Abstract

Ellipticine is a cytotoxic alkaloid that exhibits multiple mechanisms of action such as intercalation into DNA, inhibition of topoisomerase II and activation of apoptosis due to changes in protein p53. The main mechanism of its action is formation of covalent adducts of ellipticine metabolites with DNA. Inhibitors of tyrosine kinases vandetanib, lenvatinib and cabozantinib are anticancer drugs, approved for treatment of advanced metastatic thyroid gland cancer. Mechanism of their action is modulation of cell signalization pathways in cancer cells.

The aim of this thesis was investigation whether tyrosine kinase inhibitors can modulate metabolism of ellipticine *in vitro*, because metabolic activation of ellipticine dictates its pharmacological efficacy. The formation of ellipticine metabolites catalyzed by human and rat microsmes was found. Superosomes™ containing human or rat recombinant cytochromes P450 (CYP) were used to resolve, whether tyrosine kinase inhibitors affect oxidation of ellipticine by these enzymes. Other enzymes tested for possible alteration of formation of metabolites of ellipticine were peroxidases, including thyreoperoxidase. Ellipticine metabolites were separated by HPLC and quantified.

Oxidation of ellipticine by human or rat microsomal enzyme systems was inhibited by tested tyrosine kinase inhibitors, however these inhibitors had no effect on oxidation of ellipticine catalyzed by human or rat CYP1A1 and CYP1A2. The most prominent inhibition effect of tested inhibitors was inhibition of N^2-oxidation of ellipticine mediated by CYP2D6. This is considered to be a unique phenomenon for ellipticine, because oxidation of a „marker“ substrate of CYP2D6, bufuralol, was not altered. Tyrosine kinase inhibitors caused the inhibition of not only the oxidation of ellipticine by CYP3A4 and CYP2C9, but also their „marker“ substrates. Peroxidase mediated metabolism of ellipticine was essetially not modulated by tested compounds. We found that thyreoperoxidase oxidizes ellipticine, which is an uniqe result, because metabolism of xenobiotics (including ellipticine) by thyreoperoxidase has not still been found.

The results indicate that pharmacological efficacy of ellipticine might be decreased by tyrosine kinase inhibitors.

Key words: ellipticine, tyrosine kinase inhibitors, cytochromes P450, peroxidases, thyreoperoxidase, activation metabolites, pharmacological efficacy, anti-cancer drugs