Review Article

Historical Review: Problematic Malaria Prophylaxis with Quinine

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Abstract. Quinine, a bitter-tasting, short-acting alkaloid drug extracted from cinchona bark, was the first drug used widely for malaria chemoprophylaxis from the 19th century. Compliance was difficult to enforce even in organized groups such as the military, and its prophylaxis potential was often questioned. Severe adverse events such as blackwater fever occurred rarely, but its relationship to quinine remains uncertain. Quinine prophylaxis was often counterproductive from a public health viewpoint as it left large numbers of persons with suppressed infections producing gametocytes infective for mosquitoes. Quinine was supplied by the first global pharmaceutical cartel which discouraged competition resulting in a near monopoly of cinchona plantations on the island of Java which were closed to Allied use when the Japanese Imperial Army captured Indonesia in 1942. The problems with quinine as a chemoprophylactic drug illustrate the difficulties with medications used for prevention and the acute need for improved compounds.

“The use of quinine has been known for 300 or 400 years, yet no one is even now able to state how the quinine should be taken, in what manner, and in what doses.” Warrington Yorke.¹

Quinine was the first specific drug for malaria infections, derived from an alkali extract of cinchona bark from Andean forests, and supposedly was first recognized when it was used to treat tropical fever in the Countess of Chinchon in Peru. Initially introduced to Europe as Jesuit's bark in the 17th century, claims for its efficacy often varied by nationality of the physicians involved as much as the quality (bitterness) of the bark.^{2,3} As early as the Siege of Belgrade in 1717, cinchona bark was being used to suppress malaria in soldiers.⁴ James Lind of the British Royal Navy in 1777 recommended that ships on the Guinea station (west Africa) “*be supplied with a large quantity of bark in powder and of wine to be issued occasionally to those who are sent in boats up rivers and on shore.*”⁵ Cinchona bark varied greatly in its concentration of the active alkaloids, so it was not until these compounds were isolated by the French chemists Pelletier and Caventou in 1820 that dosages were even able to be estimated. Various proprietary compounds largely containing quinine such as Warburg's mixture and Sappington's fever pills were popularized as treatments for fevers and agues now thought to be due to malaria.⁶ The organized use of large amounts of quinine to prevent malarial illness was largely done by colonial military units in the tropics, especially Africa and southeast Asia.^{7–15} For unclear reasons, parasite resistance to quinine is very uncommon unlike nearly all other antimalarial drugs.¹⁶ An immense body of historical literature discusses the various aspects of using quinine for malaria prevention, and an even larger number of papers describe various aspects of an associated disease known as blackwater fever.^{17–21} This literature, particularly as it applies to military units, will be very briefly reviewed with the purpose of illustrating characteristics needed in modern drugs for malaria chemoprophylaxis.²²

CHEMOPROPHYLAXIS

Quinine is a short-acting medication where a single oral dose maintains a measurable drug concentration for a matter of hours not days. Its foul taste is recognized in the “bitters” used to prepare gin and tonic. In therapeutic doses, it often causes a set of unpleasant symptoms known as cinchonism which includes tinnitus, vertigo, headache, dysphoria, nausea, and vomiting.² It is available in a variety of salts of variable solubility ranging from dissolved liquid to rock-like pellets found in the stool after oral ingestion. As a medication to give to otherwise well soldiers in hopes of keeping them free of malaria, it has several problems relating to maintaining compliance with an unpleasant, imperfect drug.³

Even in frequent repeated doses likely to cause cinchonism, quinine does not actually prevent malaria infection either due to the more lethal falciparum or relapsing varieties such as vivax.²³ Infection occurs in the liver, which then seeds the bloodstream approximately 10 days after an infective mosquito bite. Quinine suppresses malaria infections in the blood with the aim to maintain the soldier fit for duty. Cessation of daily quinine suppression will soon result in symptomatic malaria as bloodstream infections recrudescence or latent liver parasites (hypnozoites) of vivax malaria relapse. Even high levels of medication compliance will result in occasional symptomatic episodes of malaria which discredits both the drug and the physician.^{7,9,11,24}

Ordering a military unit to take quinine to prevent symptomatic malaria was at best problematic with the risk of cinchonism seemingly poorly balanced against the modest benefit of suppressed parasites. “Prophylactic rations” of quinine were tried in the British/Indian Army during its campaigns in China in the 1860s.²⁵ Multiple comparative tests of quinine versus no medication in various military units were tried by enthusiastic medical officers in India, often with indeterminate results.^{4,9–11,26,27} When reading reports from the 19th century, it is important to realize that the parasitic nature of malaria was not understood until Medical Assistant Major Alphonse Laveran of the French Army in Algeria found microscopic parasites in 1880; its transmission by mosquitoes was revealed only after the discoveries of Surgeon Major Ronald Ross of the Indian Army in 1898, and

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FIGURE 1. Australian soldiers in Rabaul, New Guinea, receiving their daily regimen of quinine to prevent malaria, August 3, 1917 (Australian War Memorial photo A2739).

comparative clinical trials were not well designed until mid-20th century.^{28,29} Surgeon General George Sternberg of the U.S. Army recommended prophylactic quinine in his 1884 textbook, but seemed just as impressed by the benefit of a good cup of coffee.³⁰ In all cases, soldiers heartily disliked regular quinine parades and adopted multiple means to avoid ingesting the medication (Figure 1).

