The Effect of Chemoprophylaxis on Late-Onset Vivax Malaria

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The Effect of Chemoprophylaxis on Late-Onset Vivax Malaria

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ABSTRACT

**Background:** The Republic of Korea (ROK) military initiated antimalarial chemoprophylaxis with hydroxychloroquine sulfate (310mg base once weekly) and 14-days primaquine (15mg base once daily) prophylaxis in 1997 to combat the rapid resurgence of malaria along the DMZ and to reduce the potential spread of malaria throughout the Korea. The increase of annual use of antimalarial chemoprophylaxis may have contributed to the stabilization of malaria in 2000, and its decline through 2004. However, doubts have been expressed about the effectiveness of chemoprophylaxis because late-onset cases of malaria are frequently reported in the soldiers who are regularly treated with chloroquine and primaquine.

**Objective:** To investigate the epidemiologic characteristics of re-emergent vivax malaria and the effects of the chemoprophylaxis on latency of vivax malaria.

**Method:** All soldiers and veterans who entered military service in non malaria risk period between Oct 1, 1998 and Feb 1, 2001 and were exposed to malaria risk for the first time between 1999 and 2001 were followed-up for 32 months after the first
malaria risk exposure in the military service. Soldiers assigned to malaria risk areas experienced two consecutive malaria risk period and received antimalarial chemoprophylaxis both times during the 26-month mandatory military duty. Among these subjects, all microscopically confirmed 1,158 cases of malaria were included.

**Results:** Of the 1,158 cases, 731 were soldiers and 427 veterans. Ninety hundred sixty three cases occurred after second chemoprophylaxis was started. Of these cases, 353 of 598 cases (59%) in the chemoprophylaxis group are considered late-onset. In the no-chemoprophylaxis group only 80 of 365 cases (21.9%) were late-onset (p<0.001). Of the late-onset cases in the chemoprophylaxis group, 218 of 353 (61.9%) cases had taken both chloroquine and primaquine regularly. The median latency period was not affected by chemoprophylaxis both in early and late-onset cases.

**Conclusions:** Large proportion of re-emergent vivax malaria in no-chemoprophylaxis group has short latency period. Chloroquine prophylaxis increases late-onset vivax malaria due to a delay of symptom onset. In particular, primaquine was found to be inadequate against late-onset vivax malaria in ROK. Further investigations on malaria
prevention strategies are needed to ensure the control of late-onset vivax malaria, because of the inadequacies of current chemoprophylaxis.

Keywords: *Plasmodium vivax*, malaria, chemoprophylaxis
1. Introduction

Background

Plasmodium vivax, the causative agent of vivax malaria, was endemic for centuries through the 1970’s in the Republic of Korea (ROK). Beginning in the 1960’s, the number of endemic malaria cases has declined due in part, to increased socio-economic development, increased use of agricultural pesticide, and efforts of the National Malaria Eradication Service (NMES). These conditions contributed greatly to the eradication of endemic malaria that resulted in WHO declaring the ROK malaria free in 1979.¹

However, in 1993 one case attributed to autochthonous transmission was detected in Paju-gun, Gyeonggi Province near the Demilitarized Zone (DMZ), that separate the ROK (South Korea) and the Democratic People’s Republic of Korea (North Korea).² Since 1993, malaria cases increased exponentially, particularly among soldiers and veterans based near the DMZ. The civilian cases similarly occurred among residents in malaria risk areas within a distance of 10-20km from the
DMZ in Gyeonggi and in Gangwon Provinces. During 2000, over 4,000 cases were microscopically confirmed in ROK military, veterans and civilians. The number of malaria cases reported annually from counties bordering Seoul, approximately 40km south of the DMZ, is increased through 2000. 3,4 However, incidence rate of vivax malaria decreased annually in same malaria risk areas where chemoprophylaxis was initiated.

