The comparison of the KRB values before and after splenectomy and splenorenal shunt showed individual variations mainly when the values of KBB after surgery are obtained shortly after the operation. In all the patients studied for periods longer than 3 months, and in whom there was a decrease in KBB at first determination a short time after surgery, an increase in KRB values was later observed.

REFERENCES

The Use of Antimalarial Drugs

C. F. HANSFORD

SUMMARY

A general review is given of the antimalarial drugs currently available and in common use, with special reference to those found to be of most benefit in Southern Africa.


LIFE CYCLE OF THE PARASITE

Before discussing the action of antimalarial drugs some aspects of the malaria parasite cycle should be considered. The parasite is inoculated by the mosquito as the sporozoite form, which within an hour enters liver cells and commences growth and subdivision, forming primary exo-erythrocytic or pre-erythrocytic schizonts. After a few days these schizonts mature and rupture, each releasing hundreds of merozoites which invade circulating red blood cells. In Plasmodium vivax, malariae and ovale infections some of these merozoites also enter liver cells, starting a new cycle of exo-erythrocytic division called secondary exo-erythrocytic schizogony. This stage is responsible for the late relapses associated with these species of parasite. It does not occur in P. falciparum infections.

In the red blood cells the parasites become trophozoites, take 2 - 3 days to develop, divide and form mature schizonts which rupture, forming merozoites which in turn invade further red blood cells. The breaking-up of the mature schizonts releases products responsible for the pyrexial attacks typical of malaria. A few trophozoites do not form schizonts but develop into male and female gametocytes. These may continue to circulate for periods up to a month unless they are ingested by suitable mosquitoes in which they mate, develop further and subdivide, forming sporozoites which migrate to the salivary glands.

Individual antimalarial drugs do not have a similar action against all stages of malaria parasites, nor against all 4 species of human malaria, and this fact must be taken into consideration when drugs are prescribed for prophylaxis, cure or gametocidal purposes.

CLASSIFICATION OF ANTIMALARIAL DRUGS

Antimalarial drugs are commonly classified by their chemical characteristics and by their site of action on the parasite.

Aminoquinoline Drugs

Basically these have a benzene and a pyridine ring fused together and are divided into 4- and 8-aminoquinolines, depending on the position of the side chain. The 4-aminoquinoline drugs include chloroquine and amodiaquine, the most important of present antimalarial drugs. They have a low toxicity, are highly effective against the asexual blood trophozoite and for these reasons are the drugs of choice in the treatment of the acute attack. Unfortunately they have no action against any other stage of the parasite. They are rapidly absorbed, slowly metabolised and excreted, necessitating the use of a loading dose at the commencement of treatment. At the oral dosages normally employed, toxic effects are minor, usually consisting of nausea, headaches and dizziness, but care must be taken during parenteral use, especially with children, since hypotension may result.
The only 8-aminoquinoline of importance is primaquine which is effective against virtually all stages of malaria. Unfortunately it is too toxic for general use, particularly among individuals with glucose-6-phosphate dehydrogenase deficiency, and for this reason is only used under close supervision, against secondary exo-erythrocytic forms of *P. vivax*, *malariae* and *ovale* infections, to ensure radical cure.

**Folic Reductase Inhibitors**

These drugs inhibit enzymes involved in the formation of folic acid and include proguanil and pyrimethamine which are effective against the primary exo-erythrocytic forms of *P. falciparum*. Unfortunately in Southern Africa some strains of *P. falciparum* have developed resistance to these drugs, which should now only be used for prophylaxis in combination with other antimalarials. Injectable derivatives of these drugs have not given reliable protection.

The action of these drugs against circulating blood schizonts is too slow to warrant their use alone. They also prevent the further development of gametocytes in the mosquito and may be administered for this purpose.

**Quinine**

Quinine has a rapid action against asexual circulating parasites and is now principally used for the parenteral treatment of severe *P. falciparum* infections. It is also effective against the gametocytes of *P. vivax* and *ovale*. It is rapidly absorbed and excreted. A dose of 650 mg of the dihydrochloride may be slowly given intravenously and may be repeated once or at most twice in 24 hours. In children the daily parenteral dose should not exceed 20 mg/kg.

**Sulphones and Sulphonamides**

These drugs are effective against the circulating asexual forms of *P. falciparum*, but are not sufficiently active to warrant their use for curative purposes except in combination with other antimalarials. When used in combination with pyrimethamine or trimethoprim their action is potentiated and dosages may be reduced.

Side-effects may prove troublesome and their widespread use may induce resistance in malaria as well as in other organisms such as meningococci. They may become protein-bound in some individuals and ineffective against malaria parasites.

