INHIBITORY EFFECT OF VARIOUS DRUGS ON LIVER METHOTREXATE 7-HYDROXYLASE ACTIVITY

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Methotrexate (MTX), a folic acid antagonist, is widely used in treatment of acute lymphocytic leukemia and rheumatoid arthritis. We reported that MTX hydroxylating activity was predominantly due to aldehyde oxidase in vivo in rats from the fact that differences of the amounts of 7-OHMTX excreted was closely correlated with rat strain differences. We also demonstrated interindividual variation of MTX hydroxylase activity in human liver cytosol. The facts suggest that individual difference of MTX hydroxylase activity based on aldehyde oxidase content should be taken into consideration in the clinical use of MTX. In the present study, we investigated the effect of various drugs on MTX hydroxylase based on aldehyde oxidase in vitro in rat.

Aldehyde oxidase activity was assayed using benzaldehyde as a substrate. Benzaldehyde was incubated with rat liver cytosol, and benzoic acid formed was analysed by HPLC. MTX hydroxylase activity was determined by the measurement of 7-OHMTX after incubation with rat liver cytosol. Some clinical used drugs were added at the concentrations of 10^{-6}-10^{-4}M.

Raloxifene, imipramine, nifedipine and ketoconazole particularly inhibited aldehyde oxidase activity and MTX hydroxylase activity. However, ciclosporin A, quinacrine and allopurinol exhibited little or no inhibitory effects on these activities. These facts indicate that some clinical used drugs inhibit aldehyde oxidase and 7-hydroxylation of MTX. It is necessary to consider the drug-drug interactions between MTX and other drugs.