The re-emergence of malaria in ROK is a typical example of border malaria. However, unlike the border malaria reported by other countries, it is not attributed to human immigration, but to the migration of infected mosquitoes from North Korea. 5,6 Because people are not allowed to travel between North and South Korea, the only possible cause for the re-emergence of vivax malaria is sporozoite-infected mosquitoes traveling from North to South Korea across the DMZ. Although several reasons have been offered to explain this malarial re-emergence, it is now agreed that it occurs via this route. 4,7,8 However, malaria is currently endemic with local mosquitoes becoming infected and transmitting malaria in the ROK.

Healthy males over 18 years regularly enter the 26-month mandatory military
duty in the ROK. The majority of young soldiers are stationed in defined areas near
the DMZ during their entire period of duty. Soldiers stationed in risk areas are
exposed to two transmission seasons from May to September.

As part of the malaria prevention program, the ROK military adopted several
methods; chemoprophylaxis, the treatment of the battle dress uniforms (BDUs) with
permethrin, and the application of insect repellent to exposed skin surfaces and
mosquito vector control agents. In 1997, the military initiated antimalarial
chemoprophylaxis and the number of soldiers given chemoprophylaxis increased
annually through 2004 with >165,000 ROK soldiers currently on chemoprophylaxis.

A Korean vivax strain has been shown to be 100% cured by the chloroquine-
primaquine regimen,\(^9\) compared with this only a 70% cure rate against the Chesson
strain.\(^{10}\) While most strains of vivax malaria are sensitive to chloroquine recently,
there have been some doubts about the effectiveness of chemoprophylaxis due to an
increase in late-onset cases in soldiers who have previously received chloroquine and
primaquine regularly during a previous malaria risk period. It is needed to evaluate
the effect of chemoprophylaxis on vivax malaria in the ROK.
Purpose

In this study, we investigated the epidemiologic characteristics of re-emergent vivax malaria and the effect of chemoprophylaxis on latency of vivax malaria in the Republic of Korea.
2. METHODS

Chemoprophylaxis

The ROK military initiated antimalarial chemoprophylaxis in 1997 and the number of soldiers that receive chemoprophylaxis has continuously increased. In addition to chemoprophylaxis, insecticide-treated battle dress uniforms (BDUs) have been used since 1998 and the amount of insecticide was increased in 2003. About 200,000 soldiers wore insecticide-treated BDUs during the malaria risk period (Table 1).

Soldiers stationed in DMZ, a high-risk malaria area, were given both chloroquine and primaquine while in the DMZ. Chemoprophylaxis with hydroxychloroquine sulfate (310mg base once weekly) was started in the early summer and continued throughout the transmission season, and 14-days primaquine prophylaxis (15mg base once daily) was started on the first day of the last week of the chloroquine administration. Soldiers assigned to malaria risk areas experienced two consecutive malaria risk period and received antimalarial chemoprophylaxis both
times during the 26-month mandatory military duty. All soldiers assigned to malaria risk areas retiring during the malaria risk period received 4 weeks of chloroquine and 14-days of primaquine prophylaxis prior to retirement.

To increase compliance of chemoprophylaxis, all soldiers took antimalarial drug at the same time under direct supervision of military commanders or staff and signed drug administration checklist.
Table 1. Annual number of soldiers who received chemoprophylaxis and repellent in the ROK army

<table>
<thead>
<tr>
<th></th>
<th>'99</th>
<th>'00</th>
<th>'01</th>
<th>'02</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemoprophylaxis*</td>
<td>61,772</td>
<td>90,000</td>
<td>109,476</td>
<td>141,780</td>
</tr>
<tr>
<td>Duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloroquine</td>
<td>June 7</td>
<td>June 5</td>
<td>May 14</td>
<td>May 13</td>
</tr>
<tr>
<td></td>
<td>~</td>
<td>~</td>
<td>~</td>
<td>~</td>
</tr>
<tr>
<td></td>
<td>Oct 11</td>
<td>Oct 9</td>
<td>Sep 24</td>
<td>Sep 23</td>
</tr>
<tr>
<td></td>
<td>Oct 12</td>
<td>Oct 3</td>
<td>Sep 18</td>
<td>Sep 17</td>
</tr>
<tr>
<td>primaquine</td>
<td>~</td>
<td>~</td>
<td>~</td>
<td>~</td>
</tr>
<tr>
<td></td>
<td>Oct 25</td>
<td>Oct 16</td>
<td>Oct 1</td>
<td>Sep 30</td>
</tr>
<tr>
<td>Insecticide (permethrin)*</td>
<td>80,000</td>
<td>80,000</td>
<td>150,692</td>
<td>157,361</td>
</tr>
</tbody>
</table>

