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The Secretary of the Expert Committee on Malaria
has the honour to communicate hereunder
a note on the

CHEMOTHERAPY OF MALARIA

by

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At its fourth session, the Expert Committee on Malaria of WHO recommended the preparation of an authoritative brochure on the antimalarial drugs in common use. The task was entrusted to a small working party selected from the WHO Expert Advisory Panel on Malaria. For various reasons, chief among them being a serious illness of one of the working party, it has not been possible to complete this brochure in time to be presented at the fifth session of the Committee. The convener of the working party has therefore compiled the present note in an attempt to summarize the views of its members as to the present status of the antimalarial drugs now in use.

In the reports of the third and fourth sessions of the Committee it was pointed out that none of the drugs as yet tested fulfilled all the conditions required of an ideal antimalarial agent, namely that it be a causal prophylactic against all species of human malaria parasites; that it be a good therapeutic agent and at the same time be truly curative; that it possess low toxicity; and that it be readily available at moderate cost. This criticism can be applied with equal force to the present situation. But a number of important chemotherapeutic studies have been carried out since the fourth session was held, and these have added substantially to our knowledge of the properties and limitations of the drugs then available; and several new compounds have been developed.

As is now generally recognized, considerable differences exist in the reaction of various geographical strains of parasites to drug prophylaxis and therapy, and the state of premunition of the host may greatly affect the action of antimalarial drugs. The efficacy of individual compounds therefore varies considerably in different places and under different immunological conditions.

The demonstration of a pre-erythrocytic phase of Plasmodium cynomolgi in the liver of the monkey and of a similar phase of P.vivax and P.falciparum in man has shed new light on the chemotherapy of malaria. The mode of action of the various drugs must be considered in relation to the different phases in the life cycle of the parasite.

Mode of action of antimalarial drugs

In theory a drug may act on the malaria parasite in any of the following ways:

- (i) against the sporozoites when first they enter the human body;
- (ii) against the primary tissue or pre-erythrocytic phase;
- (iii) against the asexual parasites in their erythrocytic phase;
- (iv) against the sexual parasites in their erythrocytic phase;
- (v) against the late exo-erythrocytic or secondary tissue phase, to which the phenomena of latency and late relapse in vivax malaria have been attributed (a phase apparently non-existent in falciparum malaria);
- (vi) against the gametocytes in the mosquito phase of the life cycle.

The classes of drugs in common use are:

- (a) the cinchona alkaloids (quinine, totaquina)
- (b) the amino-acridines (mepacrine)
- (c) the 4-aminoquinolines (chloroquine, amodiaquine)
- (d) the 8-aminoquinolines (pamaquin, primaquine)
- (e) the biguanides (proguanil)
- (f) the diamino-pyrimidines (pyrimethamine)

No drug as yet tested has any demonstrable effect on the sporozoite stage of the malaria parasite. The cinchona alkaloids, amino-acridines, 4-aminoquinolines,

biguanides and diamino-pyrimidines have a destructive action on the asexual forms of all 4 species of human malaria parasites in the erythrocytic phase, though the action of the last two is too slow for treatment of the clinical attack in a non-immune subject. The 8-aminoquinolines do not affect the asexual parasites in the erythrocytic phase, but have a powerful destructive action on the gametocytes. They also act on the secondary exo-erythrocytic forms of P.vivax, and it is in this respect that they have their greatest value. They have an inhibitory effect on the pre-erythrocytic forms of both P.falciparum and P.vivax, but only when administered in dosage dangerously high for routine use.

The biguanides and the diamino-pyrimidines are the only classes of drugs that can be used with safety against the pre-erythrocytic phase, and so far as is known they are effective only in falciparum infections. They have no apparent action on the sexual forms of P.falciparum in the peripheral blood, but both of them have been shown to render them incapable of completing their development in the mosquito.

Drug resistance in malaria

The fact that some strains of malaria are more resistant than others to the action of particular antimalarial drugs has long been recognized, but significant drug resistance to malaria is a comparatively recent phenomenon. Acquired resistance to proguanil of P.gallinaceum was first reported in 1947. Subsequently other species of Plasmodium, including P.falciparum and P.vivax, have been shown to share this capacity for adaptation to proguanil. More recently, resistance to pyrimethamine, whose behaviour resembles that of proguanil in many ways, has been demonstrated, and cross resistance between the two drugs has been shown to exist. Drug resistance in malaria has thus become a major clinical problem.

