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THE PLACE OF CHEMOTHERAPY IN MALARIA CONTROL ¹

The place of chemotherapy in malaria control, as opposed to antimosquito measures, has been debated repeatedly in the past. Infrequently, there have been concessions by the proponents of either approach allowing for a carefully planned integrated use of both in malaria control or eradication programmes. The present dilemma, occasioned by rising malaria rates in many areas of the world and the widespread inability, for economic or technical reasons, to effectively reduce malaria incidence through any single method of control, dictates a thorough re-examination of chemotherapeutic methods for wider use in the reduction of morbidity and mortality, and as an effective means for reduction of transmission.

In theory, malaria in any given population could be eliminated through the universal availability and use of currently recommended antimalaria drugs, although even this hypothesis has been compromised to some extent by the emergence of parasite resistance to some of the better antimalaria agents in some areas of the world. From a practical point of view, such universal availability and use has been impossible to achieve, and it has been necessary to view the use of antimalaria drugs in a control programme as an adjunct to other control measures, or as a minimal method for reduction of morbidity and mortality in areas where other control measures cannot be used effectively.

The use of chemotherapeutic agents in control programmes can be categorized as therapeutic, prophylactic, or presumptive.

A. Therapeutic use would presume prior diagnosis of a malaria infection. Knowledge of the parasite species and of the spectrum of drug sensitivity in the area of origin would be important in the selection of drugs and dosages. The major objective of such treatment is for reduction of morbidity and prevention of mortality in the individual case, but the treatment of any case in an endemic area does have at least minor implications in reduction of transmission through the elimination of potential sources of mosquito infection.

The question of the use of curative or sporontocidal drugs as part of the therapeutic regimen is of some importance, both to the patient and to the community. Where a drug, such as a 4-aminoquinoline, is utilized for suppressive cure of a Plasmodium falciparum infection, the addition of even small amounts of an 8-aminoquinoline (e.g. primaquine) may rapidly eliminate infective gametocytemias which might otherwise persist for several weeks, providing a source of transmission.

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The occurrence of relapse in P. vivax infections treated only with a 4-aminoquinoline drug also poses a problem, both to the patient and to the community. While such a relapse may not be life-threatening, it may be responsible for significant disability. Because the tolerance of the patient for the infection may be greater than during a primary attack, a relapse which is characterized by less severe or even no symptoms may provide for continuous untreated low parasitaemias which are infective to mosquitos and constitute a significant source of transmission. Curative therapy in such cases is desirable, but obviously difficult to administer, since the current recommendation is for a 14-day course of primaquine. Some studies in the past have suggested that shorter courses of primaquine, e.g., 5 days or 7 days, may be effective in the prevention of relapses. A recent study in El Salvador suggests that, even though a 5-day course of primaquine did not absolutely prevent relapse in a significant number of cases, it did reduce significantly the number of relapses experienced by treated persons when compared to those receiving only a 4-aminoquinoline. There was a suggestion that even a single dose of primaquine may have had some effect on the number of relapses. These results suggest the need for a more detailed study of the potential effect of shorter courses of primaquine on the overall malaria experience in a P. vivax-infected individual as a possible approach to the reduction of the parasite pool in an endemic area.

It is recognized that problems of toxicity and cost are highly important in wide-scale primaquine usage for sporontocidal or curative purposes and would require the appropriate cost-benefit and risk-benefit considerations.

B. Chemoprophylaxis may be an individual measure or may be based on mass distribution of prophylactic drugs to entire or selected populations. Individual prophylaxis provides an effective method for preventing the development of a malaria attack in persons temporarily residing in or visiting areas of malaria risk. The current recommendations of the World Health Organization in regard to drugs useful for this purpose appear to be adequate. The occurrence of chloroquine-resistant P. falciparum in a number of areas is a significant problem and requires careful instructions to persons relying on normal 4-aminoquinoline prophylaxis in these areas. The possibility of resistant parasites and the need for prompt diagnosis and alternative treatment should be carefully explained. Alternative drugs, such as quinine should be in the possession of or available to travellers to these areas for use in the event of an illness which could represent a breakthrough of resistant parasites. Careful explanation to travellers of the potential for the relapse of P. vivax type infections subsequent to the cessation of prophylactic drug is highly essential.