Experience gained over the next few years will determine the position of these drugs for prophylaxis and treatment.

**Other Drugs**

Mepacrine is highly effective against asexual circulating parasites but on account of toxicity has been replaced by 4-aminoquinoline drugs.

**RECOMMENDED USE OF DRUGS**

**Prophylaxis**

Prophylaxis should take place at the earliest possible stage of the parasite in man. Pyrimethamine and proguanil are the best drugs in this respect, since they are effective against the pre-erythrocytic stages of *P. falciparum*, the commonest malaria species. Unfortunately in many parts of Africa *P. falciparum* has developed a resistance to these drugs, which by themselves cannot now be relied upon to give complete prophylaxis. To overcome this difficulty they may be used in combination with sulphones and sulphonamides, but more experience is required to assess their efficiency and the incidence of side-effects. Proguanil and pyrimethamine should not be given alone for prophylaxis.

Drugs acting against the asexual circulating stages of malaria parasites can also be used as suppressive prophylactics. Chloroquine or amodiaquine are recommended for this purpose, but the question is frequently raised of the desirability of using the same drug for treatment as for prophylaxis. Strains of chloroquine-resistant *P. falciparum* have developed in South-east Asia and in South America but not in Africa, where it has been shown that the local *P. falciparum* strain is basically more sensitive to chloroquine than elsewhere. For this reason and on account of their low toxicity, 4-aminoquinolines (chloroquine and amodiaquine) have been recommended as the most dependable prophylactics for African conditions and thus must be advised for individual prophylaxis. They should be administered immediately before, during, and for 4 weeks after the last exposure to malaria to allow pre-erythrocytic stages to mature and be eliminated when they develop in the circulating blood. This 4-weeks' prophylaxis after exposure to malaria is most important and failure to continue prophylaxis for this period is responsible for many malaria infections.

A combination of pyrimethamine or proguanil and a 4-aminoquinoline may be used for prophylaxis to obtain the benefit of the former's action against the early stages of the parasite and the latter's action against resistant parasites which may reach the circulating blood.

The Department of Health recommendation for prophylaxis in adults is a weekly dose of 300 mg base of chloroquine or amodiaquine to be taken for the duration of the period of exposure and for the following 4 weeks. Pyrimethamine 25 mg weekly or proguanil 100 mg daily may be given in addition.

The danger of exposure to species of malaria other than *P. falciparum* may be ignored in South Africa, but...
where it is present the additional use of primaquine after exposure should be considered to eliminate secondary exo-erythrocytic parasites and the possibility of prolonged pre-patent infections.

**TREATMENT**

Dosage recommendations for treatment vary with the immune status and defense mechanism of the host, surprisingly small dosages being required for curing infected semi-immunes. In South Africa where malaria transmission is low, all hosts must be considered non-immune and treated accordingly.

The 4-aminoquinoline drugs are the basis of treatment on account of their rapid action against asexual circulating parasites and low toxicity. Chloroquine or amodiaquine should be given in divided doses of 900 mg base on day 1 and 300 mg on day 2 and on day 3. The initial doses should be given parenterally where vomiting is present or the illness is severe. A total daily parenteral adult dose of 900 mg base should not exceed and individual doses should not exceed 300 mg base (normally 10 ml of 5% solution). This standard treatment will be sufficient for the majority of infections but occasionally a higher total dosage may be required, possibly on account of variable host responses. Quinine may be used in addition for fulminating infections. This treatment will give a radical cure for *P. falciparum* infections but not for other malaria species, when primaquine should also be given in an adult dosage of 15 mg base daily for 14 days.

Drug treatment is only part of the management of malaria infections; the control of electrolyte balance, circulatory disturbances, renal failure, etc. are equally important.

When the patient is returning to potentially malarious areas 50 mg of pyrimethamine should also be given to sterilise gametocytes and prevent their further development in the mosquito. If this is not undertaken, the patient, although clinically cured, may still be infectious to the mosquito and be responsible for a further focus of malaria transmission.

As a public health measure a single dose of 600 mg chloroquine combined with 60 mg pyrimethamine is given for presumed asymptomatic infections awaiting confirmation by blood examination. This cures the majority of infections among semi-immune hosts, but a full treatment is given on confirmation of the infection.

In South-east Asia, where chloroquine-resistant *P. falciparum* infections are common, treatment consists of a combination of two or more antimalarial drugs. The response to these drugs varies with different strains of parasite and local knowledge is useful for recommending prophylaxis and treatment.

In conclusion I would like to emphasise again that in Southern Africa pyrimethamine alone cannot be relied upon for prophylaxis — chloroquine should be the basis of prophylaxis and treatment.

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**Boeke Ontvang : Books Received**