Resistance to proguanil may appear quickly or slowly, or indeed not at all, depending on the conditions of exposure to the drug. Under artificial conditions, with deliberate under-dosage and careful gradation and timing, a high tolerance to the drug may appear within a few months. In clinical and preventive practice with efficient treatment or thorough suppression, it seems that resistance may never appear at all.

Thus in the Tampin District of Malaya, where owing to disturbed local conditions administration of the drug was irregular and inadequately supervised, resistance to proguanil began to appear with P.falciparum after two years and with P.vivax after four years had elapsed. One hundred miles away, on a malarious estate with good suppressive discipline, after continuous use at 100 mgm once or twice a week, proguanil is apparently still effective.

Certain preliminary unpublished work in East Africa suggests that periodic mass treatment with pyrimethamine may also result in the eventual appearance of resistance to this drug.

It seems that the primary factors in the causation of resistance are under-dosage and significant parasitaemia, operating together, and under field conditions found particularly in the smouldering infections partially controlled by irregular or inadequate suppressive dosage. On theoretical grounds, resistance is less likely to appear where the drug is being used for suppression than for treatment of the attack.

The evidence as regards the production of resistance to pyrimethamine is as yet incomplete; but it seems probable that the same considerations will apply to this drug as to proguanil.

Significant drug resistance has never been reported in the case of chloroquine or amodiaquine. Experimental attempts to produce resistance in avian and mammalian malaria to mepacrine, chloroquine and amodiaquine have never been successful, though in a single isolated case Fairley reported relative resistance in strains of P.falciparum observed in the Aitape-Waewak-Lee area of New Guinea.

Acquired resistance to quinine in human malaria is rare, if indeed it occurs at all, although southern European strains of P.falciparum tested at Horton have been found to require approximately eight times as much of the drug to control the attack as strains from India and Africa, and even this amount proved ineffective in producing radical cure.

Thus, the risk of drug resistance to the antimalarial compounds at present in common use is apparently confined for all practical purposes to proguanil and pyrimethamine.

SPECIFIC TREATMENT OF CLINICAL MALARIA

The chief objects aimed at are the prompt alleviation of symptoms and the radical cure of the infection, with minimum risk of toxic side effects. Sterilization of the sexual forms of the parasite, so that mosquitos which may feed upon the patient are unable to transmit the disease to others, is also desirable, and in certain circumstances may be a matter of considerable importance.

Quinine sulphate or hydrochloride, given in a daily dose of 20 to 30 grains (1.3 to 2.0 gm) will usually bring about rapid termination of the clinical attack and, in falciparum infections, a high rate of radical cure. This drug is however comparatively ineffective against certain European strains of P.falciparum. It has no effect on the infectivity of gametocytes to mosquitos, and in certain circumstances may act as a contributory factor in the precipitation of blackwater fever.

Mepacrine, when given with a loading dose of 600 to 900 mgm on the first day or first two days of treatment followed by 300 mgm daily for the rest of the week will usually effect a rapid termination of the clinical attack in all forms of malaria, and a high rate of cure in falciparum infections. It does not sterilize gametocytes and toxic side-effects, though of rare occurrence, are by no means negligible. This applies particularly to the so-called mepacrine psychosis, which may be attended by symptoms of mental aberration or even of maniacal excitement. Another drawback is the yellow discoloration of the skin which sometimes follows administration of this drug.

Chloroquine brings about rapid alleviation of clinical symptoms in all forms of malaria and a high rate of cure in falciparum infections. It has the advantage over mepacrine of not tinting the skin and of being less likely to induce disagreeable intestinal or psychotic manifestations. The regimen usually recommended is an initial dose of 600 mgm of the base, followed by 300 mgm six hours later, and a single dose of 300 mgm on each of the two following days. Amodiaquine, whose action resembles that of chloroquine, has been given in doses up to 400 mgm thrice daily for five days, and is probably equally effective. Neither of these drugs renders gametocytes non-infective to mosquitos.

Proguanil, in the absence of reinforcement with some more powerful schizonticidal drug, is too slow in action for treatment of acute malaria in a non-immune subject;

moreover it cannot be relied upon to effect radical cure even in falciparum infections. It effectively sterilizes the gametocytes of P.falciparum, a property not possessed by mepacrine, chloroquine, amodiaquine or quinine. It is moreover by far the least toxic of all known antimalarial drugs.

