

SYMPOSIUM

Year : 2006 | Volume : 52 | Issue : 4 | Page :
277-280

Treatment of falciparum malaria in the age of drug resistance**GD Shanks**

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Abstract

The growing problem of drug resistance has greatly complicated the treatment for falciparum malaria. Whereas chloroquine and sulfadoxine/pyrimethamine could once cure most infections, this is no longer true and requires re-examination of alternative regimens. Not all treatment failures are drug resistant and other issues such as expired antimalarials and patient compliance need to be considered. Continuation of a failing treatment policy after drug resistance is established suppresses infections rather than curing them, leading to increased transmission of malaria, promotion of epidemics and loss of public confidence in malaria control programs. Antifolate drug resistance (i.e. pyrimethamine) means that new combinations are urgently needed particularly because addition of a single drug to an already failing regimen is rarely effective for very long. Atovaquone/proguanil and mefloquine have been used against multiple drug resistant falciparum malaria with resistance to each having been documented soon after drug introduction. Drug combinations delay further transmission of resistant parasites by increasing cure rates and inhibiting formation of gametocytes. Most currently recommended drug combinations for falciparum malaria are variants of artemisinin combination therapy where a rapidly acting artemisinin compound is combined with a longer half-life drug of a different class. Artemisins used include dihydroartemisinin, artesunate, artemether and companion drugs include mefloquine, amodiaquine, sulfadoxine/pyrimethamine, lumefantrine, piperaquine, pyronaridine, chlorproguanil/dapsone. The standard of care must be to cure malaria by killing the last parasite. Combination antimalarial treatment is vital not only to the successful treatment of individual patients but also for public health control of malaria.

How to cite this article:

Shanks G D. Treatment of falciparum malaria in the age of drug resistance. J Postgrad Med 2006;52:277-280

How to cite this URL:

Shanks G D. Treatment of falciparum malaria in the age of drug resistance. J Postgrad Med [serial online] 2006 [cited 2015 Sep 9];52:277-280

Available from: <http://www.jpgmonline.com/text.asp?2006/52/4/277/28153>

Full Text

Over the last generation, falciparum malaria has become widely resistant to a number of common antimalarial drugs.[1],[2] By drug-resistance one means when adequate blood concentrations of the drug are no longer able to kill a previously susceptible parasite. Drug-resistance arises by the evolutionary selection of spontaneously arising mutants that are drug insensitive. When one kills all sensitive parasites, by definition the ones remaining are drug insensitive.[3] The mechanism of antimalarial drug-resistance has been investigated at the molecular level and usually it has been found to be due to point mutations that change drug accumulation /efflux in the erythrocyte or reduce drug affinity for the target molecule.[4]

Antimalarial drug-resistance may present as a treatment failure in an individual patient, but more commonly it makes its presence known by increasing the apparent number of malaria infections.[5] Individuals appear to be getting multiple infections, when in reality they have a single infection that is suppressed by inadequate treatment followed by a parasite recrudescence. At a community level this is demonstrated by increasing malaria rates, appearance of malaria in previously well-controlled areas and malaria epidemics in marginal transmission zones.[6],[7],[8],[9],[10]

Not all treatment failures represent drug-resistance. Critical questions to be asked when confronted by a falciparum malaria patient who has failed chemotherapy include whether the drug is genuine or expired, was the drug in the correct dosage actually taken by the patient and whether the administered drug was absorbed from the gastrointestinal tract. Unfortunately, counterfeit antimalarial drugs are common in Asia and those participating in this form of 'pharmacological manslaughter' often produce very convincing fakes that closely resemble the real article excepting they include no active drug.[11] Failures in medication compliance with antimalarial drugs are extremely common and one needs to be satisfied that the patient actually ingested the prescribed medication. Many antimalarial drugs are not highly bio-available which is particularly of concern when a sick patient is poorly tolerant of any oral intake.[12]

The basis of all malaria treatment is a sound diagnosis. Most febrile patients do not have malaria and most malaria patients in India do not have Plasmodium falciparum but P vivax . Clinical diagnosis of malaria is usually incorrect and cannot be the basis of any rational treatment plan. This review of treatment of falciparum malaria will make no sense whatsoever unless one proceeds from a solid diagnosis obtained by a blood film examined microscopically by a trained observer which may sometimes be replaced by a rapid chromatographic blood test strip for malaria antigen.[13],[14]

