Cytochrome P450 1A2 is the most important enzyme for hepatic metabolism of the metamizole metabolite 4-methylaminoantipyrine.

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 4627070
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Year 2022
Title Cytochrome P450 1A2 is the most important enzyme for hepatic metabolism of the metamizole metabolite 4-methylaminoantipyrine.
Journal British journal of clinical pharmacology
Volume 88(4)
Pages / **Article-Number** 1885-1896
Keywords 4-formylaminoantipyrine; 4-methylaminantipyrine; CYP1A2; CYP2C19; metamizole
Metamizole (dipyrone) is a prodrug not detectable in serum or urine after oral ingestion. The primary metabolite, 4-methylaminoantipyrine (4-MAA), can be N-demethylated to 4-aminoantipyrine (4-AA) or oxidized to 4-formylaminoantipyrine (4-FAA) by cytochrome P450 (CYP)-dependent reactions. We aimed to identify the CYPs involved in 4-MAA metabolism and to quantify the effect of CYP inhibition on 4-MAA metabolism.; We investigated the metabolism of 4-MAA in vitro using CYP expressing supersomes and the pharmacokinetics of metamizole in the presence of CYP inhibitors in male subjects.; The experiments in supersomes revealed CYP1A2 as the major CYP for 4-MAA N-demethylation and 4-FAA formation with CYP2C19 and CYP2D6 contributing to N-demethylation. In the clinical study, we investigated the influence of ciprofloxacin (CYP1A2 inhibitor), fluconazole (CYP2C19 inhibitor) and the combination ciprofloxacin/fluconazole on the pharmacokinetics of metamizole in n=12 male subjects in a randomized, placebo-controlled, double-blind study. The geometric mean ratios for the area under the concentration-time curve (AUC; 0-12h;) of 4-MAA after/before treatment were 1.17 (90% CI 1.09-1.25) for fluconazole, 1.51 (90% CI 1.42-1.60) for ciprofloxacin and 1.92 (90% CI 1.81-2.03) for ciprofloxacin/fluconazole. Fluconazole increased the half-life of 4-MAA from 3.22 h by 0.47 h (95% CI 0.13-0.81, $p<0.05$), ciprofloxacin by 0.69 h (95% CI 0.44-0.94, $p<0.001$) and fluconazole/ciprofloxacin by 2.85 h (95% CI 2.48-3.22, $p<0.001$).; CYP1A2 is the major CYP for the conversion of 4-MAA to 4-AA and 4-FAA. The increase in 4-MAA exposure by the inhibition of CYP1A2 and by the combination CYP1A2/CYP2C19 may be relevant for dose-dependent adverse reactions of 4-MAA.

ISSN/ISBN 1365-2125
Full Text on edoc ;
Digital Object Identifier DOI 10.1111/bcp.15108
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/34648192