* Insecticide: used for the battle dress uniforms (BDUs) and bed nets.

Malaria surveillance

In the ROK, all cases of malaria among military personnel must be reported to the Armed Forces Medical Command (AFMC) and cases among veterans and civilians must be reported to the Korea Center of Disease Control and Prevention (KCDC). Malaria cases among veterans are defined as those experiencing a malaria attack.
within 24 months of retirement from military service, if the attack occurs beyond this period they are reported as civilian cases.

All soldiers and veterans who were diagnosed as malaria were interviewed by physicians or trained public health specialists. Soldiers diagnosed as malaria were admitted to the military hospital for treatment and were interviewed by physicians in military hospital, while veterans were treated in outpatient clinic of community health center and interviewed by trained public health specialists.

Epidemiologic characteristics, such as age, duty station, history of travel, previous malaria attacks, history of chemoprophylaxis, etc., were collected using structured questionnaire. Chemoprophylaxis histories were allocated to three categories (complete, incomplete, and none). The complete group was composed of cases that had taken both chloroquine and primaquine regularly.

**Study Subjects**

All soldiers and veterans who entered the ROK army in non malaria risk period between Oct 1, 1998 and Feb 28, 2001 and exposed to malaria risk for the first
time in military service between 1999 and 2001 were followed-up for 32 months after the first malaria risk exposure in the military service. The malaria risk period was defined to be from May 1 to September 30. However, soldiers who entered military service between March and April were excluded because they would retire during a malaria risk period and we could not distinguish between early and late-onset of vivax malaria. Thus, subjects who experienced malaria risk for the first time between 1999 and 2001 were those who entered military service between Oct 1, 1998 and Feb 28, 1999; Oct 1, 1999 and Feb 28, 2000; and between Oct 1, 2000 and Feb 29, 2001.

A total of 1,215 vivax malaria cases were reported during the study period. Of these 1,215 cases, 56 cases had been stationed or traveled in malaria risk areas after retirement and one was infected in Africa. Thus, 1,158 cases were included in this study.

To ascertain chemoprophylaxis history and infected areas, data from the interview was compared with military service records, drug supply records, and drug administration records during the enlisted period. For readmitted or retreated cases, data collected at first presentation of disease was used.
Statistical Analysis

Chemoprophylaxis history was categorized into two groups (“Yes” and “No”) in the analysis. Early-onset was defined as cases occurring within 3 months of the last day of the malaria risk period (Sept 30), and late-onset cases as those with an onset >3 months from the last day of the malaria risk period.

To investigate the latency of vivax malaria, all cases were divided into two groups (‘before’ and ‘after’ second chemoprophylaxis started) according to the onset of symptoms. The latency period was defined as the period from the first day of exposure to malaria risk (May 1) to the first day of a symptom onset because we could not know the exact time of malaria exposure. Thus, our estimation is a maximum latency period.

Statistical analyses were performed using the $\chi^2$ test and Wilcoxon rank sum test, the later of which was used to analyze latency period differences.
3. RESULTS

A total of 1,158 cases of vivax malaria were reviewed. Of these 1,158 cases, 731 cases (63.1\%) were soldiers and 427 (36.9\%) were veterans. All cases among soldiers and veterans were infected in malaria risk areas and in non-malaria risk areas there has not been reported cases during study periods. Year of the symptom onset according to each exposure cohort is shown in Table 2.

