中国药理学与毒理学杂志 2012 26 (3): 333-339 ISSN: 1000-3002 CN: 11-1115/R

论著

水胺硫磷在大鼠肝微粒体的生物转化和代谢动力学

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收稿日期 2012-2-3 修回日期 2012-3-20 网络版发布日期 2012-7-19 接受日期

摘要 目的 探讨水胺硫磷在大鼠肝微粒体的体外代谢活化产物及代谢动力学特征。方法 应用液相色谱-四级杆-飞行时间质谱(LC/QTOF MS)筛查并鉴定水胺硫磷在大鼠肝微粒体孵育液中的氧化产物。用乙酰胆碱酯酶抑制法考察水胺硫磷及其氧化产物水胺氧磷的抑酶活性。应用液相色谱-三重四级杆串联质谱(LC/Triple-Q MS/MS)定量检测肝微粒体中的水胺硫磷及其代谢产物水胺氧磷，研究水胺硫磷及其产物的消长动力学和氧化产物生成的酶动力学。结果 筛查并鉴定了水胺硫磷在大鼠肝微粒体的氧化脱硫产物水胺氧磷。水胺氧磷对乙酰胆碱酯酶的抑制活性远高于水胺硫磷，IC_{50}值比水胺硫磷低4个数量级，表明水胺硫磷的氧化脱硫反应是一个代谢活化过程。水胺硫磷在大鼠肝微粒体中的半衰期($t_{1/2}$)为14.6 min，外推得到体内肝清除率Cl_H为43.8 ml·min^{-1}·kg^{-1}。水胺氧磷的生成符合双相酶动力学模型，$K_{m,app1}$为1.12 μmol·L^{-1}，产物生产最大速率(V_{max1})为0.43 μmol·min^{-1}·g^{-1}；蛋白$K_{m,app2}$为67.92 μmol·L^{-1}，V_{max2}为1.28 μmol·min^{-1}·g^{-1}蛋白。结论 水胺硫磷在大鼠肝微粒体中能快速代谢消除，生成抑酶活性更高的产物水胺氧磷而产生毒性。

关键词 有机磷化合物 水胺硫磷 水胺氧磷 代谢 药代动力学 毒性作用

分类号 R969.1

Biotransformation and kinetics of isocarbophos in liver microsomes of rats *in vitro*

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Abstract

OBJECTIVE To investigate the metabolic activated metabolites and the kinetic characteristics of isocarbophos in rat microsomes *in vitro*. **METHOD** Metabolites of isocarbophos were screened and identified by liquid chromatography-quadrupole-time of flight mass spectrometry (LC/Q TOF MS) in rat liver microsomes. The toxicity of isocarbophos and its metabolite was assessed by the acetylcholinesterase inhibition assay. The quantification analysis of isocarbophos and its metabolite was made using a liquid chromatography-triple quadrupole tandem mass spectrometry (LC/Triple-Q MS/MS) method to investigate the metabolic kinetics of the isocarbophos and its oxidative metabolite. **RESULTS** Isocarbophos was rapidly eliminated in rat liver microsomes, and its $t_{1/2}$ was14.6 min and the extrapolated Cl_H was 43.8 ml·min^{-1}·kg^{-1}. The major oxidative metabolite identified in incubates was its desulfuration metabolite isocarbophos oxon. The enzyme inhibition activity of the metabolite was much higher than that of isocarbophos and its IC_{50} was found to be four orders of magnitude lower than the parent, which indicated that the biotransformation of isocarbophos to isocarbophos oxon was a metabolic activation process. The kinetic curve of desulfuration to form isocarbophos oxon was biphasic, and the parameters obtained were $K_{m,app1}$ 1.12 μmol·L^{-1}, V_{max1} 0.43 μmol·min^{-1}·g^{-1} protein, $K_{m,app2}$ 67.92 μmol·L^{-1} and V_{max2} 1.28 μmol·min^{-1}·g^{-1} protein. **CONCLUSION** Isocarbophos can be metabolically activated by rat hepatic microsomes to form isocarbophos oxon. Like other phosphorothioates, the metabolic activation of isocarbophos may contribute significantly to its toxicity in bodies.

Key words organophosphorus compounds isocarbophos isocarbophos oxon metabolism pharmacokinetics toxicity

DOI: 10.3867/j.issn.1000-3002.2012.03.014

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