Pharmacology of 8-aminoquinolines

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The 8-aminoquinolines were the first group of compounds to be synthesized specifically for their antimalarial activity. A large-scale research programme in the United States of America in the 1940s produced three new antimalarial drugs—pentaquine, isopentaquine, and primaquine—of which primaquine was the most effective. This article reviews knowledge on the activity of these 8-aminoquinolines against all stages of the malaria parasite and suggests their possible modes of action. The toxic effects and possible causal mechanisms are also outlined.

The 8-aminoquinolines were the first group of compounds to be synthesized specifically for potential antimalarial activity. Initially, attempts were made to incorporate a diethylaminoalkylamino side-chain, which had been shown to enhance the activity of methylene blue, into the 6-methoxyquinoline moiety of quinine. The research of Schulmann, Schönhofer, and Roehl culminated in the introduction of Plasmochin, later called pamaquine (7).

In the 1940s, a large research programme was initiated in the United States of America, to develop more potent and less toxic antimalarial drugs. From this programme, three compounds—pentaquine, isopentaquine, and primaquine—were selected for further study. Primaquine proved to be the most satisfactory compound (2-4). Quinocide, an isomer of primaquine, is used in the USSR and East European countries as a tissue schizontocide.

The structures of the important 8-aminoquinolines are shown in Table 1.

Many analogues of the 8-aminoquinolines have been assessed for their antimalarial activity, but few have been more effective than primaquine. Peters et al. (5) synthesized and tested a large number of derivatives with substitution on the 2-, 3-, 4-, 5-, and 6-position of the ring and also in the side-chain at position 8. The two most active compounds were WR 205439 (maleate), which had a substitutionα at position 2 of the primaquine molecule, and WR 203608 (β-diresorcylate), which had 4-methyl and 6-methoxy substitution, as well as substitutionβ on the nitrogen atom of the ring. These derivatives displayed far greater causal prophylactic activity than did primaquine against Plasmodium yoelii nigeriensis and probably had greater therapeutic indices. However, no other compound has shown similar activity, and primaquine remains the most important 8-aminoquinoline antimalarial drug.

Primaquine is composed of equal parts of (+) and (−) forms because of the presence of an asymmetric carbon atom (6). The activity of the two forms against P. cynomolgi in rhesus monkeys was identical, but the toxicity of the (−) form was 3–5 times greater than that of (+)-primaquine, as judged by its hepatotoxic effects. These differences in toxicity would be important if the results were confirmed in man (7).

Table 1. The structure of the important 8-aminoquinoline antimalarials

<table>
<thead>
<tr>
<th>Drug</th>
<th>R</th>
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<tbody>
<tr>
<td>Pamaquine</td>
<td>CH(CH₃)(CH₂)₃NH(CH₃)₂</td>
</tr>
<tr>
<td>Primaquine</td>
<td>CH(CH₃)(CH₂)₃NH₂</td>
</tr>
<tr>
<td>Isopentaquine</td>
<td>CH(CH₃)(CH₂)₃NHCH(CH₃)₂</td>
</tr>
<tr>
<td>Rhodoquine (Plasmocid)</td>
<td>CH₃NH(C₂H₅)₂</td>
</tr>
<tr>
<td>Pentaquine</td>
<td>CH(CH₃)NHCH(CH₂)₂</td>
</tr>
<tr>
<td>Quinocide</td>
<td>CH(CH₃)CH(CH₂)NH₂</td>
</tr>
</tbody>
</table>

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β (CH₂)₅NHCH₂CH(CH₃)₂.
Tissue culture

Tonkin (8) adapted the technique developed by Hawking (9), for growing exoerythrocytic forms of *P. gallinaceum* in tissue culture, in order to study the effect of various antimalarials on the inhibition of growth of these exoerythrocytic forms. In this test system, pamaquine dihydrochloride showed slight inhibitory activity at a dose of 0.5 mg/litre, which was known to be toxic to macrophages.