Geographic spread of drug-resistance only requires the movement of infected persons into new areas which have competent Anopheles vectors.[5] Maps delineating the geographic extent of multiple drug resistant P. falciparum necessarily lag the movement of the parasite and should not be over-interpreted to indicate absence of drug-resistance. Multiple drug-resistance has certainly arrived in India and is particularly prevalent in the states of the Northeast.[7],[15],[16] Drug-resistance is first seen when apparently successfully treated patients recrudescence their infection often weeks after original therapy. Any determination of drug-resistance for public health purposes based on studies with anything less than four weeks of follow-up, is bound to be misleading.[17]

Continuation of a failing chemotherapy with the justification that it is helping some patients is false economy. [18],[19],[20] Drug-suppressed malaria infections beget new infections.[21] Public confidence in any malaria control program is greatly eroded once malaria patients determine that the medications they are being given do not work. Adequate chemotherapy with more expensive medications can actually be shown to save money by decreasing the total number of infections requiring treatment.[18],[22],[23] Control of epidemics and limitation of further spread of drug-resistance will occur when drugs are used to cure instead of suppress infections.

Chloroquine-resistance

For nearly a generation after its introduction, chloroquine successfully cured both falciparum and vivax malaria, greatly simplifying any malaria drug decisions.[8],[15],[24] Although chloroquine remains a very adequate therapy for vivax malaria in most areas, no one can now depend on chloroquine to cure falciparum malaria. The delayed evolution of chloroquine-resistance unfortunately lulled physicians into a false sense of security which must now be dispelled. The anti-inflammatory properties of chloroquine may make patients with nonspecific symptoms feel better, but chloroquine alone cannot be regarded as adequate treatment for falciparum malaria.[21]

Antifolate-resistance

Antifolate drugs block the parasite's synthesis of tetrahydrofolate thus stopping nucleic acid synthesis. Sequential blockades of the synthesis pathway using both dihydrofolate reductase by pyrimethamine and dihydropteroate synthetase by sulfadoxine can often produce a cure.[25],[26],[27],[28] Unfortunately, falciparum parasites are able to quickly accumulate multiple genetic mutations producing enzymes resistant to such drugs. In Thailand during the 1970s, sulfadoxine/pyrimethamine (SP) failed as primary therapy in a very short period of time once it was in general use.[5] These same resistance genes have rapidly spread across Asia and into Africa such that treatment with a single administration of sulfadoxine / pyrimethamine often fails to cure uncomplicated falciparum infections.[28],[29],[30] Once a drug fails to cure a substantial number of infections, its ability to be used in combination with another more effective drug, is also severely limited.

Mefloquine-resistance

In retrospect, it is possible to see that mefloquine-resistant parasites pre-existed the introduction of mefloquine.[31] In practical terms this meant that the widespread use of mefloquine allowed the selection of multiple drug-resistant falciparum parasites.[5],[32] Despite the operational desirability of giving treatment in a single dose, such long-acting drugs such as mefloquine or sulfadoxine / pyrimethamine hold within themselves the root of their own demise. The long elimination half-life of mefloquine allows parasites to encounter sub-inhibitory concentrations in persons treated weeks or months previously.[26] Thus the selection and establishment of mefloquine resistance is only a matter of time once it is widely used alone

without combination with another effective drug.[33]

Atovaquone-resistance

Atovaquone is a relatively new antimalarial drug that blocks the parasite's cytochrome electron transfer system.[34],[35] Unfortunately, a single nucleotide mutation in the cytochrome b gene engenders very high grade drug-resistance even within a single patient.[36] Atovaquone cannot be used alone; indeed it is only available in a combination tablet with proguanil. Atovaquone / proguanil given as an oral combination over three days results in a very high cure rate in uncomplicated falciparum patients. Atovaquone's long half-life predisposes it to selection of drug resistant strains over time.[26] Considering the expensive nature of the drug, its widespread use is unlikely thus delaying the inevitable drug-resistance to atovaquone.

