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论著

济泰片对人肝及Beagle犬肝中美沙酮代谢活性的影响

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摘要 目的 评价济泰片对人肝中美沙酮代谢活性潜在的抑制作用及对Beagle犬肝中美沙酮代谢活性潜在的诱导作用。方法 在人肝微粒体中加入济泰片1.5~150 mg·L^{-1}, CYP3A4抑制剂酮康唑及CYP2D6抑制剂奎尼丁, 再加入美沙酮进行共孵育30 min。用美沙酮的代谢产物2-亚乙基-1, 5-二甲基-3, 3-二苯基吡咯烷(EDDP)的生成速率反映美沙酮的代谢活性, 评价济泰片对美沙酮的抑制作用。Beagle犬ig给予济泰片0.1875, 0.625和1.875 g·kg^{-1}, 每天1次, 共36周后制备犬肝微粒体, 在制备的犬肝微粒体中加入美沙酮进行共孵育30 min, 检测济泰片组美沙酮的代谢产物EDDP的生成速率。结果 阳性抑制剂酮康唑、奎尼丁能显著抑制人肝微粒体中的美沙酮代谢, 而济泰片未见明显抑制作用。济泰片1.875 g·kg^{-1}组Beagle犬肝微粒体中美沙酮去甲基化反应的反应速率、代谢能力及单位体质量代谢能力均显著高于正常对照组, 分别为0.86±0.17 *vs* (0.49±0.10)cps·min^{-1}·mg^{-1}蛋白, 228±62 *vs* (115±13)cps·min^{-1}·mg^{-1}蛋白, 10.6±0.8 *vs* (24.4±5.6)cps·min^{-1}·mg^{-1}蛋白·g^{-1}(P<0.05)。结论 济泰片对人肝中美沙酮的代谢不会产生抑制作用。济泰片对Beagle犬肝中美沙酮代谢具有一定的诱导作用。

关键词 济泰片 美沙酮 药物相互作用 细胞色素P450酶系统

分类号 R969.2

Effect of Jitai tablets on metabolic activity of methadone in human and Beagle dog livers

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Abstract

OBJECTIVE To evaluate metabolic inhibition potential of Jitai tablet (JTP) on methadone in human liver and induction potential in Beagle dog liver for predicting drug-drug interactions while coadministrating. **METHODS** JTP 1.5-150 mg·L^{-1}, positive inhibitors of CYP3A4 ketoconazole and positive inhibitor of CYP2D6 quinidine were added into human liver microsome (HLM) incubation system with methadone for coincubation. Formation rate of EDDP (a metabolite of methadone) indicated metabolic activity on methadone for inhibition evaluation. After Beagle dogs were administered by JTP 0, 0.1875, 0.625 and 1.875 g·kg^{-1} for 36 weeks, dog liver microsome (DLM) was prepared. Methadone was added in DLM incubation system. EDDP formation rate and metabolic ability in JTP groups were determined for induction evaluation of JTP on methadone. **RESULTS** Significant inhibitory effect on methadone demethylation was found in ketoconazole, quinidine, and ketoconazole+quinidine groups, but there was no inhibitory effect in JTP group. The metabolic rate, metabolic ability and metabolic ability per body mass of methadone demethylation in JTP 1.875 g·kg^{-1} group were greater than those in normal control group, and were 0.86±0.17 *vs* (0.49±0.10)cps·min^{-1}·mg^{-1} protein, 228±62 *vs* (115±13)cps·min^{-1}·mg^{-1} protein, 10.6±0.8 *vs* (24.4±5.6) cps·min^{-1}·mg^{-1} protein·g^{-1}, respectively(P<0.05). **CONCLUSION** JTP has no inhibitory effect on