Avian malaria

Pamaquine administered orally at a dose of 20.25 mg of base per day for 6 days, although not curative, increased survival time in the *P. gallinaceum/Aedes aegypti* model (10).

Fink (11) showed that primaquine, when given intravenously several hours after an inoculation of sporozoites, reduced *P. cathanemeriun* parasitaemia in canaries, giving an ED₅₀ of 0.08 mg/kg of body weight. Under identical experimental conditions, pre-erythrocytic and erythrocytic forms of malaria responded to primaquine in the same way.

Rodent malaria

Most et al. (12) showed that orally administered primaquine at a dose of 50 mg/kg of body weight exerted a causal prophylactic effect in mice and rats infected with *P. berghei* sporozoites. However, it was not clear whether the drug acted solely by inhibiting pre-erythrocytic schizogony, or whether it also had a damaging effect on the cryptozoites emerging into the peripheral circulation.

Primaquine prevented parasitaemia in rats infected with *P. berghei* sporozoites, obtained from the salivary glands of infected *Anopheles stephensi*. No exoerythrocytic forms were found in the livers of these animals and malaria did not develop after splenectomy, thereby indicating that primaquine had had a causal prophylactic effect (13).

Primaquine diphosphate (40 mg/kg of body weight), encapsulated in sonicated multilamellar liposomes, cured all mice infected with sporozoites of *P. berghei*, with an LD₅₀ of 139 mg/kg of body weight compared with 39 mg/kg of body weight for the free compound. Encapsulation of primaquine in liposomes therefore seems to increase efficacy and reduce toxicity (14).

Simian malaria

A causal prophylactic effect was seen in rhesus monkeys infected with *P. cynomolgi* sporozoites and then treated with a daily dose of 1 mg of primaquine base/kg of body weight from day 1 to day 7 (15).

Rossan et al. (16) showed that, in *Aotus trivirgatus* with sporozoite-induced *P. vivax* infection, chloroquine (10, 10, and 5 mg/kg of body weight administered on 3 consecutive days) plus primaquine (1 mg/kg of body weight daily for 14 days) cured the monkeys and that splenectomy did not cause any relapse. Similar results were obtained in *Saimiri sciureus*.

Human malaria

*P. vivax*. Jones et al. (17) evaluated the prophylactic effects of pamaquine and pentaquine, and concluded that they suppressed pre-erythrocytic schizogony. Pamaquine acted as a true causal prophylactic when administered as a daily dose of 90 mg of base. Arnold et al. (18) demonstrated the complete effectiveness of 30 mg of primaquine base in causal prophylaxis.

Since pamaquine and primaquine can eradicate secondary exoerythrocytic schizont forms, they are used as antirelapse drugs in *P. vivax* and other relapsing malarial infections.

*P. falciparum*. Pamaquine and primaquine cannot be used as causal prophylactics against *P. falciparum* infection, since the high doses required are toxic to man (19).

Sporontocidal action

Pamaquine, pentaquine, and primaquine showed no significant sporontocidal activity against *P. gallinaceum* in *Aedes aegypti* (20, 21).

Pamaquine, isopentaquine, and pentaquine when fed to infected mosquitos at a concentration of 0.02% produced degenerative changes in oocyst development (22). While primaquine alone had no effect on oocysts on or the sporozoites of *P. vivax* in *Anopheles stephensi* or *A. quadrimaculatus* (23), in combination with quinine, chloroquine, or mepacrine, it showed marked sporontocidal activity.

Terzian & Weatherby (24) showed that pamaquine inhibits the infectivity of mosquitos carrying *P. falciparum*, possibly by destroying the sporozoites.