When the first large scale attempt by Lieutenant Colonel S. Price James and Captain S. Rickard Christophers to control mosquitoes to stop malaria at Mian Mir (near Lahore, now in Pakistan) failed despite filling in the canals, quinine treatment of children in the bazaar and soldiers in barracks added little in the way of efficacy.^{31,32} Lieutenant Colonel S. Price James on reviewing the results of the many years of work at Mian Mir, became a major proponent of prophylactic quinine largely due to practicality, especially cost.⁹ His advocacy of quinine prophylaxis at the League of Nations Malaria Commission was matched by massive civilian quinine distribution projects in both Italy and India.^{27,33} Whether the drug was beneficial was difficult to determine, but at least the Italian malaria mortality rates continued to decrease during the interwar period.³³ By the advent of the Second World War, multiple national armies were well aware of the limitations of quinine prophylaxis, but it remained the standard medication as the only two synthetic antimalarial drugs pamaquine and atabrine (also known as mepacrine, quinacrine, and atebrin) had severe adverse events or had not yet been widely field tested, respectively.³⁴

SEVERE ADVERSE EVENTS

Blackwater fever usually occurs in expatriates living for several years in a highly malarious area while taking intermittent and variable amounts of quinine.^{17,20} Rarely, a massive hemolytic event occurred in a person who had previously

tolerated the medication, resulting in hemoglobinuria (blackwater), sometimes progressing to acute renal failure and death. During the early 20th century, blackwater fever was the leading medical cause of death in expatriate soldiers and administrators in colonial Africa and some parts of south Asia. The relationship to quinine was not universal, but a series of blackwater fever patients showed that a larger than normal quinine dose usually preceded hemolysis by some hours. During the building of the Panama Canal from 1904–1910, Colonel William Gorgas of the U.S. Army distributed literally tons of quinine, subsequently observing 226 blackwater fever cases from a total worker population of 50,000; it occurred mostly in Spanish and Italian laborers.^{18,24} The pathophysiology of blackwater fever was widely studied, but remains poorly understood. Its association with prophylactic quinine meant that very different national policies existed, and different groups of expatriates had fixed ideas about what was or was not the appropriate use of the drug.^{1,8,19} Blackwater fever entered the folklore of African expatriates, where besides being greatly feared as supposedly always being lethal, required never moving a blackwater fever patient from his sickbed as this would surely cause immediate death.

The most definitive information on the genesis of blackwater fever was gathered by Brigadier G. M. Findlay of the British Army in western Africa during the Second World War.⁵ Hemolytic episodes rapidly increased after large numbers of British soldiers had been receiving prophylactic quinine for some months. In 1942, blackwater fever risk in British soldiers in west Africa was about 8/1000, and had approximately a 30% mortality rate. On March 15, 1943, the entire military command switched from quinine to atabrine for malaria chemoprophylaxis. It was reported that blackwater fever subsequently disappeared from British soldiers except for a few stubborn individuals that insisted on continuing to

self-administer quinine regardless.³⁵ Interestingly, it was after the switch to atabrine that hemolytic episodes in African soldiers began to increase, perhaps due to glucose-6-phosphate dehydrogenase (G6PD) deficiency.³⁶ Blackwater fever cases are still seen in circumstances when physicians revert to chronic quinine use, but its actual cause remains poorly understood as some complex interaction between falciparum malaria, G6PD deficiency, and quinine.²¹

PUBLIC HEALTH

Prophylactic quinine was aimed at the individual, but also had implications for the entire military and civilian population. Those on chronic quinine suppression in areas of high malaria endemicity might still have a few parasites seen on microscopic blood smears, indicating how imperfectly a short-acting drug dealt with chronic infections.^{27,37} Although quinine had no effect on hypnozoites in the liver, there is recent evidence that quinine can increase the switching of *Plasmodium falciparum* from the erythrocytic cycle to the sexual stage gametocytes needed to infect mosquitoes.³⁸ The best argument used by those favoring mosquito elimination against those advocating mass drug administration with quinine for malaria control was that by increasing the number of persons with gametocytes in their blood, one was actually increasing and not decreasing potential transmission to new persons. Given the epidemiological tools available, this was an untestable hypothesis which left free rein for authoritative professors to advocate their particular prejudice. Much heat with little light was generated by extensive late night discussions recorded during meetings of the Royal Society of Tropical Medicine and Hygiene in London.^{1,8,13,34,39} Review of programs of national distribution of quinine were ambiguous as to their efficacy, and were often done largely for social or political ends as in Mussolini's "bonification" of the Pontine Marshes near Rome in the 1930s.^{32,33}