Most malaria cases were concentrated in the summer season of 2\textsuperscript{nd} and 3\textsuperscript{rd} year of follow up with a peak in July and only 11 cases occurred in winter season (Dec 1\textsuperscript{st} to Feb 28) (Figure 1).
Table 2. Malaria cases among each exposure cohort in the ROK Army

<table>
<thead>
<tr>
<th>First exposure year</th>
<th>N. of patients</th>
<th>Onset of symptoms*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1st year†</td>
</tr>
<tr>
<td>1999</td>
<td>591</td>
<td>28</td>
</tr>
<tr>
<td>2000</td>
<td>369</td>
<td>30</td>
</tr>
<tr>
<td>2001</td>
<td>198</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>1,158</td>
<td>68</td>
</tr>
</tbody>
</table>

* In first and second year of follow up all cases exposed to malaria risk but in third year of follow up all cases did not exposed to malaria risk.
† Cases occurred in the first exposure year

Figure 1. Monthly distribution of vivax malaria (three years pooled data)
Of the 1,158 cases, 195 cases occurred before the second chemoprophylaxis started and 963 cases occurred after second chemoprophylaxis started.

Among the 963 cases that occurred after the second chemoprophylaxis was started, 598 cases received second chemoprophylaxis. Of these 598 cases, 353 (59.0%) were late-onset cases and 218 of 353 cases (61.9%) completely finished the chloroquine and primaquine courses, while of 365 cases that did not receive second chemoprophylaxis, only 80 (21.9%) cases were of late-onset (Table 3). The proportion of late-onset cases that received second chemoprophylaxis was higher than that of the late-onset cases that did not, regardless of first chemoprophylaxis history (p<0.001).

In cases occurred before the second chemoprophylaxis started, the proportion of late-onset cases were 66.0% in the chemoprophylaxis group and 14.8% in the no-chemoprophylaxis group.

A stratification of cases by the history of chemoprophylaxis revealed different times to onset (Figure 2).
Table 3. Malaria cases that occurred before and after second chemoprophylaxis started

<table>
<thead>
<tr>
<th>1&lt;sup&gt;st&lt;/sup&gt; chemo</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; chemo</th>
<th>N. of Patients</th>
<th>Latency period</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Early (≤ 3 month)</td>
<td>Late (≥ 3 month)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(&lt; 3 month)</td>
<td>(≥ 3 month)</td>
</tr>
<tr>
<td>Before*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>-</td>
<td>47 (100)</td>
<td>16 (34.0)</td>
<td>31 (66.0)</td>
</tr>
<tr>
<td>No</td>
<td>-</td>
<td>61 (100)</td>
<td>52 (85.2)</td>
<td>9 (14.8)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>108 (100)</td>
<td>68 (63.0)</td>
<td>40 (37.0)</td>
</tr>
<tr>
<td>After</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>443 (100)</td>
<td>221 (49.9)</td>
<td>222 (50.1)</td>
</tr>
<tr>
<td>No</td>
<td>113 (100)</td>
<td>113 (100.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>556 (100)</td>
<td>334 (60.1)</td>
<td>222 (39.9)</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>155 (100)</td>
<td>24 (15.5)</td>
<td>131 (84.5)</td>
</tr>
<tr>
<td>No</td>
<td>252 (100)</td>
<td>172 (68.3)</td>
<td>80 (31.7)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>407 (100)</td>
<td>196 (48.2)</td>
<td>211 (51.8)</td>
</tr>
</tbody>
</table>

* Eight seven late-onset cases (76 cases in chemoprophylaxis group and 11 cases in no-chemoprophylaxis group) that occurred between May and June were excluded.
a) Before the start of 2\textsuperscript{nd} chemoprophylaxis

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure_a.png}
\caption{Cumulative percentage of malaria cases that occurred before the start of the 2\textsuperscript{nd} chemoprophylaxis.}
\end{figure}

b) After the start of 2\textsuperscript{nd} chemoprophylaxis

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure_b.png}
\caption{Cumulative percentage of malaria cases that occurred after the start of the 2\textsuperscript{nd} chemoprophylaxis.}
\end{figure}

