapse is an important aspect of the *P. vivax* life cycle bearing upon chemotherapy and its assessment. Relapse refers to clinical malaria caused by parasites in the bloodstream originating from dormant liver stages called hypnozoites seeded by sporozoites from infectious anopheline mosquitoes (Fig. 1). Relapse may occur weeks to years following the primary episode of parasitemia and clinical disease. Tissue schizonticides, like primaquine, prevent relapse by killing the stages of the organism in the liver. When a parasitemia reappears after blood schizonticidal therapy, it may be a relapse from the liver, a reinfection by a mosquito, or a recrudescence originating from asexual blood-stage parasites that survived therapy (Fig. 2). The emergence of CQ-resistant *P. vivax* favors the last possibility.

**CQ THERAPY**

**Development.** The first treatment of humans with CQ occurred in 1936 in four syphilis patients in Dusseldorf, Germany, given *P. vivax* (32). An accounting of the lost records of that trial describes CQ as being “too toxic for practical use in humans.” The Germans investigated sontochin, a methylated analog, which American forces obtained in liberated Algeria in May 1943. Patents for sontochin and CQ were discovered in the United States, and both compounds went to clinical trials. That work, detailed by Wiselogle (114), proved that CQ was more effective and better tolerated.

The early nomenclature of CQ includes SN-7618 and “resochin,” identifiers used by the American and German developers, respectively. The name CQ was formally registered in the United States in March 1946. A month later Loeb et al. (71) published the seminal paper on the activity of CQ against falciparum and vivax malaria. They recommended 1.5 g of base over 48 h for the treatment of acute falciparum or vivax malaria and 0.3 g of base weekly for prophylaxis. These remain the standards for treatment and prophylaxis.

**Standard versus effective therapy.** The genesis of recommended therapy constitutes a critical factor now, 60 years later, in defining resistance by *P. vivax*. What was the minimally effective dose? Loeb et al. (71) provided no data, instead publishing the “Statement Approved by the Board for the Coordination of Malarial Studies.” Most et al. (80) published the first clinical data in November 1946: several hundred American
FIG. 1. Schematic representing the life cycle of plasmodia and the four families of antimalarial agents. Sporontocidal agents kill forms in the mosquito, including infectious sporozoites. Tissue schizonticides kill parasites developing (schizonts) or quiescent (hypnozoites) in the liver. Blood schizonticides kill the asexual blood forms (trophozoites and schizonts) that cause clinical malaria. The gametocytocides kill or sterilize the sexual forms (gametocytes) that infect mosquitoes.

soldiers were treated with 1.0 g over 12 h, 1.5 g over 96 h, or 2.0 g over 7 days. They recommended the use of 1.5 g over 48 h, a regimen not represented in their work.

In 1947, Gordon et al. (58) reported that only 0.8 g (for 6 days) had good efficacy against vivax malaria in 39 subjects. Berliner et al. (20) described total doses from 0.3 to 0.6 g as consistently curing blood-stage \( P. \) vivax (McCoy strain) in 10 subjects. However, total doses <0.3 g often failed. Others soon affirmed the sensitivity of \( P. \) vivax to substandard regimens down to a 0.3-g total adult dose. Hoekenga (65) described 0.6- or 0.45-g single-dose regimens in Honduras in 1952. Among 100 subjects receiving 0.6 g, only 1 failed the treatment. Among 120 subjects receiving 0.45 g, 5 failed the treatment. In 1950, Butts (27) reported on 202 patients in Central America treated with 0.08 to 1.56 g. Failures occurred only among those receiving <0.3 g. Wilson and Edeson (113) reported on similar findings from Malaysia; among 62 subjects treated with single doses of 0.3 to 0.6 g, none failed. According to Harinasuta as late as 1992 (as cited by Looareesuwan et al. [73]), \( P. \) vivax in Thailand remained sensitive to treatment with a single 0.35-g dose. The available data suggest a baseline sensitivity compatible with blood-stage cure of \( P. \) vivax with \( \geq 0.3 \) g of CQ base.

