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Therapeutic Screening to Differentiate Malaria from other Tropical Syndromes

BY

A. WOOD, MB. B.CH. (RAND)

King Edward VIII Hospital, Durban, Natal

In the bush and isolated areas of Africa, falciparum malaria is extremely difficult to diagnose, especially in the pernicious clinical presentation. Although the African states universally accept antimalarial precautions, malaria is still a serious problem, especially where the intensity of infection is hyperendemic and the rural medical services sparse and hospitals far removed. In Tropical Africa any acute fever of short duration may be malarial. (Gelfand, 1961).

The first infection with *P. falciparum* in infants born of immune mothers is generally associated with a low-grade parasitaemia and very mild clinical symptoms. (Garnham, 1949). This resistance to malaria infection is mainly due to the passive transfer of protective antibodies from the mother, contained in the 7S gamma globular fraction (IgG) of the serum. After the age of six months (Cohen *et al.* 1961, Edozien, 1962) the inherited antibodies are exhausted and acquired immunity is only fully developed when the child is 4 to 5 years old. During this period clinical effects are most severe and mortality is between 5-15 per cent. By the fifth year, 70-80 per cent. of children in stable malaria areas harbour the parasites in their blood (Colbourne, 1954). Thereafter, and through adulthood, the diagnosis and even death from falciparum malaria becomes increasingly difficult to determine.

The cardinal features of malaria are periodic fever, splenomegaly and slight hepatomegaly, normocytic nomochronic anaemia and leukopenia (Hunter, 1966) but the indigenous African in West or East Africa has a relative homologous immunity to *P. falciparum*, and rarely shows these classical characteristics. This immunity developed is initially an acquisition of a tolerance to the infection, generally with a cessation of clinical phenomena, despite persistence of parasitaemia, considerably in excess of initial clinical activity in childhood. Immunity depends on a persistent latent infection, but this is strictly strain specific, the individual becoming refractory. He is, however, not immune to other strains of *P. falciparum* in other areas, often only 50-100 miles away. The severity and presentation of the infection, however, is frequently modified. Thus, malaria in Africa still has a high morbidity rate and is responsible for more deaths than any other transmissible disease.

The certain diagnosis of active malaria is never easy among the "immunes" with chronic parasitaemia. Gametoyctes, even if confirmed as *P. falciparum*, may be found months and even years after an overt attack has subsided (Adams and Maegraith 1964).

The presence of trophozoits must be established, indicating the progress of an asexual cycle. Today, in clinical medicine, malaria is the greatest immitator amongst the "immunes" in Africa, often presenting clinically resembling other conditions. For instance, it may evoke a set of symptoms very similar to the acute surgical abdominal conditions such as appendicitis or peritonitis, or it may simulate pneumonis and pleurisy, especially in cases where spontaneous splenic infarcts or subcapsular haematomata have occurred.

The problem is how to diagnose and treat these malaria syndromes confidently with minimal diagnostic errors. It is often difficult for the doctor to differentiate cases of malaria from several other similar conditions; how much more so for a nursing sister! A diagnostic error of missing malaria was usually disastrous. In hospital, with doctors and pathological services, diagnosis by delay and repeated blood smears and observation is possible, but in remote areas the standard thick and thin stained smear for parasites alone, even if positive, is not always diagnostic.

THERAPY

Strains of *P. falciparum*, chloroquine resistant, were first reported in two patients from the Magdalina Valley in Columbia (Moore and Lanier 1961). The fear of progressive outbreaks of resistant malignant tertian malaria developing, has been confirmed by resistant strains being re-

ported in South America (Young, 1961), Brazil (Box 1963), Thailand (Young, 1962), Vietnam (Legters, 1965), and West Africa (Lasch, 1965). Drug resistance in malariology is defined as "the ability of a parasite strain to multiply or to survive in the presence of concentrations of a drug that normally destroys parasites of the same species, or prevents their multiplication" (W.H.O. 1965).

Then, from February 1968, exciting advances in anti-malarial management began appearing in the medical literature with a new approach (Martin and Arnold, December 1967). They had proven that Trimethoprim (T.M.) a dihyrofolate reductase, had several advantages over pyrimethamine as an anti-malarial against both normal and multi-drug resistant *P. falciparum*, as the protozoa were sensitive to a deficiency of bile acid.

Now not only could the dose of trimethoprim be reduced, but it was unlikely that resistant strains of *P. falciparum* would develop to trimethoprim. In February 1968 the first trial of trimethoprim and Sulfalene combination as antimalarials (Martin and Arnold 1968) seemed at last to hold out the hope of a one day treatment for malaria. This was further substantiated by the excellent proof of trimethoprim potentiating the effects of long-acting sulphonamides as antimalarials (Bushby and Hitchings 1968) and the safe combination of trimethoprim (TM) and sulfamethoxozole (SMZ) administered for daily periods from several months to two years (Kahn *et al.* 1968). At this time TM and SMZ, in the proportion of 1:5 became commercially available (Bactrim-Roche).

