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販売名(企業名)	新鮮凍結血漿「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」(日本赤十字社)			

研究報告の概要

○韓国におけるクロロキン耐性三日熱マラリア

韓国において、三日熱マラリア(*Plasmodium vivax* malaria)が再興した1993年以降の患者は約100万人と推定される。この状況に対処するため、1997年より韓国軍はヒドロキシクロロキンおよびプリマキンを用いた予防的化学療法を実施している。予防的化学療法を受けた韓国軍兵士の累積者数は、2007年までに140万人を超えた。広範な予防化学療法を実施することで、韓国軍におけるマラリア患者の急増を防ぐことができたが、クロロキン(CQ)耐性*P. vivax*株発現の可能性が高まった。

本調査では、2003～2007年の期間に、韓国の*P. vivax*マラリア患者の治療効果のモニタリングを行い、調査登録患者484名中2名にCQ耐性を確認した。本結果は、アジア温帯地域におけるCQ耐性*P. vivax*の初めての報告である。韓国における*P. vivax*のCQ耐性発現頻度の変動をモニターするには、継続的調査が必要である。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿「日赤」
新鮮凍結血漿-LR「日赤」

血液を介するウイルス、
細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
1997年より韓国軍はヒドロキシクロロキンおよびプリマキンを用いた予防的化学療法を実施し、マラリア患者の急増を防ぐことができたが、調査登録患者484名中2名にクロロキン(CQ)耐性*Plasmodium vivax*を確認したとの報告である。	日本赤十字社では、輸血感染症対策として問診時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。また、マラリア流行地への旅行者または居住経験者の献血を一定期間延期している(1～3年の延期を行うとともに、帰国(入国)後マラリアを思わせる症状があった場合は、感染が否定されるまでの間についても献血を見合わせる)。今後も引き続き、マラリア感染に関する新たな知見及び情報の収集、対応に努める。

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Short Report: Chloroquine-resistant *Plasmodium vivax* in the Republic of Korea

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Abstract. The number of *Plasmodium vivax* malaria patients in the Republic of Korea and North Korea since the re-emergence of malaria in 1993 is estimated to be approximately one million. To cope with this situation, the Army of the Republic of Korea has performed chemoprophylaxis with hydroxychloroquine and primaquine since 1997. The cumulative number of soldiers in the Army of the Republic of Korea given chemoprophylaxis exceeded 1.4 million by 2007. Extensive chemoprophylaxis contributed to preventing a rapid increase of malaria patients in the Army of the Republic of Korea, but increased the possibility of the occurrence of chloroquine (CQ)–resistant *P. vivax* strains. In this study, treatment responses of *P. vivax* malaria patients in the Republic of Korea monitored during 2003–2007, and CQ resistance was confirmed in 2 of 484 enrolled patients. Our results are the first report of CQ-resistant *P. vivax* in a temperate region of Asia. Continuous surveillance is warranted to monitor the change in CQ resistance frequency of *P. vivax* in the Republic of Korea.

Plasmodium vivax malaria, which was endemic on the Korean Peninsula for many centuries until the late 1970s, re-emerged in 1993 in the Republic of Korea.[1] The malaria-prevalent area has been confined to the area adjacent to the Demilitarized Zone (DMZ) from the early stage of the re-emergence, and malaria occurrence in the Republic of Korea has been directly influenced by the prevalence of malaria in the region of North Korea located near the DMZ.[1–3] The total number of malaria patients in the Republic of Korea and North Korea since the re-emergence likely approaches one million.[1–4] To cope with the situation, the Army of the Republic of Korea has performed chemoprophylaxis with hydroxychloroquine (HCQ) and presumptive anti-relapse therapy with primaquine since 1997.[5] The cumulative number of the soldiers in the Army of the Republic of Korea given chemoprophylaxis exceeded 1.4 million by 2007. This extensive chemoprophylaxis campaign has helped prevent a rapid increase of malaria patients in the Army of the Republic of Korea. However, this success is tempered by the increased possibility of chloroquine (CQ)–resistant *P. vivax* strains.[5]