Figure 2. Cumulative percentage of malaria cases that occurred before and after the start of the 2\textsuperscript{nd} chemoprophylaxis

* In figure a) the history of 1\textsuperscript{st} chemoprophylaxis was used and 87 late-onset cases that occurred between May and June were excluded, in figure b) the history of 2\textsuperscript{nd} chemoprophylaxis was used.
The median latency period of the early-onset cases that occurred before the second chemoprophylaxis started was 115 days in the no-chemoprophylaxis group and 134 days in the chemoprophylaxis group, but this difference between the two groups was not statistically significant (p=0.19). In late-onset cases that occurred after the second chemoprophylaxis started, the difference between the median latency periods of the two groups was not statistically significant (p=0.97, 445 days in chemoprophylaxis group and 442 days in the no-chemoprophylaxis group).
4. DISCUSSION

In the ROK, a total of 19,551 malaria cases were reported from 1993 through 2003. Of these, 62.7% (12,557) were reported among soldiers and veterans and 37.3% (7,294) among civilians, and most of the cases were attributed to exposure of malaria risk near the DMZ. Since 1993, the incidence of malaria rose sharply and stabilized in 1998~2000 (4,142 cases in 2000).\(^{11}\)

Due to the malaria prevention program adopted by the Korean military, malaria cases among soldiers have reduced markedly compared with civilian populations, even though soldiers have a greater exposure to potentially infected mosquitoes than civilians, since 1) they are assigned to malaria high risk areas, and 2) they have greater exposure to mosquitoes while conducting military operations (i.e., patrol, field training, and exercise). In 2003, only 282 of the reported 1,170 (24.1%) cases were soldiers as compared to 1996, when soldiers accounted for >80% of the cases.\(^{11}\)
It is well known that the liver stages of *P. vivax* can develop promptly, and that the disease can remain latent as the hypnozoite form in the liver before emerging months to years later. Blood-stage schizonticides, such as, chloroquine, mefloquine, and doxycycline, do not eliminate hypnozoite forms in liver and do not prevent either relapses or late-onset vivax malaria.\textsuperscript{12-14} Primaquine is currently the only available drug that can eliminate hypnozoites, an important latent reservoir of infection, though other drugs, such as tafenoquine, malarone, etc., are tested.\textsuperscript{14-16} However, the effectiveness of primaquine has not been assessed adequately because of difficulties associated with observed compliance and follow-up. Moreover, the use of primaquine for terminal prophylaxis or for radical cure of relapsing malaria is limited, because of the risk of hemolysis and methemoglobinemia in persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency and NADH methemoglobin reductase deficiency.

There are two different clinical types of vivax malaria, which are defined according to incubation and relapse patterns – the tropical type and the temperate type.\textsuperscript{12} The tropical type is characterized by a short latency period before frequent relapses, whereas the temperate type exhibits a long latency period of >6 months.
Previous studies performed between 1950s and 1970s have demonstrated that >75% of Korean vivax malaria has a long latency of 10 months, which is characteristic of vivax malaria in temperate regions.\textsuperscript{17,18} Recent study also suggested that two-thirds of malaria cases experienced long latency with a mean duration of 10 months, but late-onset cases might have been overrepresented because they only included veterans and soldiers who develop malaria during military service were not included.\textsuperscript{19}

In this study, vivax malaria occurred throughout the year, increased in May, and showed a peak in July, and it was also observed in veterans that were not exposed to malaria risk after retirement. These findings suggest that vivax malaria in Korea has both short and long latencies.

