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论文

抗焦虑新药AF-5及其代谢物在人肝微粒体体外温孵体系中代谢研究

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摘要:

目的研究一类抗焦虑新药AF-5及其代谢物(I,II)在人肝微粒体体外温孵体系中代谢情况.方法自制人肝微粒体,用Lowry法测定酶活性为8.79mg·mL^{-1}.以此配制人肝微粒体体外温孵体系,加入药物,温孵后,提取分离,GC-MS测定.结果鉴定了AF-5在人肝微粒体体外温孵体系中的两个主要代谢物,并阐明了其体外代谢途径为AF-5的4位首先氧化为羟基,然后氧化成羰基.结论AF-5在体外人肝微粒体温孵体系中,100min后完全代谢成羟基代谢物I及羰基代谢物II,以羟基代谢物为主要代谢产物.AF-5代谢物I在人肝微粒体温孵体系中,可转化为代谢物II,而代谢物II在人肝中则不再代谢.

关键词: 抗焦虑药 AF-5 人肝微粒体

IN VITRO METABOLIC STUDIES OF THE NOVEL ANTI-ANXIETIC DRUG AF-5 AND ITS METABOLITES IN HUMAN LIVER MICROSOME INCUBATION SYSTEM

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Abstract:

AIM To study the metabolism of a novel anti-anxietic drug AF-5 and its metabolites (I,II) in human liver microsome incubation system. METHODS Human liver microsomes were prepared, the enzyme activity was determined to be 8.79 mg·mL^{-1} by Lowry′s method. The human liver microsome incubation system consisted of: human liver microsomes 2 mg·mL^{-1} , glucose-6-phosphate (G-6-P) 0.01 mmol·mL^{-1} , glucose-6-phosphate dehydrogenase (G-6-PDH) 1 U·mL^{-1}, magnesium chloride ($MgCl_2$) 4.0 μmol·mL^{-1} , coenzyme II in oxidized form (NADP) 0.5 μmol·mL^{-1} , and coenzyme I in reduced form (NADH) 1.0 μmol·mL^{-1} . Two milligrams of AF-5 solubilized by Tween 80 was then added,the mixture was diluted to 5 mL with Tris-HCl solution and the mixture was incubated in a 37℃ water bath with shaking. Oxygen was passed over the liquid surface for 0.5 min every 20 minutes. The incubation was carried out for 40 min and 100 min respectively. Three volumes of ethyl ether were added to stop the metabolism,and more ethyl ether was used to extract the metabolites for 3 times. The ether extracts were pooled together,dried with anhydrous sodium sulfate, then evaporated to dryness. The residue was dissolved in 0.5 mL n-hexane and analyzed by GC/MS under the following conditions: 150℃(1 min)7.5℃·min^{-1} 180℃(1 min)2.5℃·min^{-1} 260℃(2 min), in the total ion current mode, EI: 70 eV, interface temperature: 250℃, ion source temperature: 200℃. RESULTS Two major metabolites were found and identified in this incubation system, and demonstrated that the *in vitro* metabolic pathway was that the carbon 4 was first oxidized to hydroxyl group, then further oxidized to a carbonyl group. CONCLUSION In human liver microsome incubation system AF-5 was completely metabolized in 100 min to the hydroxy derivative I and carbonyl derivative II, with hydroxymetabolite as the major metabolite. Metabolite I was further transformed to metabolite II, which was not metabolized any further by the human liver microsomes.

Keywords: AF-5 human liver microsomes GC/MS anti-anxietic drug

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