Multiple drug-resistance and the basis of combination chemotherapy

Multiple drug-resistance occurs when a parasite that already is resistant to one class of antimalarials develops resistance to another separate class of drug. Usually this occurs when a chloroquine resistant parasite becomes resistant to another drug such as SP. Indeed there is already solid evidence of multiple drug-resistance in India particularly in the Northeastern states.[7] Those using antimalarials must learn what physicians treating tuberculosis learned long ago; single drug therapy is not adequate and invites the public health disaster of multiple drug-resistance.[2],[30],[31]

Combination chemotherapy in malaria is typically formed when a rapidly acting drug (quinine or artemisinin) is combined with a slower acting drug (tetracycline, mefloquine etc) given over enough time (at least four parasite generations which is about eight days) to kill any residual parasites.[2] When two effective drugs are used, the probability of selecting a mutant parasite with resistance to both drugs is very unlikely. Currently available combinations which have been proven effective in field trials include quinine-tetracycline, chlorproguanil-dapsone, artemether-lumefantrine and the previously mentioned atovaquone-proguanil.[37],[38],[39],[40] As with any medication, each combination has its own advantages and disadvantages based on expensiveness, tolerability and ease of administration. The critical point is that combination chemotherapy for malaria is currently available in several forms and is not a recommendation requiring new drug development.

The standard of care for the potentially lethal falciparum parasite must be to kill the last parasite in order to ensure a cure. Anything less is an unacceptable risk both to the patient and to the public health of all living in malaria-transmission areas. The best single example of this occurred on the Thai-Burmese border during the 1990s.[32],[41] The rapid evolution of mefloquine-resistance was quickly threatening to create untreatable malaria infections. Combination of mefloquine with the artemisinin compound artesunate reversed this situation in a remarkably short period of time and largely controlled falciparum malaria among the population of displaced persons. When challenged about the inability of public health programs to afford anything other than the cheapest of drugs, one can respond simply by noting the comparative cost of continuing a failing regimen in a community. On the South African - Mozambique border malaria control was rapidly being lost in the face of widespread SP resistance.[22],[29] Switching to artemether-lumefantrine along with using more effective residual insecticide spraying resulted in far better malaria control at less cost because fewer patients had to be treated.[18],[23]

Artemisinin combination therapy (ACT)

Given the practical problems of quinine, particularly low patient compliance from frequent adverse events such as tinnitus, artemisinin compounds are increasingly used for falciparum treatment. Derived from the Chinese pharmacopoeia and a type of wormwood plant, artemisinin compounds exist in a variety of derivatives most of which appear to have as their active metabolite dihydroartemisinin. The major advantages of artemisinin compounds are their fast action in clearing the blood of parasites and preventing the emergence of the gametocyte transmission stages.[39],[40],[42] Both of these characteristics minimize the development of drug-resistance and encourage further use of artemisinin compounds in combination with other drugs as ACT. [37] There are several drugs used in combination with artemisinins to include mefloquine, pyronaridine, piperaquine, amodiaquine, chlorproguanil-dapsone and lumefantrine which have all undergone clinical field trials, in some cases with many thousands of patients. Artesunate is available in parental and well as oral form and has been shown superior to quinine for severe malaria.[43]

The modern medicines for malaria venture is actively developing new drugs and drug combinations for malaria treatment (www.mmv.org). New or improved ACT combinations currently undergoing clinical testing include pyronaridine + artesunate (PANDA), piperaquine + dihydroartemisinin (Artekin®) and chlorproguanil dapsone artesunate.[44] It is realistic to hope that these combinations will be available in the near term. None of them will be inexpensive compared to chloroquine and all will require multiple day regimens in order to cure falciparum malaria.

Conclusions

Combination chemotherapy's principles remain the same whether one is treating cancer or malaria. Full doses of effective drugs in combination should be used to result in cure and to avoid the generation of drug-resistance. Combination chemotherapy for falciparum malaria is currently available and should be the standard of care. Artemisinin compounds (an alternative possibly being quinine) are combined with a variety of partners to include mefloquine, pyronaridine, piperaquine, amodiaquine, chlorproguanil-dapsone and lumefantrine. Actual treatment regimens are undergoing rapid evolution and so a list of updated websites is provided rather than a table of treatment regimens which will be superseded in the future.

Acknowledgement

Travel to Conference paid by Department of Health and Human Services, USA

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Wednesday, September 09, 2015

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