Mass distribution of drugs has been used sporadically in a number of malaria control and eradication programmes and has met with variable success. The two significant limiting factors have been the relatively high cost of such programmes and the failure of significant proportions of the population to accept prophylactic drugs, particularly when distribution is continued over long periods of time.

A large variety of drugs and drug regimens have been used in mass drug distribution programmes. The most commonly used compounds have been the 4-aminoquinolines and pyrimethamine, with or without the addition of the 8-aminoquinoline, primaquine. Treatment intervals ranged from weekly to bi-weekly, monthly, and even semi-annually or annually. Usually the drugs have been offered to the entire population, but in some programmes have been restricted to certain groups (i.e. school children, etc.).

The acceptability of repetitive drug distribution by a population has been a major problem. None of the drugs or drug combinations are completely free from minor side effects, and the recipients are usually quick to relate these as well as any totally unrelated symptoms which may be coincidental to the regular taking of the drugs. During programmes of drug distribution, malaria symptoms become a rarity in the populations involved, and a reluctance of "well" populations to utilize prophylactic measures which may have even minor unpleasant side-effects is well demonstrated. The acceptability of drug distribution seems to be proportional to the

length of time between cycles. Populations soon tire of weekly or biweekly cycles and absenteeism and refusals increase rapidly. However, even when only 50% of the population are being treated in any single cycle, parasite rates and clinical illness usually diminish to extremely low levels.

When only a single annual drug distribution cycle, or even cycles at 6-month intervals, are utilized, one can anticipate a relatively high acceptance rate, particularly if there is a high level of clinical malaria in evidence in the area. Such widely spread distribution cycles have been utilized experimentally in several programmes and may be effective as a minimal method for reduction of malaria morbidity, particularly when used at the right time and as an adjunct to other control measures.

The potential usefulness of mass drug distribution which does not encompass the entire population requires an evaluation. Distribution to special groups, based on either special needs for protection or on ease of obtaining full acceptance and coverage, would appear to be appropriate in some programmes. School children may provide a population which is relatively easy to reach and amenable to such prophylactic measures, and which may have special needs for prevention of malaria infections which would otherwise produce high rates of severe illness and mortality. Further, such age groups may be highly important in providing the levels of gametocytaemia which constitute the most efficient source of transmission. Certain labour forces in agriculture or industry may, for national economic reasons, require protection and may also be amenable to sufficient drug discipline to ensure adequate coverage. Other "captive" or high risk groups may be appropriate for protection with a regular drug distribution programme. The selection of drugs for use in mass distribution programmes should consider not only cost and acceptability, but also the usefulness of certain combinations of drugs for community protection in addition to personal protection. The inclusion of a sporontocidal drug in a prophylactic regimen can serve to quickly reduce transmission potential and may also reduce the P. vivax relapse potential.

C. Presumptive chemotherapy has served as an integral part of a number of malaria control and eradication programmes, particularly in relation to active and passive case detection systems. Presumptive treatment is based on the administration of a single suppressive dose of drug to all persons reporting symptoms suggestive of a malaria infection. The dosage of drug is usually calculated to eliminate all erythrocytic parasites, producing suppressive cure in P. falciparum and P. malariae infections, but usually failing to prevent subsequent relapse of the P. vivax or P. ovale infection. Because of their rapidity of action, their low toxicity, and their effectiveness in eliminating the erythrocytic parasites with single doses, the 4-aminoquinolines have been widely accepted as the drugs of choice for this purpose.

The desirability of adding an 8-aminoquinoline component to the presumptive treatment has been debated extensively in the past. Such drug combinations are more costly and there may be an added potential for minor side effects and toxicity. The advantage to the recipient would be limited to a possible, but not proven, elimination of some of the P. vivax relapse activity which would be expected to ensue if treatment included only a 4-aminoquinoline. On the other hand, the amount of community protection afforded by the addition of an 8-aminoquinoline component may be significant. In areas where P. falciparum is of major concern, even a single dose of primaquine will eliminate infective gametocytes in the recipient in one or two days; with chloroquine alone, gametocytes which are present or developing at the time of treatment are affected very little or not at all, and may remain infective to mosquitos for several additional weeks. The addition of pyrimethamine to the chloroquine suppressive also provides a sporontocidal effect.

