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Review Article

Historical 8-Aminoquinoline Combinations: Not All Antimalarial Drugs Work Well Together

G. Dennis Shanks*

Australian Defence Force Malaria and Infectious Disease Institute, Enoggera, Australia; University of Queensland, School of Public Health, Brisbane, Australia

Abstract. Since their first use in the 1920s, 8-aminoquinolines have been known to have important toxicities such as methemoglobinemia and hemolysis. An empiric pamaquine (plasmochin) combination with quinine was widely used in the British military with relatively little toxicity. Attempts to use pamaquine with a new synthetic antimalarial drug (atabrine, quinacrine) in the 1930–1940s, however, resulted in hemolytic reactions and some deaths from renal failure. An improved 8-aminoquinoline, primaquine, was particularly effective against *Plasmodium vivax* relapses when combined with either quinine or chloroquine. When used in reduced daily doses (15 mg) over 2 weeks, it was safely given to many thousands of U.S. soldiers returning from Korea. CP tablets (chloroquine 300 mg, primaquine 45 mg weekly) were widely used during the Vietnam War with few hemolytic reactions and no known deaths. Efficacy and toxicity of 8-aminoquinolines is determined in part by the selection of appropriate partner drugs

The proposition that relapses can be reduced by giving ineffective doses of both drugs (quinine and pamaquine) is paradoxical. L. W. Hackett, Malaria in Europe*, 1937*[1]

Toxicity seems to be entirely eliminated by the mechanical combination of plasmochin with small quantities of quinine sulphate. Philip Manson-Bahr, The Lancet, *1928*[2]

8-aminoquinolines (pamaquine, primaquine, tafenoquine) are a class of synthetic antimalarial drugs that have had a checkered history over the past century. Meant to replace the natural product quinine, the first clinically useful 8-aminoquinoline, pamaquine (plasmochin), was empirically combined with quinine to decrease toxicity. The combination was subsequently found to be an effective means of preventing *Plasmodium vivax* relapses after toxic dosages (methemoglobinemia, hemolysis) of monotherapy were found to be impractical. Once atabrine (quinacrine) was available in the 1930s, Indian Army medical officers worked out a treatment regimen known as QAP (typically consisted of quinine 1800 mg for 3 days, quinacrine/atabrine 300 mg for 7 days, pamaquine 30 mg for 5 days), which seemed to work reasonably well while minimizing adverse events.[3] Unfortunately, uncommon hemolytic reactions likely due to the yet to be discovered glucose-6-phosphate dehydrogenase (G6PD) deficiency were observed in Indian soldiers when they were given quinacrine with pamaquine.[4] In 1951 during the Korean War, the U.S. Army introduced a less toxic, more effective 8-aminoquinoline known as primaquine and largely eliminated postdeployment relapses when primaquine was given under supervision to hundreds of thousands of soldiers who had been receiving chloroquine chemoprophylaxis.[5] Both drugs were widely used during the Vietnam War in the 1960s coformulated into the "CP tablet" (chloroquine 300 mg, primaquine 45 mg) for weekly chemoprophylaxis. Hemolysis (black urine) was occasionally observed, especially in Black soldiers, but the actual incidence cannot be estimated from existing records. All these combinations were imperfect compromises, trying to optimize efficacy versus adverse events. Although 8-aminoquinolines should be used in combination with other antimalarial drugs, new combinations cannot be assumed to be safe and efficacious unless specifically tested.

QUININE COMBINATIONS

Once pamaquine's limitations were understood after monotherapy was pushed to toxicity, quinine combinations were used to try to minimize adverse events as well as subsequent relapses. Working in a Indian hill station with chronically infected British soldiers, Sinton determined that a synergistic effect eliminating most relapses was possible when pamaquine and quinine were given concurrently; however, this was not seen if the same drugs at the same dosages were given consecutively.[6] This important clinical observation has not yet been mechanistically explained and remains paradoxical as noted by Hackett.[1] Synergy when using concurrent medication against *P. vivax* relapses was confirmed when primaquine was the 8- aminoquinoline drug used during U.S. clinical trials[7] (Table 1).

Quinine combinations with pamaquine were noted to be remarkably free of adverse events as stated by Manson–Bahr.[2] Patients had visibly less methemoglobinemia, and their chronic malaria spleens shrank more quickly than when given pamaquine alone. Even today, these observations cannot be explained mechanistically and speculation must be directed toward changes in drug metabolism caused by induced enzymes, possibly cytochromes or heme oxygenase. Because quinine was the only other specific antimalarial drug available in the 1920s, the choice of combinations was limited, and empiric regimens were devised that largely differed by the number of days during which drugs were given as monotherapy or in combination.