However, in contrast to previous studies, large proportion of vivax malaria cases in no-chemoprophylaxis group has short latency period (early-onset). This result suggests that re-emergent vivax malaria has different epidemiologic characteristics compared to the vivax malaria in 1950s–1970s and showed similar characteristics of vivax malaria in tropical areas. Although genetic evidences suggest
that the origin of the re-emerged malarial strain is China or North Korea which was previously endemic in the ROK,\textsuperscript{20,21} it is possible that the genetic variations due to the host change, chemoprophylaxis, and adapt to the climatic change, etc., might occur in re-emergent \textit{P. vivax}. Recent study demonstrated that the MSP gene nucleotide sequence of re-emergent \textit{P. vivax} in Korea was similar to that of Thai isolates.\textsuperscript{22}

Late-onset cases were significantly increased in the chemoprophylaxis group compared to the no-chemoprophylaxis group. We propose two reasons for the observed increase in late-onset cases among those who received chemoprophylaxis. First, symptom onset is delayed in patients receiving chloroquine prophylaxis, because of its schizonticidal activity against blood stage parasites. This finding concurs with the results of other recently published studies.\textsuperscript{13,23} However, in contrast to previous study, the latency period was not affected by chemoprophylaxis both in early and late-onset cases.\textsuperscript{23}

These results suggest that delayed symptom onset cases due to chloroquine did not occur immediately after chloroquine prophylaxis finished and were converted into late-onset.
Second, the effects of primaquine prophylaxis on late-onset vivax malaria appear to be limited. In this study, 61.9% of late-onset cases had taken both chloroquine and primaquine regularly. This suggests that primaquine prophylaxis does not effectively reduce late-onset cases. A recent study conducted in Korea also showed that the effectiveness of primaquine prophylaxis against late primary attacks of *P. vivax* is only 32%.\textsuperscript{24} Factors like inadequate drug dosage and absorption, altered drug metabolism, unreported missed doses, and variabilities in *P. vivax* strain sensitivity could explain this ineffectiveness of primaquine. Moreover, in view of the fact that the primaquine dosage used in this study would be considered inadequate in other countries,\textsuperscript{14,25-28} it is strongly suggested that our findings may be related to inadequate primaquine dosage.

Previous studies have experienced difficulties demonstrating the effects of chemoprophylaxis on vivax malaria latency, because their subjects were travelers, and cases that occurred during travel were not included; thus study results were probably affected by travel duration, the strain of *P. vivax* (temperate type vs. tropical type), and the duration of chemoprophylaxis.\textsuperscript{13,23} However, in the present study, all
cases that occurred during the chemoprophylaxis period or the malaria risk period in Korea were included and received the same chemoprophylaxis. Moreover, the *P. vivax* strain was probably the same because imported cases were excluded.

However, this study has several limitations. First, a misclassification bias might have occurred for the following reasons; 1) among the cases with an onset before the second chemoprophylaxis started, those that occurred before first chemoprophylaxis started were allocated to the no-chemoprophylaxis group. 2) Cases that occurred during second chemoprophylaxis period were categorized as early-onset cases although both early and late-onset cases occurred concurrently. However, because only two cases occurred before first chemoprophylaxis started, the misclassification effect is likely to be small and in view of the finding that among cases presenting before the second chemoprophylaxis period, late-onset cases were more prevalent in the chemoprophylaxis group than in the no-chemoprophylaxis group, it would appear that our results are not overly affected by a misclassification bias.
Second, the number of late-onset cases may have been over-counted. Because it is possible gametocyte-bearing persons may lead to reintroduction in mosquitoes outside the malaria risk area, all late-onset vivax malaria cases cannot be attributed to exposure to infective mosquitoes within malaria risk areas. But among soldiers who stationed in non-malaria risk areas during entire period of military duty, none of the vivax malaria cases were reported during study period. The number of civilian cases occurred in non-malaria risk areas were very small (23 of 609 cases in 2003) and almost all cases had a travel history in malaria risk areas.\textsuperscript{11} Thus, the number of secondary or tertiary transmitted cases among veterans is likely to be small, and thus should not affect the study results.