Pyrimethamine, like proguanil, is too slow in action for treatment of an acute attack in non-immunes. It shares with proguanil the property of being able to sterilize the gametocytes of P.falciparum in the mosquito. Although no serious toxic effects have as yet been reported in human subjects, animal experiments suggest that such might occur should the recommended therapeutic dosage be unwittingly exceeded. This is an additional reason why this drug should not be used for treatment of the acute attack.

RECOMMENDATIONS AS TO TREATMENT

I. Treatment of the clinical attack

(a) For non-immune subjects

For this class of patient it is necessary to employ one or other of the more powerful schizonticidal drugs, such as chloroquine, amodiaquine, mepacrine or quinine.

Quinine has the disadvantage of its association with the precipitation of black-water fever, and is comparatively ineffective against certain geographical strains of malaria parasites.

Mepacrine has a rapid action in all forms of malaria, but minor toxic manifestations and occasional psychoses of a more serious nature are definite drawbacks. The yellow discoloration of the skin sometimes produced is also undesirable.

Chloroquine and amodiaquine are probably the most effective agents for terminating the clinical attack of toxic manifestations of a serious nature are rare in either case. These two compounds are generally recognized as the drugs of choice in the treatment of acute malaria.

Neither proguanil nor pyrimethamine are sufficiently rapid in action to warrant their use for the treatment of acute malaria in non-immune subjects without reinforcement by some more rapidly acting schizonticide.

Emergency treatment

In the treatment of pernicious forms of falciparum malaria, whether cerebral, algid or gastro-intestinal, oral administration of drugs is seldom practicable, and since prompt action is necessary to save the patient's life, antimalarial drugs must be given parenterally. Mepacrine sulphonate ('atebrin musonate') may be given intramuscularly, 200 mgm being injected into each buttock and the dose repeated if necessary after six hours. Good results have also been reported with intramuscular and intravenous injections of chloroquine. Quinine hydrobromide or dihydrochloride, 10 grains (0.65 gm) in 20 ml of normal saline, may be injected very slowly intravenously, and repeated in six to eight hours if necessary. The intramuscular injection of quinine, formerly widely practised, is apt to cause necrosis of abscess, and is not recommended. As soon as the patient is able to take drugs by the mouth, all further medication should be by the oral route.

Treatment of chronic relapsing vivax malaria

If it is intended to place the patient on a suppressive regime for an indefinite period after the termination of the clinical attack, no further medication is called for. If suppressive treatment is not contemplated, radical cure may be effected in a large proportion of cases by the use of one or other of the 8-aminoquinoline group in combination with quinine. The first of this group to be used for the prevention of relapse was pamaquin, which may be given in a dosage of 0.01 gm concurrently with ten grains of quinine sulphate thrice daily for ten days. Recent work has shown that certain other members of the group - pentaquine, isapentaquine and primaquine - are more effective than pamaquin and less toxic, primaquine being probably the best of the three in both respects. The dosage recommended is the same as for pamaquin.

Careful supervision of the patient is called for with all members of this group of drugs, because of the occasional unpredictable occurrence of acute intravascular haemolysis. The routine administration of these drugs in all cases of vivax malaria is not recommended. They should be reserved for treatment of stubbornly relapsing cases, more especially in circumstances where there is no risk of reinfection.

(b) For partially immune subjects

For the dispensary treatment of indigenous populations of malarious countries, a single dose treatment of 300 mgm of chloroquine base, or 600 mgm of amodiaquine has proved effective. Good results have also been reported with a single dose treatment of 300 mgm of proguanil, and it has been suggested that pyrimethamine in a single dose of 50 mgm might prove an efficient and economical therapeutic agent under similar conditions. For reasons already stated under the heading of drug-resistance, it seems preferable to reserve both proguanil and pyrimethamine solely for prophylaxis and suppression, and to use for therapeutic purposes either chloroquine, amodiaquine, mepacrine, or even quinine should this last named drug be available at a lower price than any of the others.

II. Prophylaxis and suppression

The onset of a clinical attack of malaria may be prevented (i) by a drug acting on the pre-erythrocytic phase of the parasite (causal or causative prophylaxis) or (ii) by a drug acting on the asexual erythrocytic phase (suppression).

