ROLE & FUTURE ASPECTS OF PRIMAQUINE IN MALARIA THERAPY

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ABSTRACT

Malaria is major problem in malaria prone zone. This review gives a detail idea about primaquine role and it’s significance in malaria therapy. Nanomedicine drug-delivery systems of primaquine may be developed in the effort to overcome delivery barriers and short half life. Some research articles have shown that primaquine derivatives show better results in comparison to primaquine. In relapsing malaria treatment primaquine 30 mg daily dose is necessary. To overcome this problem transdermal drug delivery system of primaquine may be good choice. Transdermal drug delivery system can minimize side effects like abdominal pain, which produced by orally taken primaquine. In this review, the attention is focused to give a basic idea about primaquine role and its future consideration.

KEYWORDS: Malaria, Primaquine, Prophylaxis, Nanomedicine, Transdermal, Radical Cure.

1. INTRODUCTION

Malaria is a common and life-threatening disease in many tropical and subtropical areas.[¹] Around the world, the malaria situation is serious and getting worse. Malaria threatens the lives of 40% of the world’s population – over 2200 million people. Each year, there are an estimated 300-500 million clinical cases. Malaria is estimated to kill more than 1 million people annually, the majority of whom are young children.[²] This death toll exceeds the mortality rate from AIDS (acquired immunodeficiency syndrome). Efforts to control malaria have included attempts in the development of effective vaccine, eradication of mosquito
 vectors, and development of new drug.\cite{3} World Health Organization (WHO) recommends use of the drug primaquine, in conjunction with an artemisinin-based combination therapy (ACT), to block Plasmodium falciparum transmission in areas approaching malaria elimination and/or facing artemisinin resistance.\cite{4} Malaria parasites have demonstrated some level of resistance to almost every antimalarial drug available.\cite{3} Primaquine is an old drug that has been on the market for over 60 years.\cite{5} Primaquine (PQ) is one of the most widely used antimalarial drugs and is the only available drug to date for combating the relapsing form of malaria, especially in the case of Plasmodium vivax and P. ovale.\cite{6} Although its Mechanism of action (Primaquine): is not well understood. It may be acting by generating reactive oxygen species or by interfering with the electron transport in the parasite.\cite{7} It is thought to interfere with the cellular respiration of the parasite by generating oxygen free radicals and deregulating the electron transport.\cite{8} PQ is a tissue schizonticide 8-aminoquinoline group of drug that destroys exoerythrocytes and hypnozoites in the liver, thus preventing relapse and recrudescence.\cite{9} However, the drug has serious side effects including nausea, vomiting, stomach cramps, and hemolytic anemia.\cite{10} This prohibits its use in key groups, such as pregnant women.\cite{11} The PQ dose-limiting side effects including acute hemolytic anemia in individuals with glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency), methemoglobinemia, leukocytopenia, leukocytosis, gastrointestinal disturbances, and abdominal cramps are partly due to the nonspecific targeting and short half-life that necessitates frequent dosing.\cite{12} For instance, for P. vivax, the dosage is 30 mg daily for 14 days, while for P. ovale, the dosage is 15 mg daily for 14 days.\cite{6} The drug is also a casual prophylactic, especially for travelers to endemic areas \cite{13}, but the dose frequency is also relatively frequent as the dosage involves 30 mg once daily, starting the day before travel and continues up to 7 days after returning. PQ oral bioavailability is also limited due to pre-systemic metabolism and excretion.\cite{14} Primaquine is the only licensed antimalarial that kills mature P. falciparum gametocytes, but safety concerns in individuals with glucose-6-phosphate dehydrogenase deficiency (G6PDd) have deterred its use to interrupt transmission on a large scale.\cite{15,16,17}

2. METHODS

A literature search was conducted for all studies using keywords malaria and primaquine and other possible combinations. Search was performed using different databases such as PubMed, Hinari, Elsevier and Research Gate etc. Epidemiological data extracted from WHO reports of last three years and UNICEF reports. All articles were studied in English language.
3. Primaquine dose and contraindications

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Dosage regimen</th>
<th>Use in special groups</th>
<th>Main contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primaquine</td>
<td>0.25mg base/kg with food once daily for 14 days. In Oceania and south-east Asia the dose should be 0.5 mg base/kg</td>
<td>Contraindicated</td>
<td>G6PD deficiency; active rheumatoid arthritis; lupus erythematosus; conditions that predispose to granulocytopenia; concomitant use of drugs that may induce haematological disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast-feeding</td>
<td>Contraindicated&lt;1 Yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children</td>
<td></td>
</tr>
</tbody>
</table>

