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THE USE OF DRUGS IN MALARIA ERADICATION ¹

Chemotherapy is of increasing importance in all phases of malaria eradication programmes and in pre-eradication programmes.

With regard to their chemical structure the antimalarial drugs generally used can be divided into six classes: the cinchona alkaloids, the 9-amino-acridines (mepacrine), the 4-amino-quinolines (chloroquine, amodiaquine, the 8-aminoquinolines (primaquine), the biguanides (proguanil), the diaminopyrimidines. It seems that we should add today a new class of antimalarials, namely the sulfonamides and sulfones although the value of these compounds is still not fully assessed.

The cinchona alkaloids, mepacrine, chloroquine and amodiaquine have a pronounced action on the erythrocytic forms of all species of malaria parasites and are of value for treatment of the clinical attacks and for suppression. In this respect chloroquine and amodiaquine are generally far superior to other drugs.

Primaquine has a powerful action on the gametocytes of P.falciparum but its greatest practical use lies in the radical curative effect on the relapsing infections with P.vivax, P.malariae and probably P.ovale.

The biguanides and diaminopyrimidines are excellent causal prophylactic drugs with a wide range of safety, most effective against primary tissue stages especially in P.falciparum. They are also valuable for their sporontocidal effect on the malaria parasites developing in the mosquito and, therefore, of special value for prevention of transmission. They are relatively slow-acting schizontocidal drugs and liable to produce resistance more easily than others.

¹ Prepared by Dr L.J. Bruce-Chwatt, Chief, Research and Technical Intelligence Division of Malaria Eradication

All antimalarial drugs known at the present time have a selective action which varies in relation to the species and the developmental stage of the parasite. Nevertheless using a combination of various drugs one can today eliminate completely the malaria infection and achieve a permanent cure of all individual cases of malaria.

One of the main drawbacks of all antimalarials known at the present time is due to their relatively rapid elimination so that the drug administration must be repeated at short intervals. To accomplish the eradication of malaria by drugs one would have to set up a nearly perfect organization to achieve the regular drug administration in large rural areas where the population is scanty and often migratory, where the means of communications are insufficient and where the rural health service is far from complete. Moreover, one would have to obtain a constant and active co-operation of the whole population and this is difficult for any length of time.

A brief summary of the new developments in the field of chemotherapy of malaria may be of interest and value.

1. Repository injectable antimalarials

The development over the past six years of cycloguanil pamoate, an injectable depot-forming drug represents an interesting attempt to produce. The dihydrootiazine metabolite of proguanil first described by Carrington et al in 1951 was prepared as an oily suspension of the pamoic salt of the parent compound and assessed on rodent and monkey malaria with promising results. Studies on human volunteers showed that a single injection given at a dose of 5-10 mg/kg had a protective effect for several months against blood and sporozoite induced infections with the Chosson strain of P. vivax. It does not prevent relapses of this infection but may delay them. Cycloguanil pamoate has also a protective action for one year or longer against blood and sporozoite induced infections with the proguanil sensitive Mc Lendon strain of P. falciparum; suppressive effect against the partially proguanil resistant P. falciparum strain from Africa is limited but a causal prophylactic action against sporozoite induced infection with this strain was evident. However, this drug fails to achieve either a suppressive or a prophylactic effect in infections with multiresistant strains of P. falciparum from South East Asia .

The investigations carried out in the USA on some 500 human subjects were extended over the past four years to about 15 field trials involving over 4000 subjects inhabiting malarious areas of the Gambia, Tanzania, Nigeria, Senegal, Australian New Guinea, Pakistan and elsewhere. The overall results of these trials agree to a large extent with the conclusions reached recently by McGregor et al (1966) in the Gambia and by Black et al (1966) in Australia.

The duration of the protective effect in the field trials was shorter than expected and averaged 3-5 months with a wide range. Wherever prophylaxis or pyrimethamine resistance was known to exist or was discovered during the trial (e.g. Tanzania, Territory of Papua and New Guinea) the absence of parasitaemia was considerably shorter. The antiparasitic effect of cycloguanil pamoate was less pronounced in children than in adults. No systemic toxicity of the drug was obvious and the average frequency of about 20% of local reactions could be decreased by the use of appropriate injection technique.

