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＊原　著＊

臨床におけるノイロトロピン® と併用薬物との相互作用を予測するための放射性標識基質を用いた *in vitro* 薬物動態試験

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Prediction of Drug Interactions between Neurotropin® and Clinically Used Drugs by *in vitro* Methods Using Radiolabelled Substrates

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Summary

For the prediction of potential drug-drug interactions of Neurotropin®, a widely used analgesic and anti-allergic drug derived from the inflamed skin tissue of rabbits inoculated with vaccinia virus, an *in vitro* study using human liver microsomes and cytosol was performed. We tested the hypothesis that Neurotropin may interact with drugs that are metabolized by cytochrome P450 (CYP) subtypes CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP4A11, or dihydropyrimidine dehydrogenase (DPD), via inhibition of these enzymes.

Neurotropin (0.01-1 NU/mL) showed no effect on the activities of CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP4A11. However, the activities of CYP2E1, CYP3A4 and DPD were inhibited. Neurotropin reversibly inhibits these three enzymes in a competitive manner for CYP2E1 and DPD, and in a non-competitive manner for CYP3A4.

The values of the inhibition constant (Ki) were examined. However, the Ki values for CYP2E1 and CYP3A4 were more than 140 times (0.56 and 4.64 NU/mL, respectively) the maximum estimated plasma concentration (0.004 NU/mL) of Neurotropin in clinical use. Thus, interaction of Neurotropin with other drugs metabolized by CYPs seems unlikely. Similarly, the Ki value of Neurotropin for DPD was about 8 times (0.03 NU/mL) the maximum estimated plasma concentration. Metabolism of other drugs mediated by DPD may be slightly reduced by Neurotropin, but Neurotropin seems unlikely to have any significant effect in the range of plasma concentration seen in clinical use.

Key words

Neurotropin, Drug-drug interaction, Cytochrome P450, Dihydropyrimidine dehydrogenase, Human liver, Microsomes, Cytosol, Ki value, Inhibition mechanism, Radiolabelled substrates