The only classes of drugs which can achieve the former effect in non-toxic dosage are the biguanides and the diaminopyrimidines, and in both cases their action is confined in this respect to falciparum malaria. Since however they act also on the asexual erythrocytic forms in all species of malaria, their use in prophylaxis is by no means confined to falciparum infections. The dosage of proguanil recommended for prophylactic or suppressive use is 100 mgm daily for non-immune individuals, and 300 mgm in a single dose once weekly for indigenous inhabitants of malarious countries. A great advantage of this drug is that it can be placed in the hands of laymen for distribution without risk of ill-effect, even should the prescribed dose be grossly exceeded. The dosage of pyrimethamine recommended for this purpose is 25 mgm in a single weekly dose. The very small amount used is one of the great advantages of this drug, while the fact that it is tasteless renders it particularly suitable for administration to children. For this very reason, however, it is necessary to keep the bottle out of reach, for instances have been recorded where children have swallowed a number of tablets in mistake for candy. Both proguanil and pyrimethamine have the further advantage of sterilizing mosquito infections.

For the effective suppression of falciparum malaria, quinine has to be administered in doses as high as ten grains (0.65 gm) daily. Against New Guinea strains of P.falciparum even this dosage has proved insufficient. Apart from the unpleasant side effects liable to arise from prolonged administration of this amount of quinine, the association of this drug with the precipitation of blackwater fever renders it unsuitable for use as a suppressant in areas where falciparum infections are prevalent.

Mepacrine, in a dosage of 100 mgm daily, is a very effective suppressant of all forms of malaria, provided that the drug is taken for 14 days before infection and continued for one month after leaving the endemic area, but it has certain disadvantages which militate against its routine use under peacetime conditions. When taking the drug over long periods, a proportion of individuals develop skin lesions, the most common of which is a lichenoid dermatitis affecting chiefly the hands, wrists, feet and ankles. Yellow discoloration of the skin, a comparatively common feature, is a further disadvantage.

Chloroquine is probably an even more powerful suppressant than mepacrine, the dosage usually prescribed being 300 mgm of the base (500 mgm of the diphosphate salt) once weekly. Its action resembles that of mepacrine, but it is generally less toxic and does not tint the skin. The same advantages are claimed for amodiaquine, in a dosage of 500 mgm weekly.

At present the choice of drug for prophylaxis seems to lie between proguanil or pyrimethamine on the one hand and chloroquine or camoquine on the other. The first two have the advantage of sterilizing the infection in the mosquito, and at the present time, of low cost, and proguanil has in addition the advantage of extremely low toxicity. There is however the possibility of resistance appearing with either of these drugs, particularly if they are being used indiscriminately as therapeutic agents. Should this occur, the only possible course is a switch over to chloroquine, amodiaquine or mepacrine; or if none of these is available, to quinine.

SUMMARY OF RECOMMENDATIONS

Treatment of clinical attack in non-immune subjects

- (i) Chloroquine diphosphate. 1 gm immediately, 500 mgm 6 hours later, 500 mgm on each of the next 2 days.
- (ii) Amodiaquine. 600 mgm of base immediately, 400 mgm daily for the next 5 days.
- (iii) Mepacrine. 200 mgm thrice daily for first two days, 100 mgm thrice daily for next 5 days,
or 1 gm (5 doses of 200 mgm) on first day, and 100 mgm thrice daily for next 6 days.

Emergency treatment

- (i) Mepacrine sulphonate (atebrin musonate), 200 mgm intramuscularly in each buttock, repeated in 6 hours if necessary.
- (ii) Chloroquine hydrochloride 200 mgm of base in 4.5 per cent aqueous solution intramuscularly, repeated if necessary in 6 hours.
- (iii) Quinine hydrobromide or dihydrochloride 10 grains (0.65 gm) in at least 20 ml of normal saline injected intravenously very slowly (not more than 1 grain per minute), repeated after 6 hours if necessary.

Treatment of chronic relapsing vivax malaria

Pamaquin or primaquine, 0.01 gm concurrently with 10 grains of quinine sulphate or bihydrochloride thrice daily for 10 days.

Treatment of clinical attack in semi-immune subjects

- (i) Chloroquine diphosphate 500 mgm (300 mgm of base) in a single dose.
- (ii) Amodiaquine 600 mgm in a single dose.
- (iii) Mepacrine 600 mgm in a single dose.

Prophylaxis and suppression

- (i) Proguanil 100 mgm daily, or, for semi-immune subjects 300 mgm once weekly.
- (ii) Pyrimethamine 25 mgm once weekly.
- (iii) Chloroquine disphosphate 500 mgm (300 mgm of base) once weekly.
- (iv) Amodiaquine, 400 mgm of base, once weekly.