Gametocytocidal action

The 8-aminoquinolines are very efficacious in destroying gametocytes of *P. falciparum* and *P. vivax*. In Malaysia, pamaquine has been shown to render *P. falciparum* gametocytes non-infective for mosquitos (see 25). The gametocytes of the Papua New Guinea strains of *P. falciparum* and *P. vivax* lose their infectivity when exposed to pamaquine treatment.
Walker (27) has reported that isopentaquine reduces the infectivity of P. falciparum gametocytes, while primaquine has been shown to be effective against the Chesson strain of P. vivax (28) and the Panama strain of P. falciparum (29). Burgess & Bray (30) have shown that primaquine treatment leads to a progressive diminution and eventual disappearance of the gametocytes in P. falciparum infections in man. They also showed that, in the mosquito, infection of the salivary gland decreases rapidly, while that of the gut is more persistent. They concluded that primaquine did not prevent ookinite formation, but inhibited maturation and production of normal oocysts and sporozoites. In this way, it could be used to minimize the transmission of chloroquine-resistant strains of P. falciparum (31, 32).

**ANTIMALARIAL ACTIVITY AGAINST THE ERYTHROCYTIC PHASE**

**Avian malaria**

8-Aminoquinolines show marked schizontocidal activity in canaries infected with *P. relictum*. Pamaquine was found to be 60 times more effective than quinine against canary malaria (33). Also, several 8-aminoquinolines showed marked activity (100 times that of quinine) against *P. lophurae* infection in the duck. However, these compounds did not show any curative or prophylactic activity against sporozoite-induced avian infections (34), although they were active against *P. gallinaceum* infection in the chick.

The simultaneous administration of primaquine phosphate and chloroquine was effective in the treatment of African black-footed penguins infected with *P. elongatum* and *P. relictum* (35).

**Rodent malaria**

8-Aminoquinolines show schizontocidal activity against *P. berghei* infection in albino mice. Primaquine is much more potent than pamaquine with its effective dose ranging from 1.25 mg of base/kg of body weight to 2.85 mg of base/kg of body weight (36-39). There was no observable difference in the primaquine sensitivity of pyrimethamine-resistant *P. berghei* strains (40). Primaquine is also effective against *P. chabaudi* and *P. vinckei* infections in mice (41, 42).

**Simian malaria**

Davidson et al. (43) could not obtain curative effects with primaquine at doses of 31.6 mg/kg of body weight per day in trophozoite-induced *P. cynomolgi* malaria in rhesus monkeys. However, a marked suppression of parasitaemia was observed.

**Human malaria**

Primaquine and other 8-aminoquinolines are active against asexual blood forms of human malaria, but only at doses that are too toxic for general use (44).

**EXPERIMENTAL DEVELOPMENT OF DRUG RESISTANCE**

Fulton & Yorke (45) produced pamaquine resistance in a strain of *P. knowlesi* in rhesus monkeys, by doubling the dose at each passage. By the fourth passage they had a strain of *P. knowlesi* that did not respond to a dose of pamaquine (26.4 mg/kg of body weight) that was toxic to the monkey.

In contrast, more than 62 passages were necessary to attain even a modest level of resistance to pamaquine in *P. gallinaceum* in chicks (46).

Ramakrishnan & Prakash (47) and Prakash et al. (48) were the first to develop primaquine-resistant strains of *P. berghei* and *P. knowlesi*. For the *P. knowlesi* strain, 42 passages over 153 days were needed to produce an 8-fold increase in resistance to primaquine (47). Prakash et al. (48) produced a 12-fold increase in resistance to primaquine in *P. berghei*, while Peters (49), using the same technique, developed a highly resistant strain of *P. berghei*. However, these strains show some loss of resistance if passaged in untreated mice (50).

Bishop (51) succeeded in developing a primaquine-resistant strain of *P. gallinaceum* that was able to survive in chicks receiving the maximum tolerated dose of primaquine diphosphate (5 mg of base/kg of body weight).

**DRUG RESISTANCE IN HUMAN MALARIA PARASITES**

**Resistance in *P. vivax***

There are differences in the innate susceptibilities of various strains of *P. vivax* to primaquine. Primaquine was less effective in preventing relapses in infections with the Papua New Guinea Chesson strain of *P. vivax* than in those with the Korean strain (52).

