Influence of antidepressant drugs on chlorpromazine metabolism in human liver – an in vitro study

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Abstract:
The aim of the present study was to investigate the possible effects of antidepressant drugs (fluvoxamine, imipramine) on the metabolism of the antipsychotic phenothiazine neuroleptic chlorpromazine in the human liver. The experiment was performed in vitro using human liver microsomes. The kinetic analysis of chlorpromazine metabolism carried out in the absence or presence of antidepressants showed that fluvoxamine potently inhibited chlorpromazine 5-sulfoxidation (K_i = 2.8 μM), mono-N-demethylation (K_i = 1.4 μM) and di-N-demethylation (K_i = 1.1 μM) via a competitive mechanism at therapeutic antidepressant concentrations. Imipramine moderately diminished the rate of chlorpromazine 5-sulfoxidation (K_i = 8.7 μM, competitive inhibition), mono-N-demethylation (K_i = 16.0 μM, non-competitive inhibition) and di-N-demethylation (K_i = 13.5 μM, mixed inhibition).

Considering the serious side-effects of chlorpromazine and some of its metabolites, metabolic interactions between this neuroleptic and antidepressant drugs (especially the chlorpromazine-fluvoxamine interaction) may be of pharmacological and clinical importance.

Key words: imipramine, fluvoxamine, chlorpromazine metabolism, human liver microsomes, cytochrome P450, inhibition