Abstract

There are several ways for cancer treatment. One of them is chemotherapy, when cancer patients are given a cytostatic or a combination of multiple types of drugs. The aim of this bachelor thesis was to study the metabolism of the anticancer drug vandetanib. Vandetanib is a tyrosine kinase inhibitor, that has been used in Europe since 2012 for treatment of symptomatic or progressive medullary thyroid cancer.

The kinetics of vandetanib oxidation by cytochromes P450 3A5 was studied in this thesis. Oxidation was investigated by two different systems. The first were recombinant cytochromes P450 3A5 expressed in baculovirus-transfected insect cells (Supersomes^{TM}) and the second were human recombinant cytochromes P450 3A5 expressed in *E.coli* cells (Bactosomes). Furthermore, the effect of NADPH:CYP reductase and cytochrome b_5 on vandetanib oxidation was investigated.

Both systems formed the demethylated metabolite of vandetanib, *N*-desmethylvandetanib, which was separated by HPLC. The study of enzyme kinetics of vandetanib oxidation by human CYP3A5R, 3A5BR, 3A5BLR in Bactosomes indicates that two vandetanib molecules can bind into the active site of the enzyme, resulting in more efficient oxidation. The results also indicate that not only NADPH: CYP reductase, but also cytochrome b_5 affects vandetanib oxidation. However, the effect of cytochrome b_5 depends on the reductase level (activity). Cytochrome b_5 does not positive effect on the kinetics of oxidation in Bactosomes with lower reductase level, but significantly increases the stimulation of vandetanib oxidation in Bactosomes with higher reductase level and in Supersomes^{TM}.

Keywords: cancer; vandetanib; cytochromes P450; tyrosine kinase inhibitor

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