

论文

灯盏乙素酯类前药的合成、理化性质及降解研究

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摘要:

目的对口服难吸收中药活性成分灯盏乙素进行结构改造,为寻找和设计合理前药及其剂型提供依据。方法通过先成盐后酯化的方法合成灯盏乙素乙酯、苄酯并改进文献方法合成羟乙酰胺酯,用质谱和氢谱确证结构。研究3种前药在不同pH水溶液中的稳定性、溶解度、分配系数和在入血浆中的降解。制备灯盏乙素羟乙酰胺酯环糊精包合物和乳剂,比较包合物和乳剂在肠液中对前药的保护作用,考察该前药在不同肠段黏膜匀浆中的降解情况。结果合成的3种前药经确证为目标物;灯盏乙素羟乙酰胺酯在缓冲液(pH 4.2)和水中的溶解度比灯盏乙素分别提高近10倍和35倍,分配系数也由原来的-2.56提高到1.48;该酯水溶液的稳定性较好( $t_{1/2} \approx 16$  d, pH 4.2),在入血浆的半衰期最短( $t_{1/2} \approx 7$  min),但在肠黏膜匀浆中的降解可能影响酯的吸收,不同肠段黏膜匀浆降解羟乙酰胺酯的次序为:十二指肠>回肠>空肠>结肠。乳剂在肠黏膜匀浆中对前药有显著的保护作用,包合物次之。结论与灯盏乙素乙酯和苄酯比较,羟乙酰胺酯的理化性质较好,但其在肠道中的稳定性有待提高,可以选择乳剂或结肠定位给药减少前药的降解。

关键词: 灯盏乙素 前药 合成 羟乙酰胺酯 理化性质 小肠降解 乳剂 包合物

Ester prodrug of scutellarin: synthesis, physicochemical property and degradation

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Abstract:

Aim To establish the fundamentals for the design of scutellarin prodrug and formulation with feasible physicochemical and biopharmaceutical properties by esterifying scutellarin, an active component with poor absorption extracted from *Erigeron breviscapus* of Chinese medicine. Methods With the method of salifying followed by esterifying, ethyl and benzyl ester of scutellarin were synthesized. Glycolamide ester of scutellarin was also synthesized with an improved method. Their structures were confirmed by MS and <sup>1</sup>H NMR. The solubility and partition coefficient of the prodrugs were determined and their degradations were investigated in various buffers and in human plasma. The emulsion and cyclodextrin complex of glycolamide ester were prepared and the protection of the ester from degradation was compared in the intestinal tract contents. Furthermore, the degradation of glycolamide ester in the homogenates of various intestinal segments was studied. Results Three prodrugs were synthesized successfully and their structures were confirmed. Glycolamide ester of scutellarin showed better stability in the aqueous solution ( $t_{1/2} \approx 16$  d, pH 4.2) and the shortest half-life in the human serum ( $t_{1/2} \approx 7$  min). Compared with scutellarin, the solubility of glycolamide ester was increased about ten times in pH 4.0 buffer, and about thirty five times in water. Partition coefficient of the glycolamide ester increased significantly from -2.56 to 1.48. However, the ester degradation in the homogenates of intestinal mucus would be an obstacle for its absorption. The degradation rates were in the order duodenum>ileum>jejunum>colon. The emulsion showed a better protection of glycolamide ester from the degradation than cyclodextrin complex. Conclusion Glycolamide ester of scutellarin shows better physicochemical properties than ethyl and benzyl eater of scutellarin, but its stability in intestinal tract needs to be improved. The emulsion or / and colon-targeted delivery may be selected as one of strategies to decrease the presystemic degradation.

Keywords: prodrug synthesis glycolamide ester physicochemical property intestinal degradation emulsion cyclodextrin complex scutellarin

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1. 曲峻;王义明;罗国安;吴筑平.LC/MS/MS的多反应监测方法定量测定灯盏乙素[J]. 药学学报, 2000,35(2): 139-141
2. 刘奕明;林爱华;陈汇;曾繁典.灯盏乙素在兔体内药代动力学[J]. 药学学报, 2003,38(10): 775-778
3. 张海燕;平其能;郭健新;操锋.灯盏花素及其 $\beta$ -环糊精包合物在大鼠体内的药代动力学[J]. 药学学报, 2005,40(6): 563-567
4. 高慧敏;王智民;田娟.灯盏花素在正常和模型大鼠中的药代动力学及代谢物研究[J]. 药学学报, 2005,40(11): 1024-1027
5. 吕文莉;郭健新;平其能;李锦;赵雏微;张兰.注射用灯盏花素脂质体在Beagle犬体内的药代动力学[J]. 药学学报, 2006,41(1): 24-29

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