The data from areas of endemicity led to reasoned recommendations for substandard treatments in “immune” populations (22). There was no need (or reliable evidence) to invoke immunity as the basis of efficacy. These regimens had superior efficacies in nonimmune people as well.

FIG. 2. The three paths to recurrent parasitemia for malarias caused by \( P. \) vivax and \( P. \) ovale. Sporozoites from mosquitoes reinfect the livers of humans, which yields merozoites that infect blood. Some sporozoites develop to quiescent hypnozoites in the liver and later cause relapse. Subpatent trophozoites in blood cells mature to schizonts that rupture and release merozoites that infect the blood and cause a recrudescence.

RELAPSE AFTER CQ TREATMENT

In the 1940s recurrent parasitemia after effective CQ therapy defined the timing and the risk of relapse for CQ-sensitive...
be 8, 9, and 19 ng/ml. These data represent the basis of the CQ levels after a 1.3-g regimen on day 35 and found them to concentrations following therapy (approximately 200 ng/ml of parasitemia. If not, infection survived the towering drug con-

Clinicians wonder if the standard 1.5-g CQ regimen eliminates the explanation given for the delayed relapses after CQ ther-

It requires proof of adequate compliance to and absorption of therapy by reliable supervision or, ideally, by determination of the levels of drug in blood. Figure 3 illustrates data derived from clinical trials with supervised dosing and ascertainment of drug levels. Counterfeit drug, poor compliance, and emesis.
may prevent normal drug levels from being achieved. An un-
ambiguous diagnosis of CRPV infection requires the demon-
stration of parasitemia with ordinarily effective drug levels
(>10 ng/ml of plasma).

The blood challenge experiments of Berliner et al. (20) pro-
vided a definitive MEC for CQ-sensitive *P. vivax*. After CQ
treatment the relapse pattern with the plasma drug levels (Fig.
3) corroborated the estimate of the MEC. Two issues must be
c onsidered today when the MEC is applied to present assess-
ments of CQ treatment effectiveness: (i) the analytical methods
discussed the rationale for classifying the CQ susceptibilities of
strains of *P. vivax* in *Aotus* or *Saimiri* monkeys. They point to
variations in the minimal therapeutic doses for strains known
to be sensitive to CQ in humans: Vietnam Palo Alto (>18 mg),
Achiote (10 mg), and Chesson (9 mg). CQ-resistant Indone-
sian strain CDC I failed to be eradicated with 15 mg and was
classified as “possibly even more resistant than the Vietnam
Palo Alto strain.” The other strain from Indonesia failed to be
eradicated with 30 mg and was classified as resistant (37).

In *vitro* methods. The diagnosis of resistance to *P. falcipa-
rum* in vitro has been standard procedure since the 1970s.
Although *P. vivax* has not been cultivated continuously, it de-
velops for periods sufficient to assess the therapeutic response.
Methods for doing so have been described since the 1970s (24,
55, 90, 93), and there is renewed interest in these techniques
(60, 68, 98, 103, 104). No standard criteria for classifying in
vivo responses as sensitive or resistant yet exist. However,
many isolates have been characterized in Thailand, where the
clinical responses to CQ treatment remain uniformly sensitive.
This provides a baseline for in vitro sensitivity: ~50 ng/ml
consistently inhibits development by 50%. In vitro testing for
CRPV may prove useful among well-equipped laboratories.

Molecular probes. No genetic mutations have been linked to
resistance to CQ by *P. vivax*. Nomura et al. (83) investigated
mutations in the *P. vivax* ortholog of the *crt* gene of *P. falci-
parum*, which has been linked to CQ resistance. The mutations
incriminated in *P. falciparum* *crt* did not occur among CRPV
isolates, and no other mutations in that gene correlated with
the phenotype. The genetic determinants of resistance to CQ
apparently differ between *P. vivax* and *P. falciparum*. Con-
tinuous cultivation allowed the search for *crt* mutants in *P. falci-
parum*, and similar progress for *P. vivax* may be difficult; but
genomic analyses (46) may ultimately yield genetic determi-
nants of resistance.