In this study, 484 patients from 6 hospitals in the Republic of Korea (5 in the malaria-prevalent region and 1 in Seoul) were enrolled during 2003–2007. Blood samples were collected from all patients before HCQ treatment and 24 hours after completion of treatment. Treatment responses were monitored by investigation of fever clearance time and parasite clearance time. Plasma concentrations of HCQ before and 24 hours after completion of treatment were measured by validated reversed-phase high-performance liquid chromatography[6] with slight modifications.[7] Additional examinations or blood collection were not performed. The study protocols were reviewed and approved by the institutional review board of each hospital. All patients enrolled in this study were admitted to the hospitals during HCQ treatment, and HCQ was taken under the physician supervision. There were no problems with HCQ treatment compliance.

Among 484 patients enrolled in the five-year study, HCQ treatment failed in two patients (Table 1). These two patients had not been in malaria-prevalent areas in other nations during the two years prior to their present hospitalization.

Patient A was a 26-year-old man (civilian) who had been discharged from the military in May 1998. Chemoprophylaxis was not performed during his military service. He was admitted to hospital I located in Goyang, a malaria-prevalent area in Kyonggi Province, on July 30, 2003. *Plasmodium vivax* malaria was confirmed and he was administered 2,000 mg of HCQ over a three-day period. More specifically, on day 0, he was given 800 mg of HCQ, with doses of 400 mg administered 6 hours and 24 hours later (day 1), and 48 hours later (day 2). Despite administration of the first cycle of HCQ treatment, fever did not subside until day 6 and *P. vivax* trophozoites were evident in a peripheral blood smear obtained on day 6. Parasite density on day 0 (before the treatment) and day 3 (24 h after completion of HCQ treatment) were 3,500/μL and 300/μL, respectively. Gene amplification by species-specific primers for small subunit ribosomal RNA[8] showed that *Plasmodia* in the patient's peripheral blood was *P. vivax*. The plasma concentration of HCQ 24 hours after the completion of HCQ treatment was 165 ng/mL. The patient was completely cured by administration of an additional cycle of HCQ treatment commencing on day 6.

Patient B was a 72-year-old woman. She was admitted to hospital II located in Seoul on July 24, 2007 (day 0), because of fever and chills. *Plasmodium vivax* malaria was diagnosed and HCQ was administered on July 25–27 (days 1–3). Treatment was unsuccessful in resolving the fever and severe headache, and parasites were evident both microscopically and by small subunit ribosomal RNA amplification until day 4. Parasite density on days 0 and 4 was 3,800/μL.

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TABLE 1
Demographic and clinical characteristics of two patients unsuccessfully treated with the conventional HCQ regimen, Republic of Korea*

Patient	Hospital (location)	Period of HCQ administration	Plasma concentration of HCQ† (ng/mL)	Parasite density before/after† HCQ treatment (parasites/μL)	Regimen for complete cure
A	I (Goyang)	July 30–August 1, 2003	165	3,500/300	Additional administration of HCQ
B	II (Seoul)	July 25–27, 2007	150	3,800/440	Quinine sulfate and doxycycline

* HCQ = hydroxychloroquine.
† Measured 24 hours after completion of HCQ treatment.

and 440/μL, respectively. The plasma concentration of HCQ 24 hours after the completion of HCQ treatment was 150 ng/mL. Salvage treatment with quinine sulfate and doxycycline was carried out for seven days beginning on day 4, followed by administration of primaquine. This regimen completely resolved the infection.

Chloroquine-resistant *P. vivax* strains have been reported from various areas[9–12] since its emergence in Papua New Guinea in 1989.[13] In the Republic of Korea, a large-scale chemoprophylaxis campaign has been performed since 1997. However, prophylaxis has consistently failed in many cases despite attainment of sufficiently high plasma concentrations of HCQ. Moreover, the length of time required for the elimination of *P. vivax* from patients' blood by HCQ treatment has increased in the current decade.[14]