It is still too early to give a balanced assessment of the place that cycloguanil pamoate may have in the field of chemotherapy of malaria. It appears that this compound is essentially a causal prophylactic drug in P.falciparum (but not in P.vivax) with a pronounced repository action (particularly obvious in non-immunes) and with a fair degree of schizontocidal effect on species of malaria parasites susceptible to antimalarials of the anti-folic acid group. It is likely that its interesting properties will be of value in association with other compounds especially 4-aminoquinolines, sulfones or sulfonamides.

While an injectable repository drug will be undoubtedly of value we must not discount the possibility of a long acting antimalarial given by the mouth. What we need for mass chemotherapy of malaria is a drug similar to pentamidine for trypanosomiasis, which absorbed through the intestine will protect an individual for 3-6 months. The new developments in the field of sulfonamides hold some promise in this respect.

Sulfones and sulfonamides

It seems that the present interest in sulfones and sulfonamides as antimalarials repeats the history of forgotten and re-discovered drugs.

Thirty years ago, a number of sulfonamides were tested for their antiparasitological activity against several simian and human malaria. Coggeshall et al (1941) found that one of the sulfonamides (DAS) had an effect on malaria infections with P.falciparum and P.vivax, particularly on the former. Other compounds were further studied during the succeeding years but their effect, even in relatively large doses, was slight. Some ten years ago the pyrimethamine effect of the diamino-diphenylsulfone (DDS) a drug widely used for treatment of leprosy, underwent a number of studies in the laboratory on rodent and simian malaria.

The effects of DDS alone or in combination with pyrimethamine on P.falciparum and P.vivax infections were studied in India, in Nigeria, in Tanzania and it was found that this compound had a definite though slight schizontocidal effect on P.falciparum or P.vivax infections. A substantial increase of the action of DDS occurred when it was associated with pyrimethamine. Recently DDS was assessed on human volunteers in USA infected with the chloroquine resistant strains of P.falciparum from Malaya and Vietnam and it was shown that this compound maintained its suppressive action.

In the course of investigation of several hundred sulfone derivatives it was found that the diacetylaurine-diphenyl sulfone (DADDS also known as Rodilone, sulfadiazine, CI-556) had a repository action on experimental malaria and that this is reinforced when the compound is given by injection together with cycloguanil pamoate. Further evaluation of this drug association (CI-564) was carried out in Tanzania and in Australian New Guinea. The preliminary reports indicate that clearance of P.falciparum infections is achieved and maintained for about three months, which is somewhat longer than the effect of DADDS alone or of cycloguanil pamoate. In Australian New Guinea the results were very similar and in both trials it was reported that the "break-throughs" due apparently to proguanil or pyrimethamine resistant strains were delayed when the drug association was given.

A number of the available sulfones and some newly synthesised ones are now undergoing laboratory trials and it appears that at least one of them (a diformyl derivative of DDS) shows a particularly high therapeutic index and prolonged effect.

Sulfonamides were investigated side by side with sulfones for their antimalarial action ever since Coggeshall reported in 1938 that P.knowlesi

malaria of monkeys responded to sulfadiazine. A large number of other studies on various derivatives of this group were carried out with varying success and steadily decreasing interest until the observations by Koller in 1955 showed potentiation of sulfadiazine by pyrimethamine in avian malaria and the same effect was seen in human malaria in the Gambia.

Subsequently sulfadiazine has been tried either alone or in combination with pyrimethamine in a limited number of subjects infected with chloroquine or pyrimethamine resistant strains of *P.falciparum* originating from the parts of South America or from Malaya.

A number of new sulfonamides characterized by slow excretion have also been assessed in Brazil and elsewhere. Among these sulfadimethoxine (DS), "Madribon") sulfamethoxy-pyridazine (SNP, "Lederlyn", "Kymek", "Midicol") should be mentioned but sulforthomidine also called sulforthodimethoxine, (RCH-4393, "Fansil", "Fansil") has become a favourite experimental drug. This compound has an exceptionally long activity (biological half life of 100-200 hours) when taken by the mouth and is the only one of this series that underwent field trials on a fairly large scale.