There have been no reports of resistance developing as a direct consequence of the use of primaquine, pentaquine, or isopentaquine in man. However, resistance to primaquine has developed and cross-resistance to a new 8-aminoquinoline derivative, WIN 5037, has been observed (50). Arnold et al. (53), in experimental infections in human volunteers, managed to develop a resistant strain of *P. vivax* (Marvell strain) that could survive the maximum tolerated dose of 120 mg of primaquine base. This was achieved after 36 sequential passages during 250 days of continuous drug selection pressure.
A few instances of primaquine resistance in the field have been reported (54, 55). However, the development of primaquine-resistant strains of *P. vivax* has not caused any serious problem in the treatment of infected patients in Viet Nam (see 56).

**Resistance in P. falciparum**

There have been no reports of induced primaquine resistance in *P. falciparum*. The drug has a relatively low potency against the asexual blood forms, which practically precludes its use as a blood schizontocide. Therefore, it is incorrect to speak of primaquine resistance, when the normal tissue schizontoidal dose of the drug fails to eliminate the asexual blood forms. Consequently, reports of the occurrence of some primaquine resistance in association with chloroquine resistance (57, 58) need to be interpreted with care. Powell et al. (59) showed that a weekly prophylactic dose of 45 mg of primaquine and 300 mg of chloroquine base was not completely effective against the Colombian strain of *P. falciparum*, and that it failed to produce a suppressive cure in volunteers. Infections caused by a strain of *P. falciparum* acquired at Porto Velho, were not cured by the usual doses of chloroquine combined with the standard 14-day primaquine treatment (60).

There are numerous reports of the failure of primaquine to prevent outbreaks of infection due to chloroquine-resistant Asian strains of *P. falciparum*, especially the Malayan (Camp.) and the Viet Nam CV strain (60–63). Powell & Brewer (64) have demonstrated that primaquine is not completely effective in protecting non-immune volunteers against sporozoite-induced infections with the chloroquine-resistant Thailand (JHK) strain of *P. falciparum*.

**MECHANISM OF ACTION**

The mechanism of action of 8-aminoquinolines has not been fully elucidated and more work is needed in this area (65), but it is thought that their antimalarial activity is attributable to their metabolites.

Greenberg et al. (66) demonstrated that pentaquine and primaquine were inactive against *P. gallinaceum* while their metabolites were effective. Smith (67), on the basis of his studies with radiolabelled pentaqueine in rhesus monkeys, concluded that this drug was metabolized to the 5,6-diquinone derivative. Quinoline-5,6-diquinone exists in an oxidation-reduction equilibrium with the 5,6-dihydroxy derivative. It has been postulated that this product acts as an intermediate in the biological oxidation-reduction systems and disrupts their normal functions. Also, this effect may make the erythrocyte more susceptible to haemolysis and explain the adverse haemolytic side-effects of 8-aminoquinolines (68). The active metabolites of the 8-aminoquinolines are closely related to the naphthaquinone antimalarial drugs, such as meclone. Skelton et al. (69) have shown that ubiquinone-8, which is structurally similar to the naphthaquinones, was synthesized by erythrocytes infected with *P. knowlesi*, *P. cynomolgi*, or *P. berghei*. Moreover, the same workers (70) found various antimalarial drugs, especially meclone, inhibited ubiquinone-linked mitochondrial enzyme systems. Gutteridge & Coombes (71) recently suggested that the basis of the mode of action of naphthaquinones and primaquine is a link between ubiquinone and pyrimidine synthesis. Apparently the enzyme dihydroorotate dehydrogenase, which is important in pyrimidine synthesis, is linked to the oxidation and reduction of ubiquinone. The synthesis of pyrimidine is important for plasmodia and therefore the presence of foreign redox agents that are similar to the naturally occurring ubiquinone could be highly disruptive (72). Dihydroorotate dehydrogenase has been demonstrated in *P. berghei* (73) and *P. knowlesi*, and its activity is 50% inhibited by 2 x 10^8 mol/litre of meclone (72).