Hydroxychloroquine has been reported to be as active as CQ against malaria parasites,[15,16] and 400 mg of HCQ is the molar equivalent of 309.6 mg of HCQ base and 295.0 mg of CQ base. Therefore, a CQ concentration of 10 ng/mL in plasma, which is the minimum effective concentration against CQ-susceptible *P. vivax*, is equivalent to an HCQ concentration of 10.5 ng/mL of plasma. In this study, treatment with 2,000 mg of HCQ over a three-day period was not effective in 2 (0.4%) of 484 patients. For these two patients, plasma concentrations of HCQ 24 hours after completion of HCQ treatments were much higher than the minimum effective concentration of CQ against *P. vivax*.[17] For the 482 patients with successful therapeutic outcomes, the mean and the standard deviation of plasma concentrations of HCQ 24 hours after completion of HCQ treatments were 220 ng/mL and 121 ng/mL, respectively, which were in not distinct from the two patients in whom HCQ treatment failed. This indicates that HCQ was absorbed and metabolized normally in the two patients, precluding the possibility that the treatment failure was caused by personal factors. In the two patients, parasitemias were reduced markedly, but not cleared, by HCQ administration. Patient A was cured by additional administration of HCQ; this success may have been the result of the infecting *P. vivax* being exposed to an increased trough concentration of HCQ for an extended period because of the cumulative dosage.

The present observations are the first report of CQ-resistant *P. vivax* from a temperate region of Asia. Surveillance activity should be strengthened to monitor the change of CQ susceptibility of *P. vivax* in the Republic of Korea.

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REFERENCES

1. Park JW, Klein TA, Lee HC, Pacha LA, Ryu SH, Yeom JS, Moon SH, Kim TS, Chai JY, Oh MD, Choe KW, 2003. Vivax malaria: a continuing health threat to the Republic of Korea. *Am J Trop Med Hyg 69:* 159–167.
2. Yeom JS, Ryu SH, Oh S, Lee WJ, Kim TS, Kim KH, Kim YA, Ahn SY, Cha JE, Park JW, 2005. Status of *Plasmodium vivax* malaria in the Republic of Korea during 2001–2003. *Am J Trop Med Hyg 73:* 604–608.
3. Yeom JS, Kim TS, Oh S, Sim JB, Barn JS, Kim HJ, Kim YA, Ahn SY, Shin MY, Yoo JA, Park JW, 2007. *Plasmodium vivax* malaria in the Republic of Korea during 2004–2005; changing patterns of infection. *Am J Trop Med Hyg 76:* 865–868.
4. Roll Back Malaria Partnership, 2008. Democratic People's Republic of Korea: country profile. Available at: http://www.rbm.who.int/countryaction/index.html. Accessed July 11, 2008.
5. Yeom JS, Ryu SH, Oh S, Choi DH, Song KJ, Oh YH, Lee JH, Kim YA, Ahn SY, Yang HY, Cha JE, Park JW, 2005. Evaluation of anti-malarial effects of mass chemoprophylaxis in the Republic of Korea Army. *J Korean Med Sci 25:* 707–712.
6. Easterbrook M, 1999. Detection and prevention of maculopathy associated with antimalarial agents. *Int Ophthalmol Clin 39:* 49–57.
7. McChesney EW, 1983. Animal toxicity and pharmacokinetics of hydroxychloroquine sulfate. *Am J Med 75:* 11–18.
8. Snounou G, Viriyakosol S, Zhu XP, Jarra W, Pinheiro L, do Rosario VE, Thaithong S, Brown KN, 1993. High sensitivity of detection of human malaria parasites by the use of nested polymerase chain reaction. *Mol Biochem Parasitol 61:* 315–320.
9. Marlar T, Myat Phone K, Aye Yu S, Khaing Khaing G, Ma S, Myint O, 1995. Development of resistance to chloroquine by *Plasmodium vivax* in Myanmar. *Trans R Soc Trop Med Hyg 89:* 307–308.
10. Baird JK, Sustriayu Nalim MF, Basri H, Masbar S, Leksana B, Tjitra E, Dewi RM, Khairani M, Wignall FS, 1996. Survey of