QUINACRINE COMBINATIONS

Quinacrine was tried as a substitute for quinine as soon as it was commercially available in the 1930s. Chemoprophylaxis was thought to be its main indication because it was less objectionable in taste and better tolerated than quinine; quinacrine was widely used on tropical plantations and in military units.[8] Unfortunately, it did not seem to synergize with 8-aminoquinolines against *P. vivax* relapses, although nearly

*Address correspondence to G. Dennis Shanks, ADF Malaria and Infectious Diseases Institute, Enoggera, QLD 4051, Australia. E-mail: dennis.shanks@defence.gov.au

TABLE 1
Some 8-aminoquinoline combinations used historically as referred to in text and noted references

Drug	Combinations that worked well	Combinations that worked poorly	Toxicity changes induced by combinations
Pamaquine (plasmochin)	Quinine[2,7]	Atabrine (quinacrine)[3]	Better: quinine[2] Worse: atabrine (quinacrine)[10]
Primaquine	Quinine[7] Chloroquine[15]		Better: methylene blue[18]
Tafenoquine	Chloroquine[23]	Dihydroartemisinin and Piperaquine	As-yet unknown

every study had a counterpart with differing findings varying widely in populations treated and parasites inhibited. Although only understood in retrospect, quinacrine was highly protein-bound, and this appeared to displace 8-aminoquinolines and thus artificially increase the drug's concentration without contributing to improved outcomes. Spreading drug administration over longer periods of time was common with weeks-long regimens being commonly followed by convalescent periods that were often interrupted by further *P. vivax* relapses.

Whereas pamaquine and quinine combinations were introduced into the Indian Army's treatment schedules without great problems, the addition of quinacrine in the 1930s saw reports of infrequent but severe hemolytic episodes clinically resembling the feared syndrome of blackwater fever.[4] Rare deaths from renal failure usually resulted only when quinacrine and pamaquine had been used together prompting many medical officers to require a gap of a few days after ending quinacrine before starting pamaquine. Despite these difficulties, the triple drug combination QAP evolved into the British/Indian Army's standard malaria treatment regimen, which worked well until challenged by rapidly relapsing tropical vivax malaria in Southeast Asia during the Second World War.[3]

Pamaquine combinations, however, did not go so well in the U.S. Army where malaria in the Panama Canal Zone had largely been controlled by Gorgas's sanitation interventions and quinine suppression was given to soldiers on field exercises[9] (Figure 1). When large numbers of civilian laborers were imported from malarious areas of the West Indies (e.g., Jamacia) in 1943, it was decided that they should all receive chemotherapy regardless of symptoms to prevent transmission as they entered the Canal Zone. A standard regimen of quinacrine (300 mg daily for 5 days) followed a 2-day gap and then pamaquine (30 mg daily for 5 days) was used. This combination was already being used by the United Fruit Company throughout Central America as well as by the U.S. Army for civilians with asymptomatic parasitemia in Panama.[10] The crucial difference resulting in many unexpected hemolytic episodes likely was that the asymptomatic workers in Panama did not receive any initial quinine as in standard QAP treatment as there was no need to suppress symptoms such as fever. An epidemic of hemolytic reactions resulted from 4,361 persons given pamaquine, 401 ($>$ 8%) being hospitalized for drug toxicity marked by hemolytic jaundice. Sixty workers received 92 blood transfusions, but none died. The U.S. Army Surgeon General determined that pamaquine was a potentially dangerous drug and should not be used in the U.S. military, a finding that was partially reversed when large numbers of soldiers in the Southwest Pacific began to relapse frequently with vivax malaria.[11] Confirmation of the increased risk of hemolysis when giving QAP without the quinine component comes from the Indian Army in 1944, which used a preventive ("blanket") treatment course of quinacrine and pamaquine in asymptomatic soldiers prior to the monsoon during operations in Southeastern Burma.[12] This preventive measure was found to induce severe hemolysis (resulting in three deaths) in 2.6 times (0.13% versus 0.05%) more soldiers than QAP given for symptomatic malaria in the same formations of the 14th British Army.