In many antimalaria programmes, surveillance or case detection activities have relied heavily on the voluntary reporting to a health post by those in the community who are ill and believe their illness is due to a malaria infection. These health posts may be a public health clinic or a hospital, but more often consist of a community

volunteer who has been trained to acquire a diagnostic blood film and to administer treatment. While the information ultimately available from the diagnostic sample is useful, in many programmes the presumptive treatment received by the patient has been a highly significant factor in the reduction of morbidity, and, in some cases, may have been the most important factor in the virtual elimination of mortality from uncomplicated malaria.

A number of programmes have utilized active case detection, where an effort is made to visit every house and contact every person in a malarious area periodically, seeking persons who are ill with symptoms suggestive of malaria, acquiring blood films for diagnosis, and offering treatment on a presumptive basis. This has also resulted in the reduction of morbidity and mortality from malaria in areas where such methods are used.

The introduction of programmes utilizing presumptive therapy, either through passive or active search for cases, to highly endemic areas where insecticidal measures are presently impractical or ineffective would be highly desirable for an immediate effect on morbidity or mortality. If early results of such use in limited demonstration programmes in, for example, hyper- or holo-endemic areas of tropical Africa were encouraging extension of such programmes to much wider areas could be recommended. It would seem that such wide drug availability represents the absolute minimum effort that should be made towards the control of malaria wherever it exists.

Discussion

On a number of occasions since 1960, the World Health Organization has convened scientific groups which have thoroughly reviewed the chemotherapy of malaria and its application to malaria eradication and control programmes. The reports of these Groups have been published (WHO Techn. Rep. Series, 1961, no. 226; 1965, no. 296; 1967, no. 375; and 1973, no. 529), and provide a wealth of information on chemotherapy and on the problems of parasite resistance to drugs. For all of these meetings there was a tremendous effort expended by numerous authorities in the field towards the provision of working papers to be considered by the Groups; for instance, there were 49 working papers prepared for the 1960 Technical Meeting and 25 for the one held in 1967. The material in these working papers, for the most part, retains validity as applied to the problems which are being faced today, and provides a valuable resource for the future consideration of the role of chemotherapy in control programmes. It might be urged that, in the event that the WHO implements further meetings of scientific groups to consider malaria chemotherapy, these documents should be made available for review. It might even be worthy of consideration for WHO to convene a select group for the sole purpose of reviewing this documentation for information which would be useful in the application of chemotherapeutic measures.

Drug resistance continues to be one of the thorniest problems which we face and poses a number of dilemmas in the management of drug use. Reports continue to emerge relative to suspected chloroquine resistance in Africa, and even though most of these are based on marginal evidence they must be considered seriously. There seems to be little doubt that any increased use of drugs as a control method will generate further reports of resistance and the emergence of parasite strains which may already be less sensitive to a particular drug. However, it would be questionable to deny the wide use of life-saving drugs on the basis of the possible exacerbation or acceleration of drug resistance. Decisions must be faced on recommendations for the use of drugs for personal prophylaxis and for wide use in areas where resistance is known to exist as well as in areas where it does not now seem to be a problem, and there should be a high priority given to the careful assessment of parasite sensitivity to drugs in all malarious areas.

There are several specific questions which require early attention in regard to prevention and treatment of chloroquine-resistant P. falciparum malaria. There appears to be at least a slight advantage in the use of amodiaquine instead of chloroquine in the treatment of these strains. Additional field studies should be conducted to verify this advantage, and should perhaps include other 4-aminoquinolines. The usefulness of pyrimethamine-sulfonamide combinations has been well demonstrated therapeutically. It would be well to narrow down the field of combinations and to carefully consider the implications of their possible wider prophylactic and therapeutic use. The possible role and availability of quinine should be thoroughly explored and recommendations for its use restated. While mepacrine has been discarded as a useful drug because of apparent cross-resistance with chloroquine, the degree of cross-resistance should be re-examined to determine with some certainty if this drug might provide even a slight advantage:

There seems to be little purpose in detailing the current efforts towards development of new antimalaria agents. There are, apparently, a few which currently merit field trials, and efforts should be made to complete these studies as soon as possible. One can only be pessimistic about the prospects for the development of further agents because of the constraints imposed by the unavailability of clinical testing facilities and by the economics of drug development in private industry. At some point in the future the question of subsidization of drug development by national or international agencies will necessarily emerge for discussion.