Trials with sulforthomidine have so far been carried out in Brazil, in Tanzania and in Nigeria, including a total of approximately 1,000 subjects. Doses of sulforthomidine and frequencies of administration have varied widely in these trials. The drug has been given as a single dose, as a once weekly dose, and also in daily doses for 2 to 30 days. It has been used sometimes, alone, sometimes in association with other drugs, generally pyrimethamine, but in a few cases chloroquine or quinine was also used.

In Brazil where *P.falciparum* strains apparently resistant to chloroquine were inoculated into neurosyphilitics sulforthomidine alone was not very active but in association with pyrimethamine showed greatly enhanced action though the response varied in infections with different strains of the parasite.

Good effect of this compound was reported in a group showing asymptomatic parasitaemia due to pyrimethamine resistant *P.falciparum* in Tanzania. Rather less consistent results were obtained with sulforthomidine alone given as a single dose in acute malaria infections but the effect was rapid when an association of sulforthomidine with pyrimethamine was administered.

It was found in Nigeria that a single dose of 500 mg of sulforthomidine administered to 260 schoolchildren for a heliophilic area appeared to have a rather larger effect in suppressing causal falciparum paroxysms than a single dose of 300 mg of chloroquine given to a comparable group of children in the same area.

However, in Liberia chloroquine at 300 mg had a faster effect on parasitaemia; sulforthomidine with pyrimethamine was next best and sulforthomidine alone left nearly 10% of children still with parasites on the 14th day of treatment.

A comparison of the results obtained in these trials is rather difficult because of the different conditions of the patients, of the doses used and of the frequencies of administration. As one would have expected, results obtained with sulforthomidine, alone or with pyrimethamine, have been much better in semi-immune African adults and schoolchildren.

The value of different sulfonamides for treatment of infections caused by chloroquine resistant strains of *P. falciparum* is of obvious interest and several important investigations have just been completed in USA and in Thailand. It was found that sulforthomidine especially when given together with pyrimethamine has a pronounced curative effect in cases of falciparum malaria originating from South East Asia. However Brazilian studies indicate that chloroquine resistant strains present in that part of the world show a slower response to sulforthomidine even when associated with pyrimethamine.

There is little doubt that the present possibilities and the promise of future development of antimalarials have been greatly enriched by the new compounds. On the basis of available data, their value can be summarized as follows: Several sulfones and sulfonamides show considerable schizontocidal activity against *P. falciparum* including strains resistant to chloroquine; their action against *P. vivax* appears to be less pronounced. In subjects with a degree of immunity to malaria the schizontocidal action of sulfones and some sulfonamides (particularly sulforthomidine) appears to be faster than in non-immunes. They are suppressive drugs and there is little if any evidence of their causal prophylactic, gametocytocidal, sporontocidal or radical cure effect.

For suppression and for treatment of infections with chloroquine resistant strains of P. falciparum DDS and some of its derivatives as also sulforthomidine may be of value when given in association with pyrimethamine or other antifolate acid compounds. However, it should be remembered that there is much variability not only in the response of different strains of malaria parasites to these drugs but also in the response of different subjects infected with the same strain of the parasite. It is now widely held that this is due to the variable way of metabolizing these compounds by acetylation in some subjects.

It should be pointed out that recently in view of the present importance of chloroquine resistance in Vietnam the USA forces in this part of the world were put on a suppressive regimen of DES (25 mg daily) in addition to their previous regimen of chloroquine (300 mg once a week) and primaquine (45 mg once a week). Reports on the long term value of this regimen are expected.

The nature and extent of toxic effects which may arise after the administration of these compounds are now being studied and debated. Much stress has been laid on the possibility of their causing a severe form of erythema multiforme with systemic manifestations (Stevens-Johnson syndrome), usually after prolonged administration. Although the warnings issued about these compounds are necessary and timely it would be unfortunate if this should become an obstacle to the development and further trial of these drugs against malaria.

2. The use of drugs in malaria eradication programmes

The increased role of drugs in malaria eradication programmes has been recognized. Even if insecticides alone are effective in interrupting transmission, the supplementary use of drugs during the attack phase will accelerate the success of the spraying campaign.