Prophylaxis and cross-sectional studies. Among 94 study
subjects taking supervised CQ prophylaxis (5 mg/kg of body
weight weekly) in Indonesian New Guinea for 18 or 52 weeks,
29% developed *P. vivax* infections (11, 48), a rate indistinguish-
able from that for a placebo group (48). Among 41 subjects in
the same region evaluated in two other studies (8, 81), 61%
developed vivax malaria. Vivax malaria occurring during su-
 pervised prophylaxis proves resistance to CQ.

Cross-sectional analyses of CQ levels may help gauge en-
demic resistance. Collection of blood on dried filter paper and
stained blood films (and later analysis in a laboratory) allow
assessment of hundreds of people with just a single day on-site,
whereas in vivo assessments require at least 1 month on-site.
This approach requires caution, however. A patient reporting
to a clinic with concentrations in blood greater than the MEC
may have recently self-administered drug, and even sensitive
*P. vivax* may take 4 days to clear. Nonetheless, the proportion of
patients infected with *P. vivax* and having concentrations in
blood greater than the MEC provides an estimate of the risk of
resistance (14).

**OTHER APPROACHES TO DIAGNOSING RESISTANCE**

Experimental animals. Some nonhuman primate host-
adapted strains of *P. vivax* have been evaluated. Collins and
colleagues (36, 37) studied two strains of *P. vivax* acquired
from patients in Indonesia who failed CQ therapy. The ther-
apeutic profiles of CQ among well-characterized strains in
humans provide a basis for the classification of wild isolates as
sensitive or resistant in animal models. Collins et al. (36) dis-

**GEOGRAPHIC RANGE OF RESISTANCE**

**Oceania.** The data from Oceania come from just six infec-
tions acquired in Papua New Guinea, and no new report has
appeared in the past 10 years. Nonetheless, the risk of thera-
The efficacy of chloroquine (CQ) and its combination with primaquine against CrPV is reviewed. CQ efficacy in 79 patients (87%) relative to the efficacy of CQ alone. Clinical trials of mefloquine against CrPV are needed. Mefloquine. Some authorities recommend mefloquine for therapy for CrPV (29, 78). No clinical data yet support that recommendation. Mefloquine proved effective against Co-resistant *P. falciparum* and was effective against Co-sensitive *P. vivax* (3, 43, 62). Good efficacy against CrPV seems a reasonable supposition, and Collins et al. (37) demonstrated that mefloquine had good efficacy against an Indonesian CrPV strain in *Aotus* monkeys. However, work by Nomura et al. (83) points to different mechanisms of resistance between the two species, and caution is warranted.

Indirect evidence suggests that mefloquine may be efficacious against CrPV. Ohr et al. (85) demonstrated the complete efficacy of mefloquine for prophylaxis against the CrPV strain known to occur in northeastern Indonesian New Guinea. However, they also found that daily doxycycline had complete efficacy against CrPV, and Taylor et al. (106) showed doxycycline monotherapy to have only 33% efficacy against CrPV. Clinical trials of mefloquine against CrPV are needed.

**Halofantrine, CQ plus doxycycline, or primaquine.** Taylor et al. (106) evaluated CQ and doxycycline combined in Indonesia and found 71% efficacy. This was superior to the 29 and 33% efficacies of the respective monotherapies against vivax malaria but was inferior to the 91% efficacy of the combination against *P. falciparum*. Baird et al. (9) evaluated halofantrine monotherapy and CQ combined with primaquine against *P. vivax* in Indonesian New Guinea. CQ combined with primaquine (10 mg/kg over 2 weeks or 2.5 mg/kg over 48 h) provided superior efficacy in 79 patients (87%) relative to the efficacy of CQ monotherapy in 50 patients (30%). Halofantrine monotherapy cured all 19 subjects treated, although there was one recurrence on day 28 after the end of treatment. Phillips et al. (88) used CQ (25 mg/kg over 2 days) and primaquine (2.5 mg/kg over 2 days) in three patients with CrPV infections acquired in Guyana. They described this therapy as inadequate because two patients had recurrent parasitemia after 6 weeks. However, the abbreviated primaquine regimen was not intended to prevent relapse but to clear the bloodstream, and it apparently achieved this in all three patients. The best combination of CQ plus primaquine may be 0.5 mg of primaquine/kg daily for 14 days or 1.0 mg of primaquine/kg daily for 7 days. This regimen clears the bloodstream of CrPV and would prevent relapse. It should not be used for patients likely to be infected with *P. falciparum* as well, because it has no efficacy against that type of infection (19).