Whichard et al. (74) have demonstrated that pentaquine, rhodoquine, pamaquine, and primaquine, all bind to native deoxyribonucleic acid (DNA). This binding inhibits DNA function, and is therefore presumed to contribute to the antimalarial action of these agents. The technique of equilibrium dialysis has been used to show that primaquine, pentaquine, and chloroquine bind extensively to both polydeoxyribo- and polyribonucleotides (75). However, studies on the incorporation of ^32^P-labelled phosphate in DNA or ribonucleic acid (RNA) in *P. gallinaceum* or *P. berghei* have shown inhibition by chloroquine and quinine, but none by pentaquine (76). Both primaquine and pamaquine are poor inhibitors of erythrocyte-free nucleic acid metabolism in *P. berghei* as judged by incorporation of radioactivity from exogenous [^3H]-AMP into DNA and RNA (77). Lantz & Van Dyke (78) have also shown that primaquine and pamaquine inhibit the uptake of tritiated ATP by RNA, in a cell-free preparation of *P. berghei*. They suggest that this may be due either to blockade of the DNA template or to inhibition of RNA polymerase. However, the concentrations required are thought to be too high for these effects to be important in vivo (79).

Primaquine has been shown to decrease incorporation of thymidine into mammalian DNA, and of uridine and adenine into various RNA fractions of rat and mouse livers. However, leucine incorporation into the hepatic proteins in rats or mice was not affected (80). Thus, there appears to be a major difference in the response mechanisms of rodent liver

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^c^ This plasmodium enzyme has not yet been fully characterized, but it seems to resemble dihydroorotate oxidase (EC.1.3.3.1).
and *Tetrahymena pyriformis* (81) to the aminooquinolines. Conklin & Chou (82) found that chloroquine, mepacrine, quinine, and primaquine block amino acid uptake in *Tetrahymena pyriformis*. Working with *P. lophurae*, Sherman & Tangoshi (83) concluded that the inhibitory effects of chloroquine, quinine, and primaquine, on amino acid incorporation were due to their influence on the energetics of the parasites and not to a direct blockade of amino acid uptake.

Whichard et al. (84) showed that 8-aminooquinolines and two hydroxylated derivatives inhibit certain bacterial and DNA polymerases. Also, the presence of DNA-associated histone decreased the binding of 8-aminooquinolines to isolated DNA (85).

These experiments indicate that the 8-aminooquinolines probably affect several RNA functions as well as nucleic acid synthesis, but caution is needed in extrapolating these findings to the biological mechanisms of the intact organism.

Morphological changes have been observed in vivo in the erythrocytic stages of *P. berghei* and *P. falciparum*, following exposure to primaquine and mepacrine (86). It has been shown (87, 88) that primaquine and other 8-aminooquinolines can induce mitochondrial lesions in the exoerythrocytic stage of *P. falciparum* in tissue culture. The presence of [3H]-primaquine (or its metabolite) in the mitochondria of the tissue stages of *P. falciparum* was shown by high resolution autoradiography to coincide with the first observations of mitochondrial swelling (89). Although mitochondrial respiration is thought to be important in the tissue stages of *P. falciparum* and other avian malarial species, the situation in the liver stages of mammalian species is less clear, and it is apparently not important for the erythrocytic stages of mammalian plasmodia (90). However, all three stages are affected by primaquine, especially the exoerythrocytic stages.

Primaquine, chloroquine, quinine, and quinacrine inhibit proteolysis in mouse kidney phagolysosomes. This phenomenon could be used for the screening of drugs that may be potentially useful for the treatment of diseases caused by organisms that possess a lysosome-like digestive system (91).

Primaquine does not influence the folate pathway in plasmodia. Peters (49) demonstrated that the action of primaquine is not influenced by the administration of large doses of 4-aminobenzoic acid.

