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Identification of the Cytochrome P4502D6 in the Metabolism of 5-Aminosalicylic Acid: *in vitro* Investigations of Potential Co-Prescription Interactions

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Aim of the study: 5-aminosalicyclic acid (5-ASA) which is an effective drug that is currently used for treating diseases such as inflammatory bowel diseases (IBD) and particularly ulcerative colitis. It is well known that itis mainly metabolized by the acetylation via Phase II enzymes. However, there are no clear evidence about the metabolism of 5-ASA with various microsomal drug metabolizing enzymes, particularly cytochrome P450s. Thus, this study was undertaken to investigate the possible metabolism of 5-ASA (different way from the acetylation) by the microsomal drug metabolizing enzyme of cytochrome P450 2D6 (CYP2D6).

Material and Methods: A new method was developed, optimized and applied for the spectrophotometric measurement of 5-ASA. First, 5-ASA was reacted with nitrite in acidic medium and the excessive nitrite residues that may cause side reactions were removed with sulfamic acid. After the removal of residual nitrite, the resulting diazonium salt was coupled with aphloroglycinolreagent in alkaline medium. Water-soluble azo dye formed by combining diazotized 5-ASA and phloroglycinol reagent in an alkaline environment. Absorption of yellow-orange color which exhibits maximum absorption at 430nmwas measured. In order todetermine the activity of the CYP2D6 on 5-ASA, it was incubated with the pure CYP2D6 enzyme (cerosomes) in the presence of NADPH for 60 min at 37 ºC, and the remaining 5-ASA was measured as described above. Standard curve derived with use of pure 5-ASA was used to calculate the enzyme activity. The activity measurement was also performed in the presence of prototype CYP2D6 inhibitor to validate the activity measurement.

Results: It was determined that CYP2D6 catalyze the 5-ASA at 0.280 ± 0.04 pmol/min/pmol CYP2D6 rate. Thus, the 5-ASA was metabolized by this enzyme which plays a major role in drug metabolism. In addition to the drug metabolism, CYP2D6 also metabolizes several endogenous substances, such as hydroxytryptamines and neurosteroidsin the brain and liver tissues. Our results strongly suggest that the 5-ASA is a substrate for CYP2D6. Within the knowledge of the fact that the 5-ASA is used by ulcerative colitis patients for a lifetime. Therefore, it is clear that drug-drug interactions and endogenous interference with the neurosteroid metabolism might be very likely for the patients. Further studies should be carried out to clarify the uncertainties and to define the potential dangers for the patients.

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Keywords: 5-Aminosalicylic acid (5-ASA), Cytochrome P4502D6, Metabolism, Drug metabolizing enzymes, Drug Interactions.