**ALTERNATIVE THERAPIES**

**Mefloquine.** Some authorities recommend mefloquine for therapy for CrPV (29, 78). No clinical data yet support that recommendation. Mefloquine proved effective against Co-resistant *P. falciparum* and was effective against Co-sensitive *P. vivax* (3, 43, 62). Good efficacy against CrPV seems a reasonable supposition, and Collins et al. (37) demonstrated that mefloquine had good efficacy against an Indonesian CrPV strain in *Aotus* monkeys. However, work by Nomura et al. (83) points to different mechanisms of resistance between the two species, and caution is warranted.

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*a* Classified as resistant by the reporting authors.

*b* Rx, standard treatment; Px, standard prophylaxis.
Malarone. Lacy et al. (70) evaluated Malarone (250 mg of atovaquone and 100 mg of proguanil daily for 3 days; GlaxoSmithKline, London, United Kingdom) in 16 subjects with P. vivax infections in Indonesian New Guinea. They also received 0.5 mg of primaquine/kg daily for 14 days. All subjects cleared the fever and parasitemia by day 3 and remained free of parasitemia for 28 days. Malarone combined with primaquine is the only available therapy with proven efficacy (>90%) against CRPV, but that finding is from the results of a study with just 16 patients.

Tafenoquine. Tafenoquine (GlaxoSmithKline) is an 8-aminoquinoline analog of primaquine that has potent schizonticidal activity against P. vivax and P. falciparum in tissue and blood and that is now in clinical trials. This drug has been demonstrated to be effective against CRPV in nonhuman primates (39, 84).

Sulfadoxine-pyrimethamine. Recent work by Hastings and Sibley (63) suggests that P. vivax may be susceptible to antifolates and dihydrofolate reductase (DHFR). DHFR mutants in P. vivax are apparently responsible for the lack of activity among the antifolates. Hastings et al. (64) also found that quadruple mutations in dihydrofolate reductase corresponded to the therapeutic failure of sulfadoxine-pyrimethamine treatment among patients with P. vivax infections acquired in Indonesia. When quadruple P. vivax dhfr mutants do not occur, sulfadoxine-pyrimethamine may be useful against CRPV, but clinical trials are needed.

CONCLUSIONS

Infections with CQ-sensitive P. vivax were routinely cured with as little as 0.3 g of CQ base, even though 1.5 g has been the recommended therapy since 1946. The clinical failure of standard therapy therefore represents infection with an organism with a high degree of resistance. A persistent or recurrent parasitemia within 14 days of the start of treatment probably represents recrudescence by a highly resistant strain of P. vivax. A recurrent parasitemia between 15 and 35 days after the start of treatment with >100 ng of CQ-DCQ per ml is resistant to CQ, regardless of whether that parasitemia originates from a relapse, a reinfection, or a recrudescence. In general, the day of recurrence correlates inversely with degree of resistance, but isolates that cause recurrences after CQ and DCQ levels fall below the MEC (at about day 35) cannot be classified as sensitive or resistant. When 30 mg of CQ base against P. vivax in Aotus monkeys fails, the organism may be classified as resistant. When 50 ng of CQ base/ml fails to inhibit in vitro schizont development by more than 50%, the isolate may be classified as resistant. CRPV appears to be most common in eastern Indonesia, especially on the island of New Guinea. It appears sporadically elsewhere in Southeast Asia, typically among <15% of strains. No cases of CRPV infection have yet occurred in Thailand. The data supporting alternative therapies for CRPV are scanty. A small trial of Malarone combined with primaquine in Indonesian New Guinea may be the best available evidence of the good efficacy of this agent against CRPV.

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REFERENCES