**MECHANISM OF PRIMAQUINE RESISTANCE**

Howells et al. (86) studied the ultrastructural changes produced by primaquine on the asexual blood stages of *P. berghei* in mice. These workers found that some of the trophozoites that survived for 48 h after exposure to the drug appeared to have an increased number of whirled organelles, which are believed to act as mitochondrial equivalents. They suggest that the parasites overcome the damaging effects of the drug on their mitochondria by synthesizing more of these organelles to compensate for the functional loss. Also, the haemozoin of primaquine-resistant *P. berghei* forms in larger vesicles than normal and appears, even at the light microscope level, as balls of pigment that are larger and darker than those seen in normal drug-sensitive organisms (50). The importance of these observations to the mechanism by which the parasites develop primaquine resistance, is not clear.

**HAEMOLYTIC EFFECTS**

Primaquine and other 8-aminooquinolines have a haemolytic effect on glucose-6-phosphate dehydrogenase (G6PD)-deficient erythrocytes, which are especially sensitive to oxidizing agents. Cohen & Hochstein (92) suggested that the generation of hydrogen peroxide in erythrocytes by the 8-aminooquinolines plays a major role in the induction of haemolysis. They were able to demonstrate the presence of hydrogen peroxide in intact cells after the addition of primaquine, but not after the addition of the 4-aminooquinoline, chloroquine. Similarly, hydrogen peroxide was present after the addition of the hydroquinone-4-quinone reductase system but not after the addition of non-autoxidizable resorcinol. The generation of hydrogen peroxide from 8-aminooquinolines required the presence of oxyhaemoglobin, and could be blocked by the preliminary conversion of oxyhaemoglobin to methaemoglobin.

G6PD-deficient erythrocytes are incapable of sufficiently rapid regeneration of reduced nicotinamide adenine dinucleotide phosphate (NADPH). Consequently all the NADPH-dependent reductive processes in the cell are impaired. Metabolic processes are reduced to such an extent that normal vital functions can no longer proceed and the consequent alterations in the lipoprotein membrane of the cell result in lysis (68, 93).

Changes in the ultrastructure of the erythrocyte membrane and vacuolization have been observed by Ginn et al. (94) in red cells exposed to low concentrations of primaquine. The authors suggest that these changes are related to its haemolytic effects.

On the basis of studies on the haemolytic action of primaquine on normal and G6PD-deficient red cells, Fraser & Vessel (95) produced evidence to suggest that the mechanism of methaemoglobin formation by such compounds may be unrelated to that which damages the red cell membrane.

Methaemoglobinaemia occurs after administration
of high doses of 8-aminoquinolines. Observations made on military personnel in Viet Nam suggested that heterozygotes for NADPH-dependent methaemoglobin reductase are far more common than previously recognized, and that the routine use of primaquine-containing prophylactics will result in an increased incidence of methaemoglobininaemia (96).

Quinacrine greatly enhances the toxicity of 8-aminoquinolines, by increasing their plasma concentration 5–10-fold, and extends their half-life by interfering with their metabolic degradation. Since quinacrine disappears very slowly from the body, this phenomenon is observed if 8-aminoquinolines are given within 3 months of a dose of quinacrine (97).

ANTIBACTERIAL ACTIVITY

Primaquine has weak antibacterial activity against Entamoeba coli, Staphylococcus aureus, Bacillus subtilis, and Candida albicans, and modest activity against Salmonella typhi, and Streptococcus pyogenes. It also shows synergistic effects with most antibiotics (98).

EFFECT ON IMMUNE MECHANISMS

Thong et al. (99) have shown that primaquine inhibits mitogen-induced, human lymphocyte proliferative responses. They used phytohaemagglutinin or pokeweed mitogen to induce a human lymphocyte proliferative response, which was measured by the incorporation of [3H]-thymidine. They concluded that doses of primaquine in the therapeutic range for vivax malaria possessed potent immunosuppressant activity. However, it is not yet known whether patients on primaquine treatment are actually immunosuppressed (100). Direct extrapolation from experimental findings to the clinical situation must be made with care especially since the part of the immune system responsible for producing protective antibodies in malaria is unknown. To label primaquine as an immunosuppressant drug may unnecessarily discourage the use of this valuable antimalarial (101).