During the consolidation phase, the use of antimalarial drugs is of paramount importance since single-dose treatment of all persons suspected of malaria and subsequent radical treatment of all confirmed cases are the principal measures for eliminating all remaining infections and for preventing the establishment of new foci of transmission.

Finally, during the maintenance phase antimalarial drugs are essential for the rapid radical cure of every imported case of malaria in order to prevent any new spread of the disease.

The two main operational types of drug distribution used in various phases of malaria eradication programmes are suppressive treatment and radical treatment. The first type is of particular interest as it has a bearing on day-to-day problems encountered in the course of health protection in the tropics.

Suppressive treatment implies prevention or suppression of clinical symptoms by action on asexual parasites in the blood. It may be given as "presumptive treatment" that is to say a single-dose drug administration (600 mg of base) to a presumed or probable case of malaria before the result of blood examination becomes available.¹ This is an essential part of surveillance activities and the drugs used are 4-aminoquinolines, which may be associated with pyrimethamine (25-50 mg) or (rarely) primaquine (45 mg). In the late attack and consolidation phase, the addition of pyrimethamine, proguanil or eventually primaquine is advisable because of the sporontocidal effect of these drugs, particularly where the case-detecting service is inadequate.

Suppressive treatment is also the principle of mass drug administration, which can seldom if ever be carried out as a sole antimalarial measure and is used generally in conjunction with residual spraying. In eradication programmes this measure is usually applied to the entire population of an area or to the whole group when dealing with nomadic or other mobile communities.

When used together with spraying, drugs may be given fortnightly or monthly, or limited to a single dose at the time of spraying, depending on the epidemiological conditions of the area, on the efficacy of antimosquito measures and also on operational conditions of the programme.

¹ The term "presumptive treatment" has been much abused especially when employed for single or repeated drug administration on a large scale without any attempt to assess the correctness of the diagnosis of the presumed malaria infection and without any subsequent radical treatment. For the correct definition of presumptive treatment the "Terminology of Malaria and of Malaria Eradication" (WHO, 1963) should be consulted.

When drugs are used as the only measure, the frequency of their distribution must be once a week or once every two weeks, except when transmission is at such a low level that once a month may be sufficient, though effective blood-levels will not last for more than about 10-20 days. In the case of migratory groups only a single-dose treatment is usually possible.

The preferred drug is a 4-aminoquinoline (chloroquine, amodiaquine). For mass drug administration at intervals of one week, 4-aminoquinoline in an adult dose of 300 mg of the base may be adequate, but in a population with little immunity and severe exposure to the infection the dosage should be doubled. This is also needed when the intervals between drug taking are greater than once a week. The proportionate dosage for children is that advocated by Covell et al (1955) with the modification suggested by WHO (1961).

3. Pre-eradication programmes and collective drug administration

Where malaria eradication programmes have been lagging behind because of technical, administrative or financial obstacles, the concept of pre-eradication has now been applied in many countries, especially in Africa.

In attempting to implement some of the basic needs of these countries, collective drug administration as a temporary public health measure is given more prominence.

Several points should be considered when discussing the possibilities and limitations of collective drug administration: (a) value of such method as a public health measure; (b) indication for limitation of such methods of malaria control to a specific group of the population; (c) possibility of undesirable long-term effects on the community; (d) selection of appropriate drug and dosage; (e) method of its distribution, its timing, regularity, frequency, means of supervision; (f) cost. Each of these points could be discussed at length but the general consensus of opinion is that while the method is of undoubted benefit to the population exposed to malaria infection the implementation of it must be adapted to the epidemiological conditions of the area.

In areas with moderate endemicity and seasonal transmission it is conceivable that the whole population would benefit from drug distribution while in holoendemic areas the protection of young, more vulnerable age groups would be of far greater importance.

The term "collective drug prophylaxis" is a misnomer when used for the description of large scale drug administration to a stable community living in highly endemic areas and beset with malarial parasites. The real aim is the prevention or relief of symptoms of a relapse caused by the action on the erythrocytic parasites. It is obvious that the hope of an interruption of transmission by drug administration alone could not easily be fulfilled but the beneficial effects of such measure are undeniable. Such suppression of malaria, when spread widely over the relevant community will produce a cumulative effect due to the reduction of the quantity of infection.

