

Reports on Individual Drugs

Long-acting sulfonamides in antimalarial preparations

In January 1985, shortly after the antimalarial drug mefloquine was first registered, the World Health Organization, at the recommendation of its Scientific Group on Chemotherapy of Malaria, issued advice to governments intended to reduce the risk of development of mefloquine resistance in *Plasmodium falciparum* malaria (1). Two principal proposals were made: firstly, that mefloquine be reserved exclusively for treatment of acute attacks where multiple drug-resistant *P. falciparum* exists; secondly, that combination products (such as the combination of mefloquine, pyrimethamine and sulfadoxine) likely to delay the development of drug resistance be preferred to mefloquine alone for both treatment and prophylaxis, except for individuals suspected of being sensitive to one of the other components—and particularly to sulfonamides.

This advice reflected the crucial need to preserve mefloquine as an effective blood schizonticide in falciparum malaria, particularly since selection of strains naturally resistant to mefloquine as well as development of resistance in originally susceptible parasites was feared (2, 3). Since these recommendations were issued, however, a number of reports of severe skin reactions including fatal cases of Stevens-Johnson syndrome have been published. These reactions have occurred largely in travellers receiving pyrimethamine/sulfadoxine combinations for prophylaxis and they have reopened the debate on strategies by which *P. falciparum* inoculation can best be prevented and treated.

Pyrimethamine, an antifolate, was first intensively used for prophylaxis against malaria in 1952. Within eighteen months resistance was widely reported and, in some areas at least, this regressed only very slowly on withdrawal of treatment (4). However, because of the subsequent rapid emergence of chloroquine-resistant strains, pyrimethamine was later reintroduced for prophylaxis in combination with the long-acting sulfonamide sulfadoxine or the

sulfone dapsone. These drugs are slow-acting schizonticides which, used alone, have unimpressive antimalarial activity. Like pyrimethamine, however, they have an antifolate action. Used together, the two drugs act synergistically, and this provided an expectation that combination therapy might also delay the appearance of drug resistance.

The emergence of resistance to the combination appears, indeed, to have developed much more slowly than when pyrimethamine was used alone. None the less, it is now widespread in South-East Asia and it is becoming more common in East Africa and South America (4). It was on this knowledge that WHO's recommendations regarding the use of the triple combination product were based. They were also supported by experimental evidence that emergence of resistance to mefloquine in mice infected with *Plasmodium berghei* and *P. yoelii nigeriensis* is delayed in the presence of sulfadoxine and pyrimethamine (5-7). However, this work has been criticized on the grounds that it was performed with organisms that had been repassaged repeatedly in mice, but not in mosquitos.

Due consideration was given, at the time, to the serious adverse reactions that occasionally result from exposure to long-acting sulfonamides. But previous experience of their use, not only in combination with pyrimethamine but also in antibacterial combination therapy, suggested that their anticipated benefit in antimalarial therapy far outweighed their apparent risks. Isolated and occasionally fatal cutaneous reactions (erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis) had been reported in patients taking repeated doses during prolonged periods of malaria prophylaxis (8-10). But there was no reason to believe that their incidence exceeded that ascribed to antibacterial trimethoprim/sulfamethoxazole combination products which is estimated to be of the order of 1:100,000, of which about 16-20% are fatal (11, 12). Indeed, by 1982, the major manufacturer of pyrimethamine/sulfadoxine combination had received a total of only 10 notifications of serious suspected reactions by which time an

estimated 1.5 million people had used the product for malaria prophylaxis (13).

The possibility that such cases escape attention had seemed unlikely, even though evidence existed that sulfadoxine used alone at higher dosage in the treatment of other conditions resulted in a higher incidence of severe reactions (14-16). None the less, in late 1984, the Centers for Disease Control in the United States of America became suspicious that the risk had been underestimated when a cluster of four serious skin reactions was reported in individuals who had received antimalarial preparations containing sulfonamides (17). A subsequent survey of burns units throughout the USA (where many patients with such skin conditions are now treated) and of death certificates of American citizens who had died abroad between 1982 and 1984 identified a further 20 cases, seven of which were fatal (18, 19). These figures suggest that severe reactions occur in 1:5000 to 1:8000 users and that the risk of death is 1:11,000 to 1:25,000.

All but one of these patients had received chloroquine in addition to pyrimethamine/sulfadoxine combination, a finding which has raised speculation that this regimen may be particularly hazardous (20, 21). The association is, however, more readily attributable to US policy at this time to recommend concurrent use of chloroquine to provide additional protection against *P. vivax* malaria (22). Worldwide, of 81 cases of serious cutaneous adverse reactions associated with use of pyrimethamine/sulfadoxine reported to the manufacturers by late 1985, only 28 had received chloroquine (23).

