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论著

# 重组人肿瘤坏死因子相关凋亡诱导配体的药代动力学和组织分布

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摘要 目的 研究重组人肿瘤坏死因子相关凋亡诱导配体（rhTRAIL）的药代动力学和组织分布。方法 恒河猴单次静脉滴注rhTRAIL 1，5和25 mg·kg$^{-1}$及iv 5 mg·kg$^{-1}$后，采用酶联免疫吸附法（ELISA）测定rhTRAIL在恒河猴体内的血药浓度，并采用放射性核素示踪技术结合三氯乙酸（TCA）沉淀和分子排阻高效液相色谱法测定［$^{125}$I］rhTRAIL在荷瘤裸鼠组织内的含量。结果 恒河猴单次静脉滴注rhTRAIL 1，5和25 mg·kg$^{-1}$后，各剂量组的药代参数除$c_{max}$和AUC以外，均无显著差异，表现出线性动力学性质。恒河猴每天给药1次，连续7 d，药物在体内没有蓄积。恒河猴静脉滴注和iv给药对药物的体内清除过程无明显影响。［$^{125}$I］标记rhTRAIL后的放化纯度大于98%。荷瘤裸鼠iv给予［$^{125}$I］rhTRAIL后，在各组织广泛分布，总放射性在肿瘤组织中于给药后2 h达到高峰，在其他大部分组织中于给药后10 min达高峰。给药后10 min及2，8和24 h，肿瘤/血清的酸沉放射性比值分别为0.07±0.01，0.62±0.17，0.78±0.57和1.66±0.50；给药后24 h，肿瘤组织的放射性浓度高于其他组织和血清。结论 在研究剂量范围内，rhTRAIL在恒河猴体内表现为线性动力学。［$^{125}$I］rhTRAIL给药后在荷瘤裸鼠中广泛分布，在肿瘤组织中分布浓度较高，并主要经肾脏排泄。

关键词 TNF凋亡诱导配体 药代动力学 组织分布

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# Pharmacokinetics and tissue distribution of recombinant human tumor necrosis factor-related apoptosis-inducing ligand

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**Abstract**

**OBJECTIVE** To investigate the pharmacokinetics and tissue distribution of recombinant human TNF-related apoptosis-inducing ligand (rhTRAIL). **METHODS** *Macaca mulatta* was given rhTRAIL 1, 5 and 25 mg·kg$^{-1}$ by intravenous drip or iv 5 mg·kg$^{-1}$, and enzyme-linked immunosorbent assay (ELISA) was used to investigate the pharmacokinetics of rhTRAIL. Radioisotopic tracing method combined with trichloroacetic acid (TCA) precipitation and high performance liquid chromatography method was used to determine tissue distribution of ［$^{125}$I］rhTRAIL in tumor-bearing nude mice. **RESULTS** After *M.mulatta* was given rhTRAIL 1, 5 and 25 mg·kg$^{-1}$ by intravenous drip, there was no statistically significant difference between different groups in parameters except AUC and $c_{max}$. rhTRAIL complied with linear kinetics among 1-25 mg·kg$^{-1}$. Besides, there was no accumulation tendency after *M. mulatta* was given rhTRAIL 5 mg·kg$^{-1}$ once daily by intravenous drip for successive 7 d. As for the elimination process of rhTRAIL, there was no significant differences in pharmacokinetic parameters between iv administration and intravenous drip in *M. mulatta*. The purity of ［$^{125}$I］rhTRAIL was above 98%. ［$^{125}$I］rhTRAIL was distributed widely in the tissue of tumor-bearing nude mice after iv administration. Total radioactivity in the tumor reached the maximum at 2 h after administration while other tissues arrived at 10 min. At 10 min, 2, 8 and 24 h after administration, the TCA-precipitable radioactivity ratio of tumor to serum was 0.07±0.01, 0.63±0.17, 0.78±0.57, and 1.66±0.50, respectively. TCA-precipitable radioactivity of the tumor was higher than that of other tissues and serum at 24 h after administration. **CONCLUSION** rhTRAIL appears as linear kinetics among rhTRAIL 1-25 mg·kg$^{-1}$ in *M. mulatta*. ［$^{125}$I］rhTRAIL is distributed widely in tissues of tumor-bearing nude mice after iv administration. ［$^{125}$I］rhTRAIL can reach a high concentration in the intended target tumor tissue and is eliminated primarily through the kidneys.

**Key words** TNF-related apoptosis-inducing ligand pharmacokinetics tissue distribution

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