The possible undesirable long-term effects of a distribution of an antimalarial drug should be considered from two angles: toxic action of the drug and possible interference in highly endemic areas with the acquired tolerance to the infection. As far as the first point is concerned, it seems that with the exception of mepacrine, and some 8-aminoquinolines harmful effects of antimalarials can be largely discounted, particularly when assessed in the light of the benefits that the drugs confer. As for the possible long term interference of regular drug distribution with the degree of acquired immunity to malaria, definite information is lacking. Work carried out in Ghana, Nigeria and Tanzania tends to show that in school children, regular drug administration carried out for up to 2 years does not apparently interfere with their existing relative immunity and does not create any additional risks upon termination of treatment. On the other hand, some recent work done in Senegal and in the Gambia indicates that the concentration of the fraction of gammaglobulins, carriers of specific antibodies, decreases when the drug protection is maintained for several years. Some authors believe that many years of successful malaria control by residual insecticides will decrease the amount of collective immunity to malaria, but one must admit that we have few factual data on this point. At the present time there is no evidence of any significant interference with immunity in Africa, probably because in all field trials the absolute regularity of drug distribution has never been achieved and any reinforcement, even of short duration, has been sufficient to maintain a degree of immunity.

When it comes to the selection and dosage of an appropriate drug for collective protection, the general principles outlined by Covell, Courtney,

Field and Singh (1955) are still valid. The factors which operate when a good schizontocide is given at an adequate dosage are mainly limited to the suppression of all the four parasites in their asexual stage in the erythrocytic cycle and slow effect by attrition on the gametocyte reservoir. For this purpose, the 4-aminoquinolines are unsurpassed and there is little to choose between amodiaquine and chloroquine.

One might be tempted to use drugs such as proguanil, pyrimethamine, or others which have the causal prophylactic effect and also the direct sporontocidal action on the gametocyte reservoir. Their use alone is not advisable because of the probability of creating resistance in a population already infected. Their use in a combined form with a 4-aminoquinoline is much less open to objections.

The administration of any drug to the whole population or its selected group with unfailing degree of regularity will be a difficult task in developing countries. It seems that for malaria control this is not absolutely necessary and that a 70-80% coverage might be generally satisfactory.

The frequency of administration is not only related to the dosage of the drug but also to the convenience of its distribution. Generally once weekly administrations of chloroquine or amodiaquine are most appropriate to assure regularity though fortnightly distribution may be adequate. This depends on many local conditions: in schools the once weekly regimen is certainly the best to minimise the effect of one or two defaults in the weekly drug distribution. It is obvious that in areas of high endemicity the risk of reinfection is greater when the treatments are more widely spread.

As for the method of distribution the consensus of opinion is that two groups of the population should be given high priority: (a) pregnant and nursing women and (b) infants and children. The distribution of drug to these two groups is usually carried out through the basic health services and schools but there will always be a varying proportion of women and children missed in inverse relation to the socio-economic development of the country and to the population density over the area. In some cases additional arrangements with voluntary organizations are necessary.

It is obvious that the drug protection from malaria must be the responsibility of the national health services though substantial assistance to the organization and expenditure involved could be provided by international or bilateral agencies.

4. Imported malaria

The present preoccupation with problems of imported malaria into countries where this disease has been largely forgotten is justified and there is no doubt that it will lead to increased awareness of the possibility of this infection in persons coming from the tropical or subtropical areas. Rational treatment of acute malaria has been described in many excellent standard textbooks. Monographs such as that of Covell et al (1955) contain all the necessary information, presented with admirable clarity and conciseness.

It may be useful to keep in mind a few cardinal precepts, a series of medical aphorisms that have stood the test of time. No claim is made to the originality of these statements which are a sort of malariological catechism.

- (1) Malaria must be suspected in any patient with fever of unknown or doubtful origin who has ever been to a malarious viz. tropical area.
- (2) The clinical picture of malaria is of infinite variety and there is no better way of diagnosing the disease than by microscopical examination of blood carried out by an experienced person. A good blood slide using the thick film technique (or the thick and thin film) must be taken before any specific treatment is attempted.
- (3) The diagnosis of the species of malaria parasite and of an approximate degree of infection is of paramount importance and its results must be rapidly known. High parasitaemia due to P.falciparum in a non-immune patient is a medical emergency; infections due to P.vivax and P.malariae require a radical treatment to prevent relapses.