Whether the estimated incidence of serious reactions among Americans is representative of experience elsewhere remains uncertain. An unpublished survey of reactions reported in Sweden places the risk of severe reactions to pyrimethamine/sulfadoxine at less than 1:60,000. Yet a similar retrospective survey in Switzerland—where, until 1984, chloroquine was not commonly taken together with pyrimethamine/sulfadoxine—provided an estimated incidence of severe reactions of only 1:150,000 between 1974 and 1985, and no fatal cases were identified (23). The authors of the Swiss study conclude that concurrent use of chloroquine may slightly increase the risk but, unless the hypothesis

is supported by further retrospective studies, it will remain unproved.

Meanwhile, in the light of the available findings, WHO has recommended that prevention of malaria should be based, as far as is practicable, on protection against mosquito contact, and that, as a rule, travellers to areas where chloroquine-resistant *P. falciparum* infections are prevalent should use mefloquine—or pyrimethamine/sulfadoxine if mefloquine is not available—only if they develop a febrile reaction, if prompt diagnosis and medical attention is not easily available and, if the combination product is to be used, there is no suspicion that they have previously developed sensitivity to sulfonamides (20).

The treatment of confirmed cases of malaria in areas where multiple drug-resistant *P. falciparum* is known to exist raises entirely different considerations of risk and benefit. Persuasive evidence of the value of mefloquine/pyrimethamine/sulfadoxine has been obtained, for instance, in northern Thailand where, previously, many cases of *P. falciparum* malaria were resistant even to therapy with quinine. It is estimated that by March 1986 over 95% of some 80,000 infections had been successfully treated with the triple combination, and as yet there is no indication that resistant cases are becoming more common (25-27). Only two cases of severe skin reactions have been reported. Although neither of these was fatal, one resulted in a child becoming partially blind (28).

Notwithstanding this largely reassuring experience there is concern that patients are being exposed to the risks of sulfonamide therapy in an area where resistance to pyrimethamine/sulfadoxine is known to be high and in the absence of conclusive evidence that these components are necessary to prevent the emergence of mefloquine resistance. Cautious clinical trials are consequently being planned in endemic areas to compare the performance of the triple combination with mefloquine alone. The results will undoubtedly be influential in determining the future management of multiple-drug-resistant malaria. However, should they appear to justify the use of mefloquine alone, they will impose upon health authorities an onerous obligation to maintain an ever-watchful eye for early signs of resistance to this drug of last resort.

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Amodiaquine and agranulocytosis

Following reports of agranulocytosis associated with prophylactic use of the antimalarial compound amodiaquine (Camoquin®, Parke Davis), the manufacturer decided early in 1986 to remove this indication from the data sheet in all countries where the drug is marketed. It remains available for treatment of malaria when it is used for relatively short periods of time on the grounds that, in these circumstances, potential benefits clearly outweigh the risks. Its position within the WHO Model List of Essential Drugs will be reconsidered when the List is next revised in 1987.

Amodiaquine, which is chemically related to chloroquine, was originally introduced some forty years ago. However, it only became extensively used within the last few years in the expectation that it would offer useful protection against chloroquine-resistant falciparum malaria. Sporadic cases of severe neutropenia were first reported as early as 1953 (2-13). These occurred more commonly in patients receiving the drug in anti-inflammatory doses for rheumatoid arthritis, rather than for protection against malaria, and concern that this response might be frequent enough to warrant reappraisal of the safety of the drug as an anti-malarial was not forthcoming until 1986 when seven cases were described among travellers returning to the United Kingdom (14). Sales figures for the use of amodiaquine in the United Kingdom suggested that the frequency of neutropenia among people taking the drug was about 1 in 2000.

Further confirmation of the magnitude of the apparent risk was produced almost simultaneously when five further cases were reported among patients referred to a single medical centre in Switzerland within a period of five months (15). Some of these latter patients also had evidence of liver damage—a finding which has no explanation since few reports of amodiaquine-induced liver damage were previously on record (16, 17).

In all, twenty-three cases of agranulocytosis associated with the use of amodiaquine were reported in a twelve-month period ending in March 1986, seven of which were fatal (18). Nearly all of these patients had used the drug at a dosage of

400mg weekly and the period of exposure ranged from 3 to 24 weeks. Fourteen of the patients were known to have taken either pyrimethamine/sulfadoxine or proguanil concurrently. This at first aroused speculation as to whether amodiaquine is safer when taken alone (1). However, this now seems unlikely; further cases have since been reported in which there was no history of exposure to other drugs. The question remains as to whether amodiaquine is effective as an alternative anti-malarial drug in areas where chloroquine resistance is widespread. Several reports from Africa have shown that although amodiaquine is more effective than chloroquine in these areas, this advantage is likely to be short-lived (19-21). On this evidence the risk of rapid selection of resistance reduces the value of amodiaquine as an effective replacement for chloroquine in the treatment of malaria.

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