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论著

9-［2-(膦酰甲氧基)乙基］腺嘌呤一钠盐在比格犬体内的毒代动力学和毒理学研究

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摘要 目的 为9-［2-(膦酰甲氧基)乙基］腺嘌呤一钠盐（PMEA-Na）重复给药的毒性研究提供毒代动力学资料。方法 采用液相色谱质谱联用方法测定样品中的药物浓度，数据经统计矩方法处理得到毒代动力学参数，并完成血清生化学及组织病理学检测。结果 比格(Beagle)犬静脉单次及多次给药（14 d，每日1次）后，在给药剂量范围内，AUC均表现为剂量依赖性。在1.0，3.0 与6.0 mg·kg^{-1} PMEA-Na时，AUC分别为（2.3±0.5），（8.4±1.6），（17.5±3.7）mg·L^{-1}·h(单剂量)和（5.0±0.4），（15.9±3.2），(30.3±4.7) mg·L^{-1}·h（多剂量）。PMEA-Na主要经肾脏排出体外，且给药14 d后肾功能受损药物排泄能力降低。与对照组比较，6.0 mg·kg^{-1}组血清生化学检测指标丙氨酸氨基转换酶、总胆红素、尿素氮、肌酐及甘油三酯均升高，葡萄糖水平下降。6.0 mg·kg^{-1}组的组织病理学检查发现肝脏和肾脏有明显的病理形态学改变。结论 比格犬经静脉多次给PMEA-Na 14 d后出现毒性反应，毒性靶器官主要为肾脏和肝脏。

关键词 9-［2-(膦酰甲氧基)乙基］腺嘌呤一钠盐 毒代动力学 病理学

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Toxicokinetics and toxicological studies of sodium 9-［2-(phosphonomethoxy) ethyl］ adenine in beagle dogs

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Abstract

AIM To provide toxicokinetics data for toxicity studies of repeated doses of sodium 9-［2-(phosphonomethoxy)ethyl］adenine (PMEA-Na). **METHODS** The concentrations of PMEA-Na in plasma and urine were determined by HPLC/MS/MS method after single and multiple iv administrations in dogs. Data were executed by the statistical moment method to acquire the toxicokinetics parameters. Serum biochemical tests and histopathological examination were performed. **RESULTS** The system exposure of PMEA-Na in dogs was dose-dependent over the dose range of 1.0-6.0 mg·kg^{-1}. The areas under the plasma concentration-time curve of PMEA-Na after single and multiple iv administrations at 1.0, 3.0 and 6.0 mg·kg^{-1} dosage were (2.3±0.5), (8.4±1.6), (17.5±3.7) and (5.0±0.4), (15.9±3.2), (30.3±4.7)mg·L^{-1}·h, respectively. The urinary excretion of PMEA-Na in 72 h after iv administration was (87.0±4.8)% at the dose of 3.0 mg·kg^{-1}. In 6.0 mg·kg^{-1} dose group, liver enzyme activity of glutamic-pyruvic transaminase and serum levels of total bilirubin, blood urea nitrogen, creatinine and triglycerides were all significantly elevated; glucose level significantly decreased comparing with the control group. Histopathological observation showed distinct pathological changes in liver and kidney tissues of 6.0 mg·kg^{-1} dose group. **CONCLUSION** There was evidence of toxicity after repeated-dose (14 d) of PMEA-Na in dogs and the major toxicity target organs were the kidney and liver.

Key words sodium 9-［2- (phosphonomethoxy)ethyl］ adenine toxicokinetics pathology

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