- (4) One single negative report does not exclude the diagnosis of malaria. When the diagnosis is uncertain twice daily blood examinations should be carried out for 2-3 days.
- (5) The results of specific treatment of malaria must be gauged not only by the clinical response of the patient but also by the microscopical follow-up of the trend of the parasite count in the blood. In severe malaria the erythrocyte count is an additional important guide to treatment of anaemia consequent upon infection.
- (6) So called "clinical malaria" with severe symptoms and a persistently negative slide may occur in subject who have been on an inadequate suppressive drug regimen. Nevertheless this occurrence is very rare; the clinical condition usually responds to adequate treatment and this may be the criterion of the tentative diagnosis but the search for parasites must continue for a few days.
- (7) The response of the infection to treatment depends on the species and strain of the parasite, on the severity of the infection, on the immune status of the patient, the type and dosage of the drug used, the method of its administration. Each case of acute malaria may present a different picture related to the interplay of these main (and probably other) variables although a general pattern is discernible.
- (8) The "standard" adult dosage of the drug is only a guide; proper dosage should take into account the age, weight and condition of the individual patient. For children, the dosage usually calculated on the body weight basis may be preferably calculated according to the body surface area (BSA) from existing tables. Calculation of children's doses according to their age may be grossly misleading.
- (9) Generally speaking 4-aminoquinolines are the drugs of choice for treatment of malaria and there is little to choose between chloroquine and amodiaquine for oral administration. Quinine and mepacrine are the next choice. Oral medication is usually adequate but for severe malaria parenteral

administration of quinine or chloroquine may be needed and are at times life-saving. Any parenteral administration of antimalarial drugs to small children presents some risk. The principle of loading dose is of importance.

- (10) P.falciparum malaria can be rapidly fatal with little warning or can be disguised as heat-stroke, mania, shock. Any infection with a parasite count of about 100,000 per mm³ or more requires immediate treatment especially if the erythrocyte count is low.
- (11) Seriously ill patients require general systemic treatment just as much as specific treatment. Anaemia may need blood transfusion, dehydration requires replacement of fluids and electrolytes; symptomatic treatment of hyperpyrexia, coma, vomiting, cerebral irritation, shock are of obvious importance. When serious ("pemicious") symptoms develop the experience of the attending physician should guide him, whether general treatment should precede the specific medication or vice versa. Often the two can be combined as a life saving operation.
- (12) P.falciparum malaria of moderate severity will usually yield quickly to an adequate regimen of an appropriate drug. Resistance may be suspected when there is no decrease of parasitaemia after several days of treatment in spite of the absolute certainty that the patient took the drug and absorbed it. Recrudescence of parasitaemia with or without symptoms after an initial satisfactory response to the treatment does not necessarily mean that the parasite is resistant to a specific drug.
- (13) The pattern of relapses in P.vivax malaria varies greatly in relation to the strains of the parasite. Radical cure of relapsing malaria in patients is important where malaria is either absent or of low prevalence; there is little use in attempting it in highly endemic areas with continued transmission and it may be preferable to maintain the patient on a suppressive regimen.

- (14) Any individual proceeding to a malarious area for a temporary stay or travelling by sea or air with a possibility of a brief disembarkation at a harbour or airport situated in an endemic malarious country is exposed to the infection. Any subsequent febrile disease occurring a few weeks or months later may be malaria.

On the other hand, a febrile disease occurring during the drug suppression does not denote either the "drug-resistance" or a "break-through" unless the presence of malaria parasites in the blood is reliably proved and the actual taking of the adequate dose of a proper antimalarial compound is absolutely certain.

- (15) Protection from malaria can normally be obtained by the use of the prophylactic drugs (proguanil, pyrimethamine) or by suppressive treatment with one of the 4-aminoquinolines providing that they are given at an appropriate dosage shortly before, during and for some time (2-4 weeks) after the exposure to infection.

Regularity of drug taking is as important as the frequency of it. The best way to assure regularity is to take the drug every day or once a week depending on the type of the compound. Methods of individual protection from mosquito bites should not be ignored or neglected.