Use of primaquine for treatment of malaria.\[^5\]

4. Future aspects with primaquine

a. Development of Nanomedicine system

Nanomedicine drug-delivery systems present the ability to enhance the therapeutic properties of current antimalarial. Nanomedicine drug-delivery systems including liposomes, dendrimers, lipids, pheroids, solid lipid nanoparticles (SLNs), polymeric nanoparticles, and nanocapsules have been developed in the effort to overcome delivery barriers.\[^18\] PQ-SLNs were successfully formed by Wesley Nyaigoti Omwoyo \textit{et al.} Efficacy evaluation in mice showed that the nanoformulated PQ was 20% more effective as compared with the conventional oral dose.\[^19\] Nanoparticle drug delivery systems using microemulsion have the potential to improve drug therapeutic properties and enhance bioavailability by improving solubility of the drugs.\[^20\] Entrapping drug compounds in microemulsion could lead to a reduction in the toxicity effect of the therapeutic doses administered to patients.\[^21\]

b. Development of transdermal drug delivery system

PQ has an extremely unpleasant bitter taste. It has been reported that PQ depolarize taste cells by closing K+ channels and produce bitterness.\[^22\] Palatable formulation development is one of the most difficult tasks, although various taste masking techniques such as the addition of sweeteners and flavors \[^23\], coating with polymers,\[^24\] adsorption to ion-exchange resin \[^{25,26}\], and chemical modifications such as the use of insoluble prodrugs have been reported.\[^{27,28}\] Each technique has its own disadvantages. Reduction of bad tastes by beta-cyclodextrin (CD) is a long known method.\[^{29,30}\]
The transdermal route of administration of a very active anti malarial drug whose use is limited by its toxicological effects.\textsuperscript{[31]} TTS (Transdermal therapeutic system) or skin patch is used for the delivery of a controlled dose of a drug through the skin over a period of time.\textsuperscript{[32,33]} P. Mayorga et Al. have proven that the activity of PQ on asexual blood forms of two rodent malaria parasites (P. v. petteri and P. y. nigeriensis) was evaluated following a single TTS patch application. Sustained plasma concentration values were observed for about 60 hours.\textsuperscript{[34]} Therefore, the use of transdermal drug delivery system, can reduce the side effects associated with oral administration of the drug.\textsuperscript{[35]}

c. Other opportunities with primaquine in malaria therapy

Notwithstanding that the situation is very serious; some positive aspects can be identified in malaria control over recent years.\textsuperscript{[36,37,38]} Several peptide and amino acid derivatives of primaquine and other 8-aminoquinoline antimalarials have been synthesized to reduce the metabolic oxidative deamination pathway, as well as to reduce toxicity of the parent drug.\textsuperscript{[39,40,41,42]} To improve the therapeutic efficacy of the drug and diminish its toxicity, various approaches have been examined. These include linking the drug to a carrier protein such as albumin,\textsuperscript{[43]} linking peptide derivatives of the drug onto biodegradable polyacryl starch microspheres,\textsuperscript{[44]} and encapsulation in polycyanoacrylate and polylactide nanoparticles.\textsuperscript{[45,46]} in erythrocytes\textsuperscript{[47]} and in liposomes.\textsuperscript{[48,49]} One approach to enhance the enzymatic stability of amino acid or peptide derivatives of primaquine toward proteolytic degradation at the mucosal absorption barrier or in the blood is the development of a double prodrug.\textsuperscript{[50]} To this end, imidazolidin- 4-one formation was introduced as a useful prodrug approach to protect the $N$ terminal amino acid residue of di- to pentapeptides against aminopeptidase catalyzed hydrolysis.\textsuperscript{[51,52,53,54]}

5. CONCLUSION

Malaria situation is very serious in throughout the world. To minimize this problem drug derivatives and new drug delivery system should be developed by researchers. Primaquine is well known and well tolerated antimalarial drug. Primaquine is only licensed drug for relapsing malaria. It is widely used in almost all type of malaria except patient having G6PD deficiency. Primaquine is used as chemoprophylaxis agent, particularly for traveler’s malaria. Novel formulation of primaquine can be prepared for travelers to reduce frequent/daily doses, due to short half life. Nanomedicine drug-delivery systems can reduce frequency of dose and
enhance the therapeutic properties of current antimalarial drugs. Primaquine derivative may show better results in comparison to primaquine.

Transdermal preparation of primaquine; alone and along with other drug can be prepared in future to overcome re-occurrence of malaria in malaria prone zone. It may be better opportunity in malaria therapy.

REFERENCE