CHLOROQUINE COMBINATIONS

Chloroquine was not initially thought to be a useful addition to malaria chemotherapy because its toxicity was overestimated from its severe cardiac effects on dogs.[13] Once the French experience in Tunisia was appreciated by the U.S. military who obtained the Pasteur Institute records in 1943, chloroquine was put into clinical trials in the United States in 1944 and found superior to quinacrine in all aspects after 5,000 cases were treated by 1946.[13] Chloroquine was used as the primary form of chemoprophylaxis for the U.S. Army in Korea and given the great sensitivity and seasonality of Korean vivax, it was successful in preventing acute infections. Unfortunately, this did not apply to relapse infections which typically occurred in the year after initial infection.[14] Primaquine was the preferred 8-aminoquinoline based on estimates of its toxicity compared with pamaquine, so chloroquine-primaquine combinations were tested and found effective.[15] Just as quinine showed genuine synergy when simultaneously used in combination with pamaquine, a similar synergistic effect for concurrent medication was observed with chloroquine and primaquine.[7] This was exploited by the mass treatment of $>$ 300,000 U.S. soldiers returning from Korea with 2 weeks of daily 15 mg of primaquine.[5] Despite the large number of soldiers involved, only two cases of methemoglobinemia and one case of hemolytic anemia were reported. It is important to note that all soldiers had been receiving 300 mg chloroquine weekly while in Korea, so the postdeployment eradication treatment that was actually a delayed form of combination therapy.[14]

Therefore, a large epidemic of postdeployment *P. vivax* relapses during the Korean War was ended by the mandatory use of 2 weeks of primaquine (15 mg daily) given to soldiers after having received chloroquine chemosuppression while in Korea.[14] The original dosage of 30 mg primaquine daily was not tolerated by Black soldiers, which lead to the discovery of glucose-6-phosphate dehydrogenase deficiency as the likely cause for hemolytic reactions.[16] Interestingly although Italian and Greek soldiers were in the U.S. Army in nearly equal numbers to Black soldiers, hemolytic reactions were almost entirely reported in Black soldiers despite the Mediterranean version of G6PD deficiency being