CARDIOVASCULAR PHARMACOLOGY

The frequent administration of high doses of pentaquine monophosphate has been shown to cause marked postural hypotension (102). Since the adrenaline responses were unaltered, the hypotension was explained in terms of an impairment of the central sympathetic system. Moe et al. (103) found that large doses of pamaquine, pentaquine, and isopentaquine, when administered over a long period to dogs and monkeys, produced impairment of the sympathetic cardiovascular reflexes, which was believed to be due to the destruction of medullary cell groups.

Fries et al. (104) administered pentaquine to patients suffering from essential or malignant hypertension. The drug produced a significant decrease in blood pressure but the toxic reactions were too frequent and severe for its use as an antihypertensive.

EFFECTS ON THE MYOCARDIUM

Pamaquine and primaquine have been shown to exert quinidine-like effects on the myocardium. These compounds are known to increase the refractory period and conduction time in dogs, and have been shown to be better than quinidine in protecting the heart against auricular fibrillation produced by the application of acetylcholine or aconitine, and against auricular flutter from crush stimulation in anaesthetized dogs. They did not protect against epinephrine-induced arrhythmia (105).

Primaquine has been shown to possess an antiarrhythmic effect in experiments where arterial fibrillation was induced by intravenous injection of acetylcholine into neostigmine-pretreated animals. Primaquine was as active as quinidine, and did not affect the ionic concentrations, or ionic fluxes, of the myocardial tissue (106).

Pamaquine and primaquine inhibited stimulus initiation, atrioventricular conduction, and intraventricular transmission of impulses.

At low concentrations, primaquine produced a transient positive chronotropic and ionotropic effect in isolated guinea-pig heart, which could be attributed to its ability to release adrenaline. Higher concentrations of primaquine produced sustained negative chronotropic and ionotropic effects, which were still preceded by a transient sympathomimetic effect (107).

ANTIMUSCARINIC ACTIVITY

Primaquine has been shown to possess antimuscarinic activity on the guinea-pig bladder, and on gastrointestinal tract motility, as judged by the transport of a charcoal meal. These experiments indicate that primaquine is a competitive antagonist of acetylcholine, and that it acts synergistically with atropine on intestinal musculature in vivo (108).
**EFFET ON CLOTTING MECHANISMS**

The administration of primaquine to cattle infected with *Thuleria sergenti* caused a moderate extension of clotting time, a decrease in platelet adhesiveness, clot retraction, and changes in the thromboelastogram. These changes persisted for 5–10 days after cessation of the treatment (109).

Primaquine has no antipyretic, analgesic, or musculotrophic effect (97). The only published report on the effects of primaquine on the central nervous system is that by Schmidt & Schmidt (110), which deals with its neurotoxicity in rhesus monkeys.

**TOXIC EFFECTS**

Daily administration of an oral dose of 12–24 mg of primaquine/kg of body weight caused sublethal to lethal intoxication in rhesus monkeys. In addition to central nervous system lesions, the animals exhibited cyanosis, anorexia, malaise, weight loss, marked methaemoglobinemia, anaemia, leukopenia, neutropenia, reduction in myeloid elements of bone marrow and, in some cases, a yellow and grossly enlarged liver (110).

The intramuscular administration of 4–6 mg of primaquine/kg of body weight to rabbits produced changes in liver function, including increases in cephalin-cholesterol flocculation, icterus index, and serum levels of aspartate aminotransferase and alanine aminotransferase. Choline dihydrogen citrate was very effective in protecting the liver against primaquine toxicity (111). Intraperitoneal administration of 45 mg of primaquine/kg of body weight increased liver tryptophane oxygenase activity in rats (112).

Rhodoquine (Plasmocid) has been shown to damage cardiac and skeletal muscle. Single doses produced cardiac necrosis, secondary inflammation, and calcification, which were preceded by a disturbance in cardiac glycogen metabolism, and interference with 5'-nucleotidase activity in the capillaries (113).

