Model Farmakokinetik/Farmakodinamik Populasi Primakuin dan Analisis Faktor Genetik Enzim CYP2D6 Terkait Kejadian Relaps Malaria Vivaks = Population Pharmacokinetics/pharmacodynamics Model of Primaquine and Analysis of CYP2D6 Enzyme Genetic Factors Associated with the Relapse Event of Vivax Malaria

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Abstrak

Relaps masih menjadi masalah dalam eradikasi malaria vivaks. Primakuin adalah satu-satunya antihipnozoit yang saat ini tersedia di pasaran. Efikasi primakuin diperoleh oleh farmakokinetik dan farmakodinamik obat. Kemampuan CYP2D6 memetabolisme primakuin menjadi bentuk aktif akan memengaruhi kadar primakuin dan efikasi klinisnya. Pada penelitian ini dilakukan analisis farmakokinetik dan farmakodinamik primakuin dengan pendekatan populasi pada subjek dengan malaria vivaks; serta menganalisis hubungan variasi jumlah salinan gen CYP2D6 dengan kejadian relaps.
Subjek studi adalah 174 orang Tentara Nasional Indonesia yang terinfeksi malaria vivaks dan diterapi dengan kombinasi skizontisida dan primakuin selama 14 hari. Kejadian relaps diamati selama satu tahun. Model farmakokinetik-farmakodinamik primakuin yang dikembangkan dengan metode mixed effect non linier menggunakan piranti lunak NONMEM versi 7.4.1. Kuantifikasi jumlah salinan gen CYP2D6 dilakukan pada 49 subjek. Jumlah salinan ditentukan berdasarkan nilai Cq hasil amplifikasi intron 6 dengan qPCR real-time. Jumlah salinan dihitung sesuai dengan rumus 2-ΔΔCq x jumlah salinan DNA Kalibrator, ΔΔCq = ΔCq (kalibrator)  ΔCq (sampel) dan ΔCq = Cq (CYP2D6) - Cq (RNAse P). Hubungan jumlah salinan gen CYP2D6 dan kejadian relaps malaria vivaks dianalisis dengan uji Chi-square.
Hasil penelitian menunjukkan bahwa kadar primakuin plasma paling baik dideskripsikan oleh model satu kompartemen dengan penyerapan orde pertama. Berat badan diimplementasikan sebagai fungsi alometrik pada clearance (CL) dan distribusi volume (Vd). Piperakuin maupun pironaridin menurunkan CL dan Vd primakuin sebesar 3354%. Faktor genetik CYPD6 tidak memengaruhi CL primakuin. Risiko kejadian relaps malaria vivaks dideskripsikan dengan model constant hazard pada model time-to-event. Peningkatan satu poin skor aktivitas gen CYP2D6 menurunkan risiko relaps sebesar 88,3%, sehingga dapat disangkal bahwa faktor genetik CYP2D6 menjadi salah satu faktor yang dapat memengaruhi risiko kambuh vivaks malaria. Tidak didapatkan hubungan antara AUC primakuin dan kejadian relaps, sehingga hasil ini tidak dapat digunakan untuk menghitung dosis primakuin yang optimal. Kuantifikasi jumlah salinan gen CYPD6 dilakukan pada 21 subjek relaps dan 28 subjek kontrol. Mayoritas subjek memiliki jumlah salinan ≥ 2 (39 dari 49 orang). Tidak ditemukan hubungan antara jumlah salinan gen CYP2D6 dan kejadian relaps (p = 0,155).
Relapse is still a problem in vivax malaria eradication. Primakuine is the only antihipnozoite currently available on the market. The efficacy of primaquine is obtained by the pharmacokinetics and pharmacodynamics of the drug. The ability of CYP2D6 to metabolize primaquine to its active form will affect primakuine levels and clinical efficacy. In this study, a pharmacokinetic and pharmacodynamic analysis of primaquine was carried out with a population approach in subjects with vivax malaria; and to

analyze the relationship between variations in the number of copies of the CYP2D6 gene with the incidence of relapse.
Study subjects were 174 Indonesian National Armed Forces infected with vivax malaria and treated with a combination of schizonticides and primaquine for 14 days. Relapse incidence was observed for one year. The primakuine pharmacokinetic-pharmacodynamic model was developed using a non-linear mixed effect method using NONMEM software version 7.4.1. Quantification of the number of copies of the CYP2D6 gene was performed in 49 subjects. The number of copies is determined based on the Cq value of the intron 6 amplification with real-time qPCR. The number of copies is calculated according to the formula 2-ΔΔCq x number of copies of the DNA Calibrator, ΔΔCq = ΔCq (calibrator)  ΔCq (sample) and ΔCq = Cq (CYP2D6) - Cq (RNAse P). The association between copy number of CYP2D6 gene and the incidence of vivax malaria relapse was analyzed using Chi-square test.
The results showed that plasma primquine levels were best described by a one-compartment model with first-order absorption. Body weight is implemented as an allometric function on clearance (CL) and volume distribution (Vd). Piperakuine and pyronaridin reduce CL and Vd primakuin by 3354%. CYPD6 genetic factor does not affect CL primaquine. The risk of vivax malaria relapse was described using the constant hazard model in the time-to-event model. One point increase in the CYP2D6 gene activity score reduced the risk of relapse by 88.3%, so it can be denied that CYP2D6 genetic factor is one of the factors that can affect the risk of malaria vivax relapse. There was no relationship between AUC of primaquine and the incidence of relapse, so these results cannot be used to calculate the optimal primquine dose. CYPD6 gene copy count quantification was performed in 21 relapsed subjects and 28 control subjects. The majority of subjects had a number of copies ≥ 2 (39 of 49 people). No association was found between the number of copies of the CYP2D6 gene and the incidence of relapse (p = 0.155).