THIORIDAZINE-FLUOXETINE INTERACTION AT THE LEVEL OF THE DISTRIBUTION PROCESS IN VIVO

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The aim of the present study was to investigate the effect of the distribution interaction between thioridazine and fluoxetine in vivo. Experiments were carried out on male Wistar rats. Animals received thioridazine and fluoxetine separately or jointly, at a dose of 10 mg/kg ip. Concentrations of thioridazine and its metabolites and fluoxetine in the plasma and tissues were measured at 1 h after administration of the drugs (HPLC). Effects of distribution interactions were estimated on the basis of the calculated tissue/plasma and lysosome-poor/lysosome-rich tissue concentration ratios, considering the heart and muscles as lysosome-poor tissues and the lungs, liver and kidneys as lysosome-rich ones.

Fluoxetine diminished the tissue/plasma concentration ratio of thioridazine for the lungs, but elevated this ratio for the muscles and heart. On the other hand, thioridazine elevated the brain/plasma and heart/plasma concentration ratios of fluoxetine. Consequently, the thioridazine lysosome-poor/lysosome-rich tissue concentration ratios significantly increased in the presence of fluoxetine. At the same time, thioridazine raised (or showed such a tendency) the heart/lysosome-rich tissue concentration ratios of fluoxetine, not changing significantly the muscles/lysosome-rich tissue concentration ratios of the antidepressant.

The presented results provide evidence that the distribution interactions between thioridazine and fluoxetine observed in vitro occur also in vivo, leading to a shift of the drugs from organs rich in lysosomes to those poor in these organella, in particular to the heart. Thioridazine and fluoxetine mutually increased their heart/plasma and heart/lysosome-rich tissue concentration ratios, i.e. the heart/lung, heart/liver and heart/kidneys ratios. Similar results were obtained with lysosome-poor muscles in the case of thioridazine. The obtained results confirm that, apart from the lysosome density in the investigated tissues, the potential metabolic interactions in the liver and the pattern of drug circulation in a body have an important impact on the calculated drug concentration ratios. Moreover, considering serious side-effects of thioridazine (cardiotoxicity, anticholinergic activity), the administration of thioridazine-fluoxetine combination studied herein should be approached with caution, considering appropriate dose adjustment.

Key words: thioridazine, fluoxetine, lysosomal trapping, distribution interaction

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