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论文

HPLC/MS法研究左旋黄皮酰胺及其代谢物在Beagle犬血浆中的药代动力学HPLC/MS法研究左旋黄皮酰胺及其代谢物在Beagle犬血浆中的药代动力学

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摘要：

目的用HPLC/MS法研究左旋黄皮酰胺［(-)-clau］及其代谢物6-羟基-黄皮酰胺(6-OH-clau)在Beagle犬血浆中的药代动力学过程。方法Beagle犬灌胃左旋黄皮酰胺30 mg·kg^{-1}，采集静脉血样，血浆经乙酸乙酯萃取分离后，用HPLC/MS选择性正离子检测内标(格列吡嗪，［M+H］$^{+}$，*m/z* 446)法测定左旋黄皮酰胺(［M+H］$^{+}$，*m/z* 298)及6-羟基-黄皮酰胺(［M+H-H_2O］$^{+}$，*m/z* 296)的浓度，以甲醇-水-冰醋酸(60∶40∶0.8)为流动相，流速1.0 mL·min^{-1}。用3P97软件计算药代动力学参数。结果左旋黄皮酰胺和6-羟基-黄皮酰胺分别在1.0～200 ng·mL^{-1}和0.2～40.0 ng·mL^{-1}线性关系良好(r>0.999)，萃取回收率均大于85%。原药及其代谢物的体内过程均符合二室模型；左旋黄皮酰胺及6-羟基-黄皮酰胺的C_{max}分别为(21±10) ng·mL^{-1}和(3.9±2.2) ng·mL^{-1}；T_{max}分别为(0.8±0.5) h和(1.3±0.5) h；$T_{1/2}\alpha$分别为(0.9±0.6) h和(1.4±0.6) h；$T_{1/2}\beta$分别为(19±23) h和(13±12) h；$AUC_{0-24\ h}$分别为(69±14) h·ng·mL^{-1}和(12±7) h·ng·mL^{-1}。结论Beagle犬灌胃左旋黄皮酰胺后迅速吸收，血药浓度一相消除很快，但末端消除较慢；其代谢物6-羟基-黄皮酰胺血药浓度经时过程与左旋黄皮酰胺相似，但血药浓度相对较小。

关键词： 左旋黄皮酰胺 6-羟基-黄皮酰胺 药代动力学 高效液相色谱/质谱法

Pharmacokinetics of (-)-clausenamide and its major metabolite 6-hydroxyl-clausenamide in Beagle dogs by HPLC/MS

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Abstract:

AimTo establish a sensitive and accurate method to study the pharmacokinetics of (-)-clausenamide ［(-)-clau］ and its major metabolite 6-hydroxyl-clausenamide (6-OH-clau) in the plasma of the Beagle dog. Methods(-)-Clau was orally administered to six Beagle dogs at the dose of 30 mg·kg^{-1}, venous blood from front leg was sampled and plasma was separated for analysis. After extraction with ethyl acetate, the plasma samples were analyzed by HPLC/MS and the mobile phase was a mixture of methanol-water-acetic acid (60∶40∶0.8) at the flow rate of 1.0 mL·min^{-1}. The API-ES positive ion SIM detection was carried out for the detection of both (-)-clau (［M+H］$^{+}$, *m/z* 298) and 6-OH-clau (［M+H-H_2O］$^{+}$, *m/z* 296) with glipzide (glip) (［M+H］$^{+}$, *m/z* 446) as internal standard. The pharmacokinetic parameters were calculated by 3P97 software. ResultsThere was good linear relationship (r>0.999) between the SIM responses and the concentrations for (-)-clau and 6-OH-clau at the range from 1.0 to 200 ng·mL^{-1} and 0.2 to 40.0 ng·mL^{-1}, respectively. The absolute recovery was greater than 85%. The plasma concentration-time curves of (-)-clau and 6-OH-clau were both best fitted to a two-compartment model. The C_{max} of (-)-clau and 6-OH-clau were (21±10) ng·mL^{-1} and (3.9±2.2) ng·mL^{-1}, T_{max} were (0.8±0.5) h and (1.3±0.5) h, $T_{1/2}\alpha$ were (0.9±0.6) h and (1.4±0.6) h, $T_{1/2}\beta$ were (19±23) h and (13±12) h, $AUC_{0-24\ h}$ were (69±14) h·ng·mL^{-1} and (12±7) h·ng·mL^{-1} respectively. ConclusionThe established HPLC/MS method was sensitive and specific for the determination of (-)-clau. It was shown that the absorption and first phase elimination of (-)-clau were very quick in Beagle dogs, but the terminal elimination was very slow. The plasma concentration profile of its major metabolite 6-OH-clau was similar to (-)-clau and the AUC was relatively small in comparison with (-)-clau.

Keywords: 6-hydroxyl-clausenamide pharmacokinetics HPLC/MS (-)-clausenamide

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