DRUG SUPPLY

Quinine was subject to the first global pharmaceutical cartel when the usually noninterventionist Dutch government saw falling prices nearly destroy the commercial viability of its East Indies (Indonesia) cinchona plantations.^{2,3,40} The conflict between plantation owners, mostly in the East Indies, wanting high prices and quinine manufacturers, predominately in Germany, wanting low prices with a steady supply of bark seemingly could not be managed solely by market forces. This resulted in a series of Quinine Agreements from 1913, whereby the Dutch government sought to control the price of cinchona bark while maintaining the financial health of the cinchona plantations.⁴¹ All cartels have unintended consequences, and the Quinine Agreements resulted in a near monopoly of cinchona grown in the Dutch colonial East Indies, while discouraging any industrial innovation that might have produced a synthetic substitute for quinine. This was the proximate cause of the military supply crisis generated when the Japanese Imperial Army captured the East Indies, and acquired essentially the entire world's supply of quinine. Desperate efforts in 1942 were made to provide quinine for Allied soldiers, which included Colonel N. Hamilton Fairley of the Australian Army bargaining directly for a ship load of cinchona in Batavia

that was later intercepted or diverted, and Colonel Arthur Fischer of the U.S. Army flying out of Mindanao, in the Philippines, on the last surviving aircraft holding a box of cinchona seeds that were eventually planted in Costa Rica.^{2,41} An emergency scientific effort to develop new antimalarial drugs was second in priority only to the Manhattan Project (nuclear weapons) in the U.S. military's Second World War research and development activities.

CONCLUSION

The history of prophylactic quinine indicates that medical officers were doing their best under the circumstances with an unpopular and imperfect drug. Multiple studies failed to show substantial differences between those given quinine and comparator groups, which often generated polarized opinions regarding why the study was not done to an adequate standard versus why the drug cannot possibly accomplish the task assigned.^{9,11,13,14,37} Blackwater fever generated its own subculture of fear and mystery which has still not been penetrated.^{17,20,21} Prophylaxis of an individual does not always translate to epidemiological advantage for a population. A single source of vital drug supplies risk disruption when an unanticipated event intervenes.^{40,41} Quinine was eventually superseded by better chemoprophylactic medications, and now is largely of historical interest.

By the end of the 20th century, three different antimalarial drugs were available for malaria chemoprophylaxis: doxycycline, atovaquone with proguanil, and mefloquine. Despite having access to effective medications far superior to quinine, both soldiers and travelers continue to be infected by malaria in the tropics, often becoming critically ill on return. Information gathered by the U.S. Centers for Disease Control invariably shows that the greatest number of malaria cases reported in the United States either received no medication for prevention or a regimen outdated by drug resistance.⁴³ Although better than quinine, both doxycycline and atovaquone with proguanil still require daily medication and some continued use after return from the endemic area. The adverse event profile of doxycycline commonly includes gastrointestinal upset rather than cinchonism. The rare neuropsychiatric adverse events of mefloquine mean that few people are willing to take it, especially after reading various internet posts. The same problems initially seen with quinine consisting of common nonserious adverse events, fear of rare serious adverse events, and availability or cost issues are the usual reasons why modern soldiers and travelers report noncompliance. Given human nature, it is unlikely that these impediments will ever disappear regardless of the medication used.

History indicates what is needed in the future for malaria chemoprevention without having to painfully repeat all the lessons of the past. Medications that are difficult to administer or unpopular to ingest are not good drugs to give to otherwise well persons. When the benefit of the medication is only the future absence of illness, then the perceived risks need to be very low. Severe adverse events, no matter how rare, once associated with a medication often dictate policy despite, or perhaps because of, the inability to estimate the actual risk to an individual. Critical pharmaceutical supplies need to have multiple sources to avoid unanticipated disruptions. It is greatly hoped that future medications for malaria chemoprophylaxis provide a substantial improvement over

current medications and the inevitable problems that arise when introducing a new medication for malaria can be successfully managed.⁴²

Received February 22, 2016. Accepted for publication April 16, 2016.

Published online May 16, 2016.

Acknowledgments: I thank the many unnamed historians, medical librarians, and archivists who have unselfishly provided references, data, and ideas for this essay.

Disclaimer: The opinions expressed are those of the author and do not necessarily reflect those of the Australian Defence Force or the U.S. Department of Defense.

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