METHODS

I devised the following *single dose treatment* for use as an unselected screening regimen for differentiating *P. falciparum* malarial infections presenting in a pernicious form from the other fevers in the tropics, often mistaken for malarial fever. The differentiation was simply by a 24-48 hour therapeutic cure after the administration of a *single dose of 10 tablets* (Bactrim) containing a total dose of 800 mg trimethoprim and 4 gm of sulfamethoxazole. The patients, all African, were seen on an outpatient basis, and they all lived in the coastal belt of Southern Mocambique near the Zululand border. After blood smears had been taken, they were given 10 tablets as a single dose which were swallowed in the sister's presence. Thereafter they were allowed to rest for the next 24-48 hours for observation. If, after this period there were no signs of improvement or cure, the patients were removed to the nearest hospital as the diagnosis was then certainly not malaria.

The patients presenting with bizarre symptoms and signs were divided into five groups, according to the main presenting features when first seen.

Group I

Confusion and disorientation of sudden onset and short duration. Seventeen cases were seen and out of these 12 cases were confirmed as acute malaria and cured after the single dose therapy.

Group II

Acute diarrhoea either with mucus or blood. Forty-seven cases were seen and 13 cases confirmed as dysenteric malaria.

Group III

Mild fever, headaches and body pains. Twenty-seven cases seen and 10 cases confirmed as acute malaria.

Group IV

Indicative of acute respiratory pathology. Seventeen cases seen and 6 cases confirmed as malaria.

Group V

Presented with acute abdomen pathology. Seventeen cases seen and 4 cases only confirmed and cured of malaria.

If the single therapeutic dose cured the patient in 48-72 hours, then it was recorded as malaria positive. The initial pre-treatment thick and thin smears were later confirmed by a specialist malariologist as acute *P. falciparum* malaria. The confirmation strengthened the original accepted clinical cure.

In this initial single dose therapeutic trial, differences in sex, racial groups and patient's weights were not recorded. Only adult patients were included in the trial. Any minor differences on the above parameters were not taken into consideration in this study, because I felt that in a first small test these differences would not be of statistical importance.

	Total No. Cases	Positive Malaria	Other Conditions
Group I	17	12	5
Group II	47	13	34
Group III	27	10	17
Group IV	17	6	11
Group V	17	4	13
	125	45	80

Group I (17 Cases)

Clinical presentation: acute psychotic and confusional manifestations with disorientations or even mania.

Four of these cases presented with meningismus. Cerebral malaria in Africans in endemic areas is rare. The above presentation was associated with, or initially thought to be, acute alcoholism or dagga smoking.

24-48 hours after the initial single dose, 12 cases were compltely cured. The remaining 5 were transferred to hospital and diagnosed as meningococcal meningitis or encephalitis.

Group II (47 cases)

Clinical presentation: watery (greenish-yellow) diarrhoea with mucus and a little blood, or a frank bloody diarrhoea. Initially thought to be acute bacillary dysentry or acute amoebic enteritis.

48 hours after initial screening by single dose Bactrim as the only therapy, 13 cases were cured and confirmed as dysentric falciparum malaria.

The remaining 34 cases were later confirmed as other conditions on transfer to hospital, viz., typhoid fever and amoebic hepatitis.

Group III (27 cases)

In this group the presentation is complex and is suggestive of influenza, with general muscle pains and spasms, cramps in limbs, weakness, and backache in most cases, or an erythematous urticaria and headaches. The temperature is either normal or slightly raised (99 or 100). The skin is hot and dry and in three cases there was some cyanosis of the extremities. In a few cases the only presentation was a myalgia and arthralgia with some sensory clouding.

In endemic areas it is always essential to exclude malaria before making the diagnosis of heatstroke; or any of the short-term fevers, viz., dengue and sandfly (Phlebotomus) fever are most typical. Forty-eight hours after the single dose, 10 cases were completely cured and smears confirmed *P. falciparum* infection.

The remaining cases, after removal to hospital, were confirmed as tick typhus, undulant fever, trypanosomiasis, and even of heatstroke. Malarial pyrexia is clinically indistinguishable from heat pyrexia.

Group IV (17 cases)

Presenting symptoms are: unproductive cough, occasionally associated with a small haemoptysis and chest pain, pleural pain and basilar rales. This respiratory presentation is difficult to differentiate from bronchial or cavitating tuberculosis, ulcerative endocarditis or liver abscess.

Of these cases six were confirmed as malarial infection; two associated with splenic infarcts; three other cases were active tuberculosis; a few cases were basal bronchopneumonia, but one case was a primary atypical pneumonia difficult to diagnose as some patients develop pneumonia simultaneously with the acute attack of malaria, while others develop a secondary pneumonia.

Group V (17 cases)

Here the presentation was periumbilical or lower abdominal pain, associated with nausea and some vomiting or colic, suggesting the passage of gall stones or renal stones. This surgical abdominal presentation may readily be mistaken for appendicitis, acute cholecystitis or pancreatitis, especially if associated with jaundice.

The vomiting may be persistent and contain bile and often coffee grounds or unchanged blood, suggesting a form of malarial bilious remittent fever. In all the cases the 10 tablets Bactrim were administered orally, associated with intramuscular antiemetics. Four cases were proven malaria.

