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EFFECT OF YOKUKANSAN ON THE CYTOCHROME P450

Mariko Yoshizawa¹, Saori Ichisawa¹, Nobutomo Ikarashi¹, Kiyomi Ito¹, Wataru Ochiai², Junko Watanabe², Masanao Kanitani², Yoshih Kase² and Kiyoshi Sugiyama¹

¹ Department of Clinical Pharmacokinetics, Hoshi University, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan
² TSUMURA Research Laboratories, Tsumura & Co., 3586 Yoshiwara, Ami-machi, Inashiki-gun, Ibaraki 300-1192, Japan

[Purpose] Donepezil, a drug used for the treatment of Alzheimer’s disease, is metabolized mainly by CYP3A4 and CYP2D6 in humans, and its plasma concentration is elevated by coadministration of ketoconazole or cimetidine. Previously Yokukansan has been shown to improve behavioral and psychological symptoms of dementia (BPSD) in Alzheimer’s disease. So, it is likely that Yokukansan is prescribed in combination with donepezil. We investigated whether Yokukansan affects the disposition of donepezil in rats.

[Methods] Yokukansan (1 g/kg/day) was administered orally to male Wistar rats once a day for 7 days. On the 8th day, donepezil hydrochloride (5 mg/kg) was administered orally and plasma donepezil concentrations were measured up to 8 hours by HPLC-UV. Donepezil disposition after intraperitoneal injection of ketoconazole (10 mg/kg) or cimetidine (200 mg/kg) was also investigated as a positive control.

[Results and Discussion] The areas under the plasma concentration–time curve (AUC) of donepezil were higher in the ketoconazole- or cimetidine-coadministered group than in the control group. In contrast, plasma donepezil concentrations did not differ significantly between the Yokukansan coadministration group and the control group, suggesting that Yokukansan has no effect on the disposition of donepezil.

[Conclusions] Yokukansan is unlikely to cause pharmacokinetic interactions when coadministered with donepezil in clinical practice.

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MECHANISM FOR DECREASED DIGOXIN CONCENTRATION BY FEXOFENADINE IN HEMODIALYSIS PATIENTS

Daisuke Shima, Masayuki Tsujiimoto, Shima Hiraoka, Ayaka Miyoshi, Tetsuya Minegaki and Kohshi Nishiguchi

Department of Clinical Pharmacy, Kyoto Pharmaceutical University, Misasagi, Yamashina-ku, Kyoto 607-8414, Japan

[Purpose] We reported previously that the digoxin (DX) concentration was remarkably decreased by co-administration of fexofenadine (FEX) in two hemodialysis (HD) patients. It is thought that this interaction occurred due to the facilitation of hepatic excretion and/or the inhibition of intestinal absorption, but the mechanism is currently unclear. It was previously reported that the DX concentration in HD patients was significantly altered by gene polymorphisms of liver specific transporter OATP1B3 and up-regulation of intestinal MDR1 expression. Therefore, these transporters might be responsible for DX-FEX interaction in HD patients. This study examined the possibility of a functional variation of hepatic OATP1B3 and intestinal MDR1 induced by FEX.

[Methods] Hep3B and Caco-2 cells were selected as models of hepatocytes and small intestinal epithelial cells, respectively. We examined the uptake of DX and Rhodamine123 (Rh123), a model substrate of MDR1, into those cells in the presence of FEX only during the uptake experiments (simultaneous treatment), as well as after incubation with FEX for 48 hours and continuing throughout the uptake experiments (continuous treatment). Intracellular amounts of DX and Rh123 were measured by HPLC-UV assay and fluorometry, respectively. MDR1 mRNA expression was assessed by real-time RT-PCR assay. [Results & Discussion] Initial uptake rate of DX into Hep3B cells receiving continuous treatment was higher than that in those receiving simultaneous treatment, suggesting that FEX increases hepatic uptake of DX. In addition, the accumulation of Rh123 in Caco-2 cells receiving continuous treatment was significantly lower than that in control cells and those receiving simultaneous treatment, suggesting that FEX facilitates the function of MDR1. However, because MDR1 mRNA expression was not changed, the mechanism remains unclear. [Conclusion] This study suggests that the decrease in DX concentration by FEX in HD patients was partly due to the facilitation of hepatic uptake mediated by OATP1B3 and intestinal secretion mediated by MDR1 induced by the high FEX concentration in HD patients.