Some Pharmacological Aspects of Antimalarial Drugs

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SUMMARY

A short review is given of antimalarial drugs currently in use.

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CLASSIFICATION

The chemotherapy of malaria may be conveniently classified as (*i*) casual prophylaxis; (*ii*) suppressive treatment; (*iii*) clinical cure; (*iv*) radical cure; and (*v*) gametocytocidal drugs.

Causal Prophylaxis

Causal prophylaxis prevents demonstrable infection by exerting a lethal effect on the parasites during the pre-erythrocytic stage. Primaquine is the most effective agent against the primary tissue stage — but impracticable due to side-effects. Pyrimethamine and chloroguanide are active against this stage of *P. falciparum* but weak against *P. vivax* infections.

Suppressive Treatment

Suppressive treatment causes the inhibition of the erythrocytic stage of development so that the individual is kept free of clinical manifestations. Chloroquine (preferably with pyrimethamine) and, rarely, chloroguanide are used (a chloroquine-pyrimethamine combination is preferred), and in multiresistant strains, pyrimethamine with dapsone, and pyrimethamine (or trimethoprim) with a long-acting sulphonamide. Suppressive cure occurs eventually in *P. falciparum* malaria, and sometimes with *P. vivax* infections, but the latter usually recurs.

Clinical Cure

The clinical cure is the termination of the clinical attack by interruption of erythrocytic schizogony. Drugs of choice are the 4-aminoquinolines, and in multiresistant forms, quinine or a combination of a diaminopyrimidine with a long-acting sulphonamide.

Radical Cure

A radical cure implies elimination of the secondary tissue phase, usually of *P. vivax* malaria, as well as the erythrocytic phase. The 8-aminoquinolines are the only really effective drugs against the secondary tissue schizonts, although the diaminopyrimidines may have some effect.

Gametocytocidal (or Static) Drugs

These drugs prevent transmission via the mosquito by an effect on gametocytes, either in the human host or by preventing development of sporozoites in the mosquito (pyrimethamine and chloroguanide affect both *P. vivax* and *P. falciparum*). All the remaining antimalarials are active against *P. vivax* gametocytes in the blood, but *P. falciparum* gametocytes are sensitive only to primaquin.

MECHANISM OF ACTION OF ANTI-MALARIAL AGENTS

The 'older' agents with a rapid schizontocidal action are the 4-aminoquinolines, quinine and acridines. They interact with, and alter, DNA. The reasons for their selective toxicity are accumulation in the parasitised cell due to an affinity for nucleates and their partition profiles, which determine passive diffusion into the cell.

The dihydrofolate reductase inhibitors (chloroguanide, diaminopyrimidines) prevent folinic acid formation. Trimethoprim's action (in combination with a sulphonamide) is more rapid and it is less vulnerable to induction of resistance than pyrimethamine, probably because the latter not only attaches to the reductase, but also protects it against the proteolytic enzyme, pronase. The selective toxicity of these agents is due to differing sensitivities of the various dihydrofolate reductases to inhibition. The sulphonamides and sulphones act in sequence with the abovementioned drugs by competing with PABA in the synthesis of folic acid.

Both G-6-PD-deficient erythrocytes and the secondary tissue schizonts appear to have a similar enzyme defect involving the pentose-phosphate pathway, making them susceptible to oxidation damage by the quinoline-quinone metabolites of the 8-aminoquinolines (primaquin). (NADPH is not regenerated rapidly enough to reduce the oxidised glutathione to reduced glutathione which protects SH-dependent enzymes from oxidation.)

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PHARMACOLOGICAL CHARACTERISTICS PERTINENT TO THERAPEUTICS

Chloroquine

This drug is well absorbed after oral administration (decreased by diarrhoea). Tissue concentrations are higher than those in plasma (leucocytes have 200 times the plasma concentration). Parasitised red cells contain a high concentration. In 'resistance' this does not occur. Brain levels are 10 - 30 times those in plasma. In spite of tissue affinity, a steady state is achieved after 10 daily 310-mg (base) doses (but a loading 'dose' is necessary in clinical attacks). Plasma levels maintain a plateau of ±125 μg/litre only after 5 weeks of weekly doses. Plasma half-life varies, increasing as concentration falls. A dose of 310 mg (base) weekly results in peak levels of 150 - 250 μg/litre with a half-life of 3-5 days, falling to 20 - 40 μg/litre immediately before the succeeding dose. Complete suppression may, according to some authors, be possible at plasma concentrations of 8 - 10 μg/litre. Urinary excretion is slow, but can be increased by an acid urine, since 70% is excreted unchanged. Other 4-aminoquinolines raise the plasma level of chloroquine.

Its efficacy as a causal prophylactic is nil. It is effective for suppression and against clinical attack, but it is ineffective against sexual forms of *P. falciparum*.

Quinacrine

Quinacrine is similar in many respects to chloroquine, but it has a very high affinity for tissues, and therefore a loading dose 2 weeks before entering a malarious area is necessary. To maintain adequate blood levels for suppression, daily doses are given.

