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EFFECTS OF EXPERIMENTAL RENAL FAILURE ON THE PHARMACOKINETICS OF CIBENZOLINE IN RATS

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Purpose: Cibenzoline (CBZ) is an antiarrhythmic agent used for patients with supraventricular or ventricular arrhythmias. CBZ is mainly excreted in urine, and renal failure was reported as a risk factor for its adverse effects such as hypoglycemia. The purpose of the present study was to clarify the effect of experimental renal failure on the pharmacokinetics of CBZ in rats.

Methods: Male Wistar rats weighing 210-280g were used. Renal failure was produced by bilateral ureter ligation about 24 hr before the experiment (UL rats) or an intraperitoneal injection of cisplatin at 5mg/kg about 72-96 hr before the experiment (CDDP rats). Control rats underwent sham-operation or an intraperitoneal injection of saline, respectively. CBZ was injected intravenously at a dose of 5mg/kg, and blood samples were taken from the carotid artery. Serum concentration of CBZ was determined by HPLC.

Results and Discussion: Serum concentration of CBZ in rats with experimental renal failure was higher than that in control rats. The total body clearances of CBZ in UL and CDDP rats were decreased by 41% and 24%, respectively. These results suggest that renal failure may increase the risk for severe adverse effects of CBZ.

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DETERMINATION OF GENETIC POLYMORPHISM OF CYP2C9 AND VKORC1 AS A CONTRIBUTOR OF WARFARIN DOSE IN INDONESIAN POPULATION

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Objectives: The genetic polymorphism of CYP2C9 and VKORC1 significantly contributed to warfarin efficacy and toxicity. VKORC1 has an approximately three-fold greater effect than CYP2C9. To elucidate the genetic factors and the clinical factors that cause large inter-patient variability and ethnic differences in warfarin efficacy, we investigated variations of CYP2C9 and VKORC1 polymorphism in Indonesian subjects.

Methods: Gene variations of VKORC1 and CYP2C9 in 103 Indonesian healthy volunteers were analyzed. The participants consisted of 47 male and 56 female; the majority of them were come from West Java (54%), and their age range were 19-66 years (mean±SD : 22.7±7.2 years).

Results: The frequencies of VKORC1-1639GG, GA and AA genotypes in the Indonesian were 4.9, 26.2, and 68.9%, respectively. The frequencies of (CYP2C9*1/*1), (CYP2C9*1/*2 and *1/*3), and (CYP2C9*2/*3, *2/*2 and *3/*3) genotypes were 95.1, 4.9 and 0%, respectively.

Conclusions: The frequencies of VKORC1-1639GG and GA genotypes in Indonesian population were higher than in Japanese, whereas the frequencies of CYP2C9*2 and *3 were similar in both population.

Keyword: CYP2C9, VKORC1, genetic polymorphism, warfarin, pharmacogenetics.