Price et al. (114) have shown by electron microscopy that rhodoquine produces selective actin filament and Z band degeneration in the muscle fibres of the rat diaphragm. It also produces sequential muscular necrosis, which is closely correlated with serum aminotransferase activity and the presence of large amounts of taurine in the urine (115). Rhodoquine injections (80 mg/kg of body weight) raised serum creatine phosphokinase levels in rabbits, which closely paralleled the occurrence and the degree of morphological degeneration (116, 117).

**RÉSUMÉ**

**PHARMACOLOGIE DES AMINO-8 QUINOLÉINES**

Parmi les amino-8 quinoléines dont l'activité comme schizontocides tissulaires a été éprouvée cliniquement, la primaquine reste le meilleur composé. Elle est formée de parties égales des formes (+) et (−) du fait de la présence d'un atome de carbone asymétrique. L'activité de ces stéréoisomères contre *P. cynomolgi* chez le singe est identique, mais la toxicité de la (−)-primaquine est trois à cinq fois supérieure à celle de la (+)-primaquine, si l'on en juge par ses effets hépatotoxiques. Ces différences pourraient être importantes si elles se confirmaient chez l'homme. Si la (−)-primaquine était réellement moins toxique chez l'homme, on pourrait augmenter encore son indice thérapeutique en la liant à des peptides.

On postule que la primaquine agit par l'intermédiaire de son métabolite diquinone-5,6, qui est en équilibre d'oxydoréduction avec le dérivé dihydroxy-5,6, mais il se peut que les effets toxiques et les effets sur le plasmodium soient produits par des composés différents; à l'heure actuelle, les résultats semblent favoriser l'hypothèse d'une action des produits métaboliques dans les deux cas. Les métabolites agissent comme intermédiaires dans les systèmes biologiques d'oxydoréduction, qu'ils rompent. Ils ressemblent à l'ubiquinone-8 naturelle et inhibent les systèmes mitochondriques liés à cette substance. On a proposé comme base du mode d'action de la primaquine une liaison entre l'ubiquinone et la synthèse de la pyrimidine. La primaquine se lie à l'ADN isolé et on présume que l'inhibition de la fonction ADN qui s'ensuit est liée au moins en partie à l'effet antipaludique. La primaquine induit des lésions mitochondriales dans les stades exérythrocytaires de *P. falciparum* en culture tissulaire, et la présence de primaquine triétiée ou de ses métabolites a été démontrée par autoradiographie à haute résolution simultanément à l'observation d'un gonflement des mitochondries.

La primaquine produit des effets hémolytiques sur les érythrocytes carencés en G6PD, particulièrement sensibles aux oxydants. Ces érythrocytes sont incapables de régénérer suffisamment vite leur NADPH du fait de leur déficit en G6PD.

A dose modérée et forte, la primaquine provoque une méthémoglobinémie, qui se manifeste par de la cyanose chez les sujets présentant une baisse de l'activité de la NADPH méthémoglobin réductase.

La méparacrine augmente considérablement la toxicité des amino-8 quinoléines, et cet effet peut persister pendant trois mois.
Il a été démontré que la primaquine inhibe la réponse lymphocyttaire induite par des mitogènes chez l'homme, mais les conséquences de cette observation pour l'emploi clinique ne sont pas encore claires.

La primaquine et les autres amino-8 quinoléines ont des effets hypotenseurs chez l'animal. La primaquine a une activité évoquant celle de la quinidine et augmente la période réfractaire et le temps de conduction dans le cœur du chien. Elle possède une activité analogue à celle de l'atropine. Il est nécessaire d'obtenir des données sur les effets de la primaquine sur le système nerveux central et le système cardiovasculaire au moyen de techniques modernes sophistiquées de pharmacologie clinique.

REFERENCES

1. MühlenS, P. Naturwissenschaften, 14: 1162 (1926).
PHARMACOLOGY OF 8-AMINOQUINOLINES