In the ROK, the number of malaria cases has been markedly reduced and reported cases are limited to the DMZ region. However, after retiring, soldiers stationed in malaria risk areas travel to and reside in areas with little or no malaria. Therefore, soldiers may have a direct impact on the spread of malaria, and thus it is vital that the number of late-onset cases be reduced to achieve effective malaria control.
Although several limitations exist, our study demonstrates that chloroquine prophylaxis increases late-onset vivax malaria, and indicates that chloroquine should not be used as single prophylactic agent and that drugs targeting the liver stage of vivax malaria must be added to chloroquine prophylaxis. However, in Korea, even primaquine does not effectively reduce the number of late-onset cases.

Further investigations on malaria prevention strategies are needed to ensure the control of late-onset vivax malaria and to prevent the resistance or tolerance to antimalarial drugs, though no report on treatment failure has been issued in the ROK.
5. CONCLUSION

Our study demonstrates that re-emergent vivax malaria in the ROK has different epidemiologic characteristics compared to previously endemic vivax malaria and chloroquine prophylaxis increases late-onset vivax malaria. Chloroquine should not be used as single prophylactic agent and that drugs targeting the liver stage of vivax malaria must be added to chloroquine prophylaxis.
6. REFERENCES


20. Kho WG, Park YH, Chung JY, Kim JP, Hong ST, Lee WJ, Kim TS, Lee JS. Two new genotypes of *Plasmodium vivax* circumsporozoite protein found in the


화학적 예방요법이 장기 잠복 삼일열 말라리아에 미치는 영향

배경: 우리나라에서는 1993년 말라리아 환자가 최초로 발생한 이후, 비무장지대에 인하여 급격히 증가하는 말라리아 환자의 발생을 감소시키고, 비위험지역으로의 말라리아 전파를 차단하기 위해 1997년부터 클로르퀸(400mg, 매주 1회)과 프리마퀸(15mg/일, 14일간)을 이용한 화학적 예방요법을 시작하였다. 화학적 예방요법으로 인하여 2000년을 경점으로 말라리아 환자의 발생은 지속적으로 감소하는 경향을 보이고 있다. 그러나, 최근 예방약을 완전하게 복용하고 전역한 장병들에서 장기 잠복환자가 지속적으로 발생하는 것으로 보고되어 화학적 예방요법의 효과에 대한 평가가 필요한 것으로 생각된다.

목적: 재발생 말라리아의 역학적 특성을 파악하고, 화학적 예방요법과 삼일열 말라리아의 잠복기간의 관련성을 분석하고자 하였다.

결과: 총 1,158명의 환자가 삼일열 말라리아로 확진되었으며, 군인은 731명.
전역후 발생한 환자는 427명이었다. 군복무중 두 번째 예방약 복용이 시작된 시점
이후에 발생한 환자는 963명이었으며, 예방약을 복용한 경우는 598명이었다.
예방약 복용 집단에서 장기 잠복환자는 59%(353명)가 발생하였지만, 예방약
미복용 집단에서는 365명중 80명(21.9%)이 장기 잠복환자로 발생하였다 (p<0.001).
예방약 복용 집단에서 발생한 장기 잠복환자의 61.9%(218명)는 클로르퀸과
프리마퀸을 규칙적으로 복용한 것으로 조사되었다. 그러나 단기와 장기 잠복환자에서
잠복기는 예방약 복용여부와 관련이 없었다.

결론: 예방약 미복용 집단에서 발생한 삼일열 말라리아는 대부분의 환자와 단기
잠복환자로 발생하는 경향을 보였다. 또한, 클로르퀸 예방요법은 삼일열 말라리아의
임상증상 발생을 억제시킴으로써 장기 잠복환자의 발생을 증가시키는 것으로
조사되었으며, 우리나라의 경우 프리마퀸 예방요법은 장기 잠복환자를 효과적으로
감소시키지 못하였다. 따라서 장기 잠복환자의 발생을 예방하기 위하여 화학적
예방요법에 대한 추가적인 연구가 필요한 것으로 판단된다.

핵심되는 말: 삼일열 말라리아, 말라리아, 화학적 예방요법