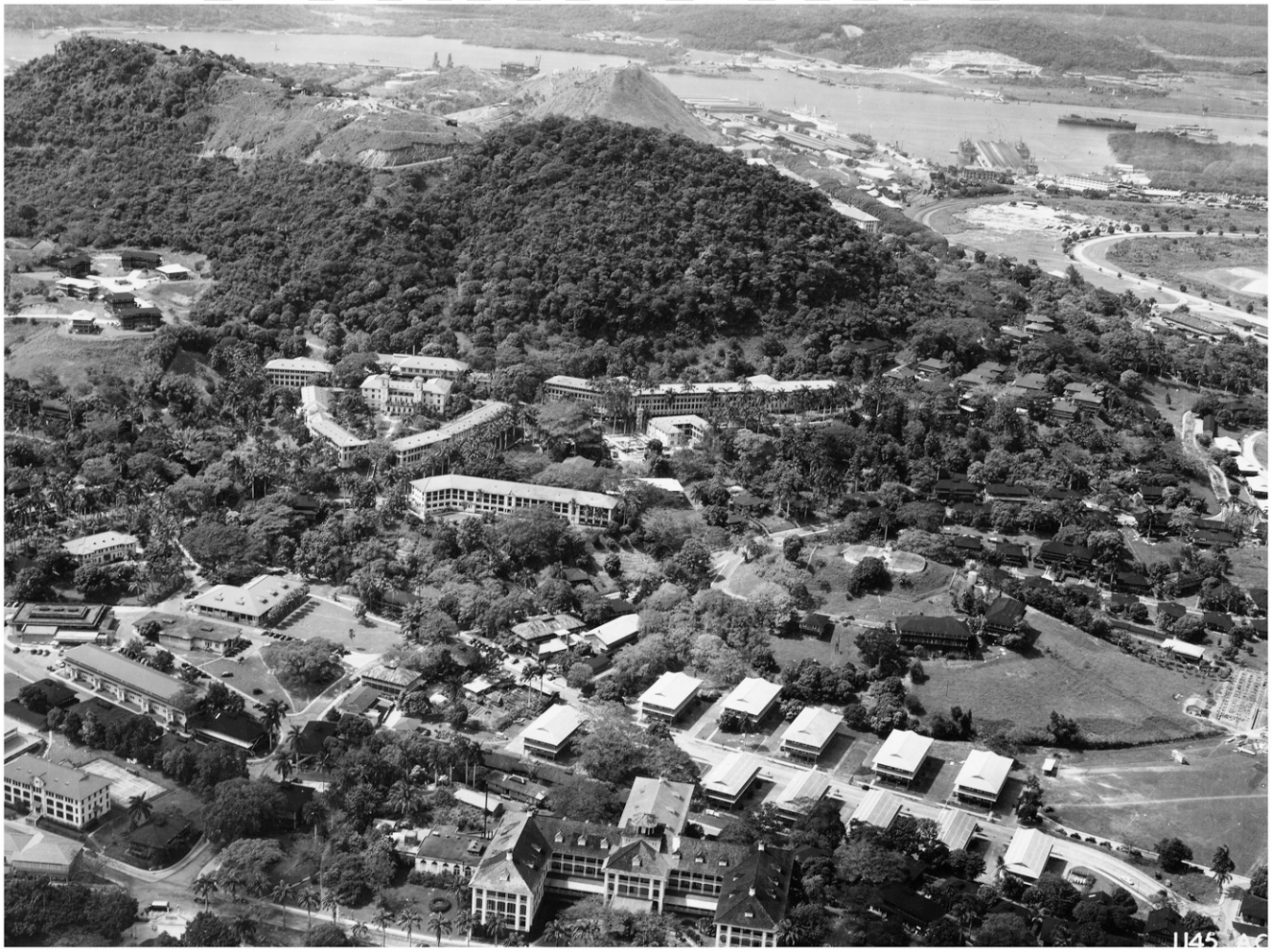

FIGURE 1 Photo of ANCON (later known as Gorgas Memorial) Hospital in the Panama Canal Zone where many of the workers experiencing hemolytic reactions after receiving quinacrine followed by pamaquine were treated in 1943.[10] Photo from National Archives and Records Administration (NARA 68147526).

more severe. Some reports of severe hemolysis in Italian and Greek soldiers exist, and it should not be assumed that primaquine can be safely given without accounting for G6PD deficiency.[17] Primaquine given in very large dosages (120 mg daily) produced much lower concentrations of methemoglobin, when instead of being used as monotherapy, it was combined with chloroquine, quinine, or methylene blue by uncertain mechanisms likely related to changes in redox chemistry.[18]

The Vietnam era CP tablet was perceived as problematic as it was based on the Korean experience and certainly did not adequately suppress chloroquine-resistant falciparum malaria, which was emerging in Southeast Asia in the early 1960s.[19] However, if the soldiers took the medication under strict military discipline, the efficacy markedly improved, pointing out that the major problem was compliance with the assigned regimen.[20] Unlike the Korean War, Vietnam-era U.S. soldiers were mostly flown back to the United States at the end of their military service, thus removing the option of enforced compliance with daily primaquine. Soldiers were instructed to take eight weekly CP tablets as terminal prophylaxis with mixed results. The malaria cases observed in Vietnam veterans after return to the United States were largely due to noncompliance and split between both vivax and falciparum malaria.[21] Malaria transmitted to U.S. civilians by veterans through mosquitoes was extremely rare or nonexistent, although multiple cases of transfusion (blood and intravenous drug use) malaria occurred.[20]

Considering that during the Vietnam War the weekly combination CP tablet was given to more than two million U.S. soldiers, severe adverse events were reported infrequently. Although well known for creating some mild gastrointestinal adverse events, CP tablets apparently caused few hemolytic reactions, even though they were given to $>$ 20,000 Black soldiers with likely G6PD deficiency (up to 10% of Black males).[17] As renal failure was handled in specialist medical units, it can be stated that there were 12 cases of acute renal failure due to hemolytic reactions in the U.S. Army during the Vietnam War, many of which were related to nonmalaria infections (scrub typhus, leptospirosis), and few serious hemolytic reactions were due solely to primaquine. In comparison, 42 U.S. soldiers suffered acute renal failure from falciparum malaria. No U.S. soldiers appear to have died during the Vietnam War due to primaquine-induced hemolysis despite the large numbers of CP tablets used.[22]

Good clinical practice with 8-aminoquinolines appears to be balanced on a knife-edge of redox activity sufficient to inactivate hypnozoites and prevent relapses without overly damaging erythrocytes leading to clinical hemolysis. Different drug partners both affect redox metabolism and drug protein-binding, which often cannot be predicted before actual clinical testing. As-yet unpublished studies in Indonesia of the INSPECTOR trial (abstract 1501, ASTMH 2020) indicate that the newest 8-aminoquinoline, tafenoquine, cannot be used with dihydroartemisinin and piperaquine to prevent relapses, despite optimism that a single combination would work for both falciparum and vivax malaria. These disappointing findings contrast with tafenoquine's success when combined with chloroquine and highlight our inability to predict the usefulness of new antimalarial drug combinations prior to full-scale field trials.[23] A century on, we do not yet understand 8-aminoquinoline metabolism and have only vague notions of hypnozoite biology. Empiric 8-aminoquinoline combinations have been given to literally millions of people with malaria successfully, but these regimens were slowly worked out in large series and apparently were fairly specific to the human and parasite populations involved. The last human parasite standing in a nearly eliminated area will almost always be one that can relapse from hypnozoites in the liver. History teaches us that improved and adapted 8-aminoquinoline combinations will be required, if malaria elimination is to be achieved.

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Author's address: G. Dennis Shanks, ADF Malaria and Infectious Diseases Institute, Enoggera, QLD 4051, Australia. E-mail: dennis.shanks@defence.gov.au.

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