Quinine

A peak plasma level is reached after about 3 hours and falls to zero after 24 hours. No cumulation occurs. Only 5% is excreted unaltered. A daily suppressive dose of 1 g results in plasma levels of 7 mg/litre, but to maintain a plateau, 6-hourly administration is called for.

Its efficacy is the same as chloroquine, but it is used mostly in acute attacks caused by chloroquine-resistant *P. falciparum* strains.

Chloroguanide and the Diaminopyrimidines

They are slowly but adequately absorbed. Chloroguanide is rapidly excreted (within 24 hours). No cumulative effect occurs and daily dosage is necessary. Erythrocytes concentrate the drug. Sixty per cent is excreted as the parent drug.

It has a weak action on exo-erythrocytic schizonts. It is effective as a gametocytocide (*P. vivax*) and sporontocide (*P. vivax* and *P. falciparum*), and also for suppression, although resistance occurs readily. The action is too slow for use in clinical attacks.

Pyrimethamine

Pyrimethamine differs from chloroguanide in that it is excreted much more slowly — a single 25-mg dose can confer protection (suppression) for up to 2 weeks. Significant plasma levels are still found after one week (±200 μg/litre). Maximal plasma levels are attained within 4 hours. The efficacy is similar to that of chloroguanide, but the tendency to induce resistance is less. The drug is excreted in the milk of nursing mothers.

Trimethoprim

Trimethoprim is well absorbed, peak plasma levels occurring in 2 - 4 hours, and some drug persists for 24 hours. The half-life is about 16 hours. Tissue concentrations are higher than those in plasma. It is used in combination with a sulphonamide against the acute attack where multiresistant strains are involved. Induction of resistance is low thus far.

Long-Acting Sulphonamides

Two preparations have had limited trials in combination with (*a*) pyrimethamine for acute attacks and suppression, and (*b*) trimethoprim in clinical attacks. They are sulphamethoxypyrazine (Kelfizina) with a serum half-life of about 65 hours, and sulphormethoxine (Fanasil) with a half-elimination time of 100 - 200 hours. Combined with the folate reductase inhibitors, their antiplasmodial action is rapid enough for use in the acute phase.

The Stevens-Johnson syndrome has been described, as well as the emergence of resistant *E. coli* strains, when these preparations have been used as suppressive agents.

Dapsone

Peak plasma levels are reached after 1 - 3 hours, and the drug is detectable for 8 - 12 days. The kidneys are the main pathway for excretion. The drug is also excreted in milk. It is used in conjunction with pyrimethamine as a suppressant, with no indication of resistance developing after one year.

The most common untoward effect is haemolysis of a varying degree. Doses of 100 mg or less in 'normal' persons, and 50 mg or less in people with glucose-6-phosphate dehydrogenase deficiency do not produce haemolysis. Methaemoglobinaemia can occur. This drug also has antimicrobial actions, albeit limited, and can induce resistance in potentially pathogenic micro-organisms.

Primaquin

Plasma concentrations are maximal after 6 hours but barely detectable after 24 hours due to the rapid biotransformation to active quinoline-quinone derivatives. Plasma levels do not correlate well with antimalarial activity.

Quinacrine greatly enhances plasma concentration and sojourn in the body. Doses are given daily for curative purposes.

DRUG-RESISTANT STRAINS

Resistance may be acquired, or a strain may be naturally insensitive, or relatively so, to a particular agent. Acquired resistance may be the result of 'overgrowth' of the naturally occurring resistant mutants, or the resistance can be induced by inadequate blood levels of the therapeutic agents.

A high degree of resistance can be induced against chloroguanide and pyrimethamine, less easily so against the 4- and 8-aminoquinolines and acridine derivatives. Quinine is usually helpful against these multiresistant strains, but should resistance to this alkaloid develop, recourse is taken to the use of combinations, e.g. pyrimethamine with either a sulphonamide or dapsone, or trimethoprim with a sulphonamide.

PREVENTING OR LIMITING RESISTANCE

The use of a combination of drugs prevents or limits resistance. The combination must be chosen so that the half-lives of the components are similar (to ensure a continuous combined effect), e.g. chloroquine and pyrimethamine or the latter with either a long-acting sulphonamide or dapsone. One particular combination should be employed until proof of the emergence of a resistant strain is evident. Only then should the reserve combination be administered. Likewise, combination drugs should be held in reserve for treatment of the acute attack, until evidence exists that strains in that area are resistant to the conventional drugs (4-aminoquinolines).

Intermittent and inadequate chemosuppression of non-immune and partially immune populations, who are constantly being reinfected from indigenous reservoirs of parasites, greatly favours the emergence and spread of drug-resistant strains of malaria. Immune populations should not be given chemosuppressives unless dosage regimens are adequate and strictly adhered to.

In this context two factors must be stressed, i.e. the unreliability of patients in taking medication, and factors affecting bio-availability of the drug in question. The adequacy of the treatment regimen can in many cases be assessed by determination of plasma levels of the drug, and reliability of ingestion of the drug by a qualitative urine test.

Many so-called drug-resistance cases may be the result of inadequate drug levels at the site of action.