The remaining cases were pyelitis, hepalitis and one case of perirenal abscess.

DISCUSSION

Single dose treatment of acute *Falciparum malaria* is desirable and advantageous, especially in Africa where the best time to achieve any results of note is to administer the therapy completely at the time of consultation.

In all, 125 outpatients with tropical fevers were treated by random non-selection with Bactrim. In 48 hours by single dose diagnostic therapy 45 patients were confirmed as malaria and classed as cured. Unfortunately, it was not possible for any accurate lengthy followup for recurrences, but a positive observation was that relapses seemed to be absent in the treated cases that were possible to follow for some weeks. The 45 cures suffered little morbidity and nil mortality. Knowledge about malaria acquired from the management of the afflicted non-immune soldiers in Vietnam had reduced the total case fatality rate to 0,3 per cent. (Blount, 1967). The method I have tried and put forward may offer 10 per cent. cures and nil mortality but would require a more extensive trial in various areas, especially in management of chloroquine-resistant *Falciparum malaria* and long-term environment follow-up.

The effectiveness of TM and SMZ combination is evident from the fact that 45 cases of pernicious malaria were cured in 48 hours. Good results with Bactrim, although in a different management method, have been reported by others (Wolfensberger, 1970).

The dosage used in this trial exceeded the maximum recommended dosage (Roche) and may have been greater than required for the excellent clinical response, but patients may deteriorate rapidly with *P. Falciparum malaria*, especially the pernicious presentations, so an urgent diagnostic and radical therapeutic regimen was necessary. The rapid absorption of highly diffusible TM and SMZ and speedy action was observed in all cases.

Numerous confirmations of this effect have been reported (Herrero, 1967). Studies with other drug combinations (Chin *et al.* 1966) reported slow action in termination of clinical attack. Speed of action was the most important consideration of the drug combination in clearing parasitaemia, especially where incipient coma may be imminent (Woodruff, 1968).

Effective anti-malarial drugs must rapidly enter the red blood cells in sufficiently high concentrations to act against the erythrocytic schizonts. The sulphonamide (SMZ) presumably acts as a competitor of para-aminobenzoic acid in the synthesis of folic acid. SMZ combined with TM gives high plasma levels and localisation in red cells, resulting in its rapid effective clearing of parasitaemia and lysis of fever.

Trimethoprim is rapidly absorbed completely and has a relatively short half-life, only 14 hours. This was important, for the diagnostic results of the therapy were required rapidly. SMZ almost has the same half-life, about 11 hours, with some 50 per cent. of the drug bound to plasma proteins. In the dosage used in this trial clinical adverse reactions, in the form of gastro-intestinal distress, were seen in a few patients, but since most of the patients presenting prior to treatment already had nausea, the therapy was not contra-indicated. Nausea and vomiting are occasionally major problems in malaria management. If present, I followed the programme of splitting the loading dose into three or five portions and each portion was given at 20 minute intervals as recommended by Jopling (1968).

In anti-malarial management, low drug toxicity is of paramount importance. At the dosage found effective, viz., TM and SMZ in the ratio 1:5, there was no reduction of RBC, WBC or platelet count (Hunsicker 1969). Comparing the side-effects of all the drugs used in the chemotherapy of malaria (L. Meyler, 1968), the TM and SMZ combination is the least toxic. Most of the side-effects of the anti-malarial drugs are common, with a variable incidence. However, with Bactrim the tolerance is high, and toxic side-effects few. Various blood dyscrasias and skin rashes have been observed (1968). Greying and bleaching of the hair, and abnormal pigmentations after anti-malarial drugs have been described (Tuffanelli, 1963), but in the 125 cases in this trial, no toxic effects were observed.

Resistance may develop when one or both members of the combination therapy are found in a low concentration in the host early on in the clinical attack. The TM/SMZ combination in the single dose therapy that I have tried results in extremely high plasma and RBC levels within a short time after administration. This early high concentration and rapid complete clearing of the parasitaemia provided the major factor in the excellent results achieved. The recrudescences after only 24 hours therapy, reported in a 12 case series by letter to the Editor by Clyde, D. F. (July, 1969), were probably due to inadequate host concentrations of combination drugs.

Trimethoprim plus SMZ clears the parasitaemia in a significantly shorter time than any other drug combination (Dunno, 1969). To date resistance of the plasmodia to trimethoprim has not been demonstrated.

Thus I would like to recommend the use of BACTRIM (ROCHE) as the ideal drug for the wide-scale use in acute *P. Falciparum malaria* in Africa.

SUMMARY

Combined therapy with a single dose of sulphamethoxazole (SMZ) and trimethoprim (TM), as BACTRIM (ROCHE), was found to be effective alone for the treatment of *Plasmodium falciparum* infection. The TM and SMZ therapy was 100 per cent. effective in control of the clinical disease, without any recrudescences. This combined therapy is suggested as the ideal anti-malarial drug; as the trial shows this therapy is the least toxic and unlikely to result in the development of any resistant strains of *P. Falciparum malaria.*

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