Manuscript ID : 00001-51433

Source ID : 00000494

Mediterranean Journal of Pharmacy and Pharmaceutical Sciences

Volume 2, Issue 1, March 2022, Pages 1-6, Page Count - 6

ROLE OF HUMAN LIVER MICROSOMES IN IN VITRO METABOLISM OF METAMIZOLE

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Abstract

Metamizole or Novalgin® is a widely used well tolerated analgesic drug which is however compromised by agranulocytosis as adverse effect. Subsequent to nonenzymatic hydrolysis, the primary metabolic step is N-demethylation of 4-methylaminoantipyrine (4-MAA) to 4-aminoantipyrine (4-AA). The aim of the present study was to identify the human cytochrome P-450 enzyme (CYP) mediating this reaction. This study identified the relevant CYP using virus expressed isolated human CYP, human liver microsomes and rat liver microsomes with chemical inhibition studies. The substrate of 4-methylaminantipyrine was employed at six different concentrations (25, 50, 100, 400, 800 and 1200 µmol per l) with varying concentrations of selective inhibitors of CYP1A2 (furafylline, fluvoxamine), CYP3A4 (ketoconazole), CYP2A6 (coumarin), CYP2D6 (quinidine), CYP2C19 (omeprazole, fluvoxamine, tranylcypromine), CYP2C9 (sulphaphenazole) and CYP1A1 (alpha-naphthoflavone). 4-MAA and 4-AA were analyzed by HPLC and enzyme kinetic parameters (K_m and V_max) were determined by regression (Sigma plot 9.0). The Ndemethylation of 4-MAA by microsomes prepared from baculovirus expressing human CYP was pronounced with CYP2C19. Intrinsic clearance of the most active enzymes were 0.092, 0.027 and 0.026 for the CYP enzymes 2C19, 2D6 and 1A2, respectively. Metabolism by human liver microsomes was strongly inhibited by fluvoxamin, omeprazole and tranylcypromine (IC_{50} of 0.07, 0.07 and 0.18, respectively) but with coumarin, sulphaphenazole, ketoconazole, moclobemid, quinidine alpha-naphthoflavone and furafylline were 0.79, 1.20, 1.36, 1.44, 3.46, 4.68 and 8.41, respectively. The enzyme CYP2C19 apparently has an important role in Ndemethylation of 4-methylaminoantipyrine which should be further analyzed in clinical studies and which may also be interesting concerning the agranulocytosis.

Author Keywords

4-aminoantipyrine (4AA), 4-methylaminoantipyrine (4-MAA), human CYP2C19, metabolism, metamizole

ISSN Print:
Source Type: Journals
Publication Language: English
Abbreviated Journal Title: MJPPS
Publisher Name: Libyan Association for Pharmacists
Major Subject: Life Sciences

Subject area: Pharmacology

ISSN Online: 2789-1895
Document Type: Journal Article
DOI:
Access Type: Open Access
Resource Licence: CC BY-NC
Subject Area classification: Pharmacology, Toxicology and Pharmaceutics
Source: SCOPEDATABASE