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论文

MN9202在Beagle犬肝微粒体酶中的代谢动力学

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摘要：

目的研究MN9202在Beagle犬肝微粒体酶中的代谢。方法差速离心法制备Beagle犬肝微粒体酶，0.4 μmol·L^{-1}的MN9202与1.0 g·L^{-1}的肝微粒体酶在37 ℃水浴中孵育30 min，加入0.5 mL碱化液终止反应，然后采用RP-HPLC法测定孵育液中MN9202原形药物的浓度。根据所测浓度与反应速度做Lineweave-Brurk双倒数曲线，推导出药物的米氏常数K_m和最大反应速度V_{max},并计算机体内在清除率。同时观察不同浓度和不同种类的人肝微粒体酶(CYP450)抑制剂对MN9202代谢的影响。结果MN9202在Beagle犬肝微粒体酶中的K_m为(22.6±8.0) μmol·L^{-1}；V_{max}为(0.54±0.17) μmol·g^{-1}·min^{-1}；CL_{int}为(0.024 2±0.000 9) L·g^{-1}·min^{-1}。醋竹桃霉素(Tro)和酮康唑(Ket)能够显著抑制MN9202的代谢；反苯环丙胺(Tra)对MN9202的代谢也有一定的抑制作用，而其他CYP450抑制剂对MN9202的代谢无明显影响。结论CYP3A和CYP2C19参与了MN9202的代谢，人CYP3A和CYP2C19的抑制剂可能使MN9202的代谢受到抑制，造成药物的药效或毒性的增加。

关键词： 1,4-二氢-2,6-二甲基-4-(3′-硝基苯基)-3,5-吡啶二甲酸甲戊酯 代谢 肝微粒体酶 高效液相色谱法

Metabolic kinetics of MN9202 in Beagle dog liver microsomes

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Abstract:

AimTo study the metabolic kinetics of MN9202 in Beagle dog liver microsome. MethodsBeagle dog liver microsomes were prepared by using ultracentrifuge method. After incubating 0.4 μmol·L^{-1} MN9202 with 1 g·L^{-1} microsomes for 30 min at 37 ℃, the reaction was terminated by adding 0.5 mL alkalization. The RP-HPLC was used to determine the drug in the incubation mixture. The Michaelis-Menten parameters K_m and V_{max} in Beagle dog liver microsomes were initially estimated by analyzing Lineweave-Brurk plot. Various selective CYP inhibitors were used to investigate their inhibitory effect on the metabolism of MN9202. ResultsThe K_m, V_{max} and CL_{int} of MN9202 were (22.6±8.0) μmol·L^{-1}, (0.54±0.17) μmol·g^{-1}·min^{-1} and (0.024 2±0.000 9) L·g^{-1}·min^{-1}, respectively. The metabolism of MN9202 was significantly inhibited by ketoconazole (Ket) and troleandomycin (Tro) in Beagle dog liver microsomes. Tranylcypromine (Tra) could inhibit the metabolism of drug as well. While other inhibitors showed little inhibitory effect on the metabolism of MN9202. ConclusionIt was shown that CYP3A and CYP2C19 were involved in MN9202 metabolism. The inhibitors of human CYP3A and CYP2C19 may have potential interaction with MN9202, and this can reduce the metabolism rate and increase the toxicity of MN9202.

Keywords: metabolism liver microsomes HPLC 1,4-dihydro-2,6-dimethyl-4-(3′-nitrophenyl)-3,5-pyridinedicarboxylic acid pentyl methyl ester

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