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论文

单链尿激酶型纤溶酶原激活剂在兔及猕猴中的生物转化和药代动力学

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摘要：

目的：研究重组单链尿激酶型纤溶酶原激活剂(rh-sc-uPA)单链和代谢物双链(tc-uPA)的药代动力学和转化。方法：^{125}I标记结合生化反应及RP-HPLC测定血浆^{125}I-sc-uPA和^{125}I-tc-uPA浓度；平板溶圈法测定血浆溶纤组分浓度。结果：兔iv ^{125}I-sc-uPA后单链呈双指数消除，$T_{1/2\alpha}$和$T_{1/2\beta}$分别为7和43 min，双链呈单指数消除$T_{1/2}$=9 min，约有38%单链转化为双链。猕猴静脉推注不同剂量rh-sc-uPA后血浆纤溶组分浓度呈单指数下降，T1/2分别为(6.3±1.8) min, (11.5±2.1) min和(12.3±2.9) min，CLS随剂量变慢。推注n-tc-uPA $T_{1/2}$=(13.7±2.7) min。结论：兔iv ^{125}I-sc-uPA后可检测到^{125}I-rh-sc-uPA与^{125}I-tc-uPA。猕猴iv rh-sc-uPA后血浆溶纤组分浓度呈非线性变化。

关键词： 单链尿激酶 双链尿激酶 反相高效液相色谱 ^{125}I标记 药代动力学 溶纤活性

BIO-TRANSFORMATION AND PHARMACOKINETICS OF SINGLE CHAIN UROKINASE-TYPE PLASMINOGEN ACTIVATOR IN RABBITS AND RHESUS MONKEYS

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Abstract:

AIM: The concentration profiles of recombinant human single chain urokinase-type plasminogen activator (rh-sc-uPA) and bio-transformation to two-chain metabolite (tc-uPA) were studied after iv bolus injection of ^{125}I-rh-sc-uPA in rabbits. Fibrinolytic components-time curves in plasma were determined after iv bolus injection at different doses of rh-sc-uPA in rhesus monkeys and were compared with natural urokinase (n-tc-uPA). METHODS: Aprotinin was added into plasma immediately after sampling for preventing the conversion of single-chain to two-chain. Plasma ^{125}I-sc-uPA concentrations was determined by RP-HPLC of dithiothreitol (DTT) treated plasma, while concentrations of ^{125}I-sc-uPA+^{125}I-tc-uPA was obtained by analysis of untreated DTT plasma. Concentration of fibrinolytic components was assayed by fibrin plate method *in vitro*. RESULTS: The ^{125}I-sc-uPA and ^{125}I-tc-uPA were both detected after iv bolus injection of in rabbits. The ^{125}I-sc-uPA concentrations were best fit by a two-compartment model with $T_{1/2\alpha}$ and $T_{1/2\beta}$ equaled to 7 and 43 min, respectively. ^{125}I-tc-uPA concentrations were best fit by a one-compartment model with elimination $T_{1/2}$ of 9 min. Nearly 38% of ^{125}I-sc-uPA transformed to ^{125}I-tc-uPA. Concentration of fibrinolytic components decreased rapidly after iv bolus injection of 7.5×10^4, 1.5×10^5, and 3.0×10^5 U.kg^{-1} rh-sc-uPA in rhesus Monkeys. Elimination $T_{1/2}$ were 6.3±1.8, 11.5±2.1 and 12.3±2.9 min, respectively (P<0.05～P<0.01). Systemic clearance were 0.051±0.030, 0.022±0.006 and 0.016±0.003 L.min^{-1}.kg^{-1}, respectively (P<0.05). Concentration of fibrinolytic components after 1.5×105 U.kg^{-1} of rh-sc-uPA was significantly lower than that after n-tc-uPA. CONCLUSION: ^{125}I-rh-sc-uPA and its active metabolite-^{125}I-rh-tc-uPA were detected after iv of ^{125}I-rh-sc-uPA in rabbits, their pharmacokinetic behaviors were different. Deposition profiles of fibrinolytic components after iv of various doses of rh-sc-uPA in monkeys follows non-linear pharmcokinetics.

Keywords: two chain urokinase type plasminogen activator RP-HPLC ^{125}I-radiolabeling pharmacokinetics fibrinolytic activity single chain urokinase-type plasminogen activator

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