

Considerations on the Use of Sulphones and Sulphonamides with a Pyrimidine Derivative

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SUMMARY

Trials conducted with sulphones and sulphonamides combined with a pyrimidine derivative for the assessment of their value in the treatment of malaria are reported, and reasons for the use of one of these combinations — Maloprim — by the Malaria Service of Mozambique are presented.

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In the chemotherapy of malaria, quinine has, as is known, a place all of its own. For long the sole effective antimalarial in use, it still has today, under special circumstances, an appreciable use. Scarcity of quinine in world markets forced research into substitutes and thus, gradually, several synthetic antimalarials were found and are now widely used, their therapeutic efficiency only occasionally being queried.

Recently, however, the discovery was made of resistance to synthetic antimalarials of *P. falciparum*, at first to the biguanides and diaminopyrimidines and, lately, to 4-aminoquinolines, especially chloroquine. This situation is evidently causing concern among clinicians and others responsible for the preparation and execution of control and eradication programmes. More particularly among malariologists, forced to regard malaria as a public health problem, affecting extensive areas and millions of people, this concern is added to their ever-present desire to find an ideal antimalarial.

Research into new means to face this understandably troublesome situation has resulted in a better knowledge of the previously known antimalarial action of sulphones and sulphonamides, especially when combined with a pyrimidine derivative (pyrimethamine or trimethoprim) because of their synergic and potentialising action. The Malaria Service of Mozambique has undertaken trials with the drug association mentioned. It should be mentioned that it has not been possible, for various reasons, to use the recommended and demanding scientific precision in the preparation, execution and analysis of these trials. Performed by personnel unfamiliar with this type of work, under rural conditions, they suffer naturally from deficiencies which, however, do not entirely rob them of value and practical utility.

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PYRIMETHAMINE-DAPSONE

The first trial was done with the combination pyrimethamine-dapsone, Maloprim (12.5 mg pyrimethamine and 100 mg dapsone) provided by Burroughs Wellcome. It was undertaken during the maximal transmission season, in 186 immune individuals with *P. falciparum* infection, living in scattered settlements in an area of mes-endemic malaria under 2 cycles of intradomiciliary DDT applications. Maloprim was given as a single dose of one tablet for adults and less for children.

The results were a notable schizonticidal action on *P. falciparum*; probably radical cure of infection since no relapses were seen during a reasonable period of observation; and presumably a reasonably prolonged prophylaxis.

Other findings during this trial were: in the 186 cases, 22 showed sexual forms of the parasite at the first examination, of which 3 persisted for 48 hours; at the end of 48 hours gametocytes were seen in 13 individuals not showing these forms previously; and no gametocytes were found in later examinations. The behaviour of these sexual forms of the parasite was, thus, ambiguous in the presence of the drug.

MALOPRIM PLUS CAMOPRIM

A new trial was organised, utilising the association of Camoprim, 2 tablets, with an increased amount of Maloprim, 2 tablets per adult and corresponding lower doses in children. This trial was undertaken in 242 cases in a population of 1 687 living in 10 localities of 2 areas not included in the house-spraying operations.

Follow-up of these cases showed (excluding absentees) the behaviour of gametocytes to be similar to that observed with the administration of Maloprim alone. The therapeutic action of a single tablet of Maloprim is comparable to that obtained with the combination of 2 tablets of Camoprim (schizonticide and gametocide containing a total of 300 mg amodiaquine and 30 mg primaquine) and 2 tablets of Maloprim.

I should add that with this dosage a few cases of jaundice were observed, probably haemolytic. Attention is drawn to this occurrence, inasmuch as there is, at times, a tendency for the simultaneous or sequential administration of antimalarial drugs each exhibiting haemolytic properties, without due regard of these properties.

In a further trial in an area with a high parasite index (70%), 229 cases with *P. falciparum* infection — of which 41 showed sexual forms of this parasite and 49 had asexual forms of *P. malariae* — were treated with a single

tablet of Maloprim and 2 tablets of Camoprim in adults (and corresponding doses in children) with similar results.

SULPHONAMIDE AND PYRIMETHAMINE

Brief mention is now made of a trial with the combination of a long-acting sulphonamide and pyrimethamine—Fanasil-pyrimethamine (500 mg Fanasil plus 25 mg pyrimethamine) kindly provided by Hoffmann-La Roche. The tablets were given in a single dose, 2 to 3 tablets in adults and lower doses in children. The trial was undertaken in an endemic area, with a prevalence of about 68%, where no antimalarial measures were in effect on 276 patients.

All had *P. falciparum* infections, of which 33 showed sexual forms and 49 were also infected with *P. malariae*.

The results showed a notable schizonticidal effect against *P. falciparum*; a marked gametocidal action particularly during the 5th week, whence its special epidemiological interest; and a notable and rapid schizonticidal action against *P. malariae*, with negative parasitaemia up to the 5th week.

SULPHONAMIDE AND TRIMETHOPRIM

The Malaria Service of Mozambique has a trial under way in which use is made of a combination of a delayed action sulphonamide with trimethoprim.

It is not yet possible to mention results, but observations can be made from the treatment of 4 acute cases where I personally used this compound, administered in a single dose of 6 tablets per adult. The patients were immune, and clinical improvement was seen at the end of 24-48 hours.

In this trial, as in those mentioned before, the appearance after treatment of gametocytes is obvious in individuals not showing them at the initial observation. This apparent gametocytogenesis, initially intriguing, should cause no worry, as has, indeed, been shown by others. It is believed, on good grounds, that these are degenerating forms and, due to the action of pyrimethamine, unviable; thus, a problem would only be present in the case of pyrimethamine-resistant strains.

DISCUSSION

In view of the results registered in the various trials mentioned above and of those reported in the literature, the Malaria Service of Mozambique has for some time, presumptively, been using, in preventive and radical treatment, especially in mass treatment, the combination dapsone plus pyrimethamine — Maloprim.

The Service is not unaware that in Africa so far no *P. falciparum* strains resistant to the 4-aminoquinolines have appeared (Technical Report, 1967; Richard Lenoble, 1971) and we have reached the same conclusion. We are also aware of the recommendation that these new therapeutic weapons should be held in reserve against the eventuality of the appearance of chloroquine-resistant parasite strains.

We further know that mass administration of sulphones and sulphonamides without the recommended and necessary regularity — seldom possible under our conditions — may lead to the appearance of resistant strains among pathogenic micro-organisms responsible for endemic tropical infections, although — I would stress — an association of drugs, each interfering at two different points of the parasite's metabolic chain — as is the case in point — should destroy this hypothesis of resistance.

Malaria is a prevalent endemic disease in Mozambique, against which the responsible State Health Service is waging, on a priority basis, an extensive and intensive campaign. In this effort, chemotherapy has a prominent place, and the drug has to be carefully chosen.

From our essentially practical point of view, the combination of dapsone and pyrimethamine, widely used by us, exhibits the following useful qualities: (a) economy of mass prophylaxis and cure: low cost, single dose; (b) easy and rapid administration: water-soluble, tasteless tablets; (c) simultaneous schizonticidal, sporonticidal and gametocidal action of undoubted clinical and, more notably, epidemiological usefulness; (d) good tolerance; (e) multi-efficiency: a wide spectrum antibacterial action of great advantage in the effort directed against some of the various endemic diseases in Mozambique, in a co-ordinated large-scale public health campaign evolving towards greater validity and efficiency.