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8-Hydroxylation and glucuronidation of mirtazapine in Japanese psychiatric patients: Significance of the glucuronidation pathway of 8-hydroxy-mirtazapine.

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OBJECTIVE To investigate the metabolism of mirtazapine (MIR) in Japanese psychiatric patients, we determined the plasma levels of MIR, *N*-desmethylmirtazapine (DMIR), 8-hydroxy-mirtazapine (8-OH-MIR), mirtazapine glucuronide (MIR-G), and 8-hydroxy-mirtazapine glucuronide (8-OH-MIR-G). **METHODS** Seventy-nine Japanese psychiatric patients were treated with MIR for 1–8 weeks to achieve a steady-state concentration. Plasma levels of MIR, DMIR, and 8-OH-MIR were determined using HPLC. Plasma concentrations of MIR-G and 8-OH-MIR-G were determined by total MIR and total 8-OH-MIR (i.e., concentrations after hydrolysis) minus unconjugated MIR and unconjugated 8-OH-MIR, respectively. **RESULTS** Plasma levels of 8-OH-MIR were lower than those of MIR and DMIR (median 1.42 nmol/L vs. 92.71 nmol/L and 44.96 nmol/L, respectively). The plasma levels (median) of MIR-G and 8-OH-MIR-G were 75.00 nmol/L and 111.60 nmol/L, giving MIR-G/MIR and 8-OH-MIR-G/8-OH-MIR ratios of 0.92 and 59.50, respectively. Multiple regression analysis revealed that smoking was correlated with the plasma MIR concentration (dose- and body weight-corrected; $p=0.040$) and that age (years) was significantly correlated with the plasma DMIR concentration (dose- and body weight-corrected; $p=0.018$). **CONCLUSION** The plasma concentration of 8-OH-MIR was as low as 1.42 nmol/L, whereas 8-OH-MIR-G had an approximate 59.50-times higher concentration than 8-OH-MIR, suggesting a significant role for hydroxylation of MIR and its glucuronidation in the Japanese population.