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# Safety issue of codeine may be different according to genetic polymorphism

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Genetic polymorphism of drug metabolizing enzyme gene could lead to inter-individual differences of drug response. The life-threatening adverse reaction of codeine by CYP2D6 genetic polymorphism gives rise to safety issues. The people who have multiple copies of CYP2D6 active genotype (*1/*1XN, *2/*2XN) can rapidly metabolize codeine to morphine, the active metabolite and it causes rapid increase of morphine in blood. CYP2D6 UM genotypes may different among ethnic groups, 29 % in African, 6.5 % in Caucasian however, 1.2 % in Korean. In this study, we intended to investigate the effects of CYP2D6 genetic polymorphisms on pharmacokinetics of codeine in Korean. 37 healthy Korean subjects separated out three groups by CYP2D6 genotype analysis, UM (Ultra-rapid metabolizer, *1/*1XN, n=1), EM (Extensive metabolizer, *1/*1, *1/*2, *2/*2, n=15) and PM (Poor metabolizer, *10/*10, *5/*10, n=21). All subjects were administered orally 20 mg of codeine. 11 points of blood samples were collected during 14 hours. Concentration of codeine and its metabolites (morphine, morphine-3-glucuronide, morphine-6-glucuronide) in plasma were determined by UPLC-MS/MS. The pharmacokinetic parameters were calculated using WinNonlin ver.6.2. As a result, $C_{max}$ of morphine in PM group was 5 times lower than that in EM group. Also, AUC of PM group was 3.5 times decreased and CL/F was 3.3 times increased than those in EM group. However, pharmacokinetic parameters in UM group not made a large difference than EM group. The results suggest that pharmacokinetic response of codeine may differ by CYP2D6 genotypes and because of CYP2D6 UM genotype ethnic differences, the safety issues of codeine may less occur in Korean.

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