resistance to chloroquine by *Plasmodium vivax* in Indonesia. *Trans R Soc Trop Med Hyg 90:* 409–411.
11. Soto J, Toledo J, Gutierrez P, Luzz M, Llinas N, Cedeno N, Dunne M, Berman J, 2001. *Plasmodium vivax* clinically resistant to chloroquine in Colombia. *Am J Trop Med Hyg 65:* 90–93.
12. Kurcer MA, Simsek Z, Kurcer Z, 2006. The decreasing efficacy of chloroquine in the treatment of *Plasmodium vivax* malaria, in Sanliurfa, south-eastern Turkey. *Ann Trop Med Parasitol 100:* 109–113.
13. Rieckmann KH, Davis DR, Hutton DC, 1989. *Plasmodium vivax* resistance to chloroquine? *Lancet 2:* 1183–1184.
14. Park JW, 2007. Analysis of drug susceptibility of anti-malarial agents in Korean (in Korean). Korea centers for disease control and prevention. *Biological Strategies against Plasmodium vivax Malaria and Vector Control in Korea (Report of Research Results).* Seoul: Ministry of Health and Welfare, 89–103.
15. Nieto-Caicedo M, 1956. Hydroxychloroquine in the treatment of malaria. *Am J Trop Med Hyg 5:* 681–685.
16. McChesney EW, Fitch CD, 1984. Aminoquinolines. Peters W, Richards WH, eds. *Handbook of Experimental Pharmacology.* Berlin: Springer Verlag, 3–60.
17. Baird JK, 2004. Chloroquine resistance in *Plasmodium vivax* (minireview). *Antimicrob Agents Chemother 48:* 4075–4083.

医薬品　研究報告　調査報告書

識別番号・報告回数		報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
			2009年3月13日	該当なし	
一般的名称	別紙のとおり	研究報告の公表状況	Simian Malaria in a U.S. Traveler --- New York, 2008	公表国：米国	
販売名（企業名）	別紙のとおり				

研究報告の概要

問題点：サルマラリアである*Plasmodium knowlesi*のヒトへの感染例がマレーシアおよびその周辺の広範囲において多数報告され、人畜共通感染症の病原体として新興している可能性が示されている。

4種のプラスモディウム属の赤血球内原虫（熱帯熱マラリア原虫；*P. falciparum*、三日熱マラリア原虫；*P. vivax*、四日熱マラリア原虫；*P. malaride*および卵形マラリア原虫；*P. ovale*）がヒトでマラリアを起こすことが知られている。しかし、最近のアジアからのレポートで、5番目のマラリア原虫として*Plasmodium knowlesi*が人畜共通感染症の病原体として新興している可能性が示されている。20種類以上のマラリア原虫がヒト以外の霊長類に感染するが、これまでサルマラリアのヒトへの自然感染は、公衆衛生学に重要でない稀な事象とされてきた。光学顕微鏡による観察では、多くのサルマラリア原虫はヒトにマラリアを起こす4種のマラリア原虫との鑑別はほぼ困難で、PCRやマイクロサテライト分析といった分子的技術が種の確定に必要である。
最初の*P. knowlesi*感染は、1965年に東南アジアの任務から戻ってきた米国の兵士であった。その後の報告はほとんどなく、2002年にマレーシアの研究者らが非典型的な特徴をもつ四日熱マラリア症例の増加や、より重篤な臨床症状、より高度な寄生虫血症に気付いている。nested PCR assayにより、これらのマラリア症例の50%以上が*P. knowlesi*であると確認された。最初に顕微鏡診断されていた四日熱マラリアは1例もなかった。2001～2006年に同じ研究者らによって行われたレトロスペクティブな調査では、マレーシアのSarawak州の患者からの960検体のうち28%が*P. knowlesi*であった。以前は、そのほとんどが形態学的に四日熱マラリアと診断されていた。このグループはまた、四日熱マラリアによる重症のマラリアと考えられていた4例の異常な死亡が、後にPCRによって*P. knowlesi*と確認されたことも報告している。さらにヒトの*P. knowlesi*感染は、シンガポール、タイとミャンマーの国境、フィリピン、中国の雲南省、フィンランド（マレーシアから帰った旅行者が最初熱帯熱マラリアと誤診されていた）からも報告されている。

使用上の注意記載状況・その他参考事項等

記載なし

報告企業の意見	今後の対応
別紙のとおり	今後とも関連情報の収集に努め、本剤の安全性の確保を図っていきたい。