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奥替拉西钾血药和尿药浓度的测定及其药代动力学和药物蓄积性评价

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中文摘要:本实验建立了人血浆及尿液中奥替拉西钾（potassium oxonate，Oxo）的LC-MS/MS测定方法，研究单次及多次给药替吉奥胶囊（S-1）后，Oxo在晚期胃癌患者体内的药代动力学特征，并评价多次给药后Oxo在人体内的药物蓄积情况。12名晚期胃癌患者分别按体表面积（BSA）口服S-1：单次给药，受试者于早餐后给药60 mg；多次给药，连续28d，每天2次，于早餐后给药60mg；晚餐后给药60 mg（BSA≥1.5m ^{2}）或40 mg（1.25m ^{2} 2）。采用LC-MS/MS法分别测定血浆及尿液中Oxo药物浓度，计算其药代动力学参数，评价其药代动力学特征和药物蓄积现象。血浆及尿液中Oxo测定的线性范围为分别为2~400 ng/mL，0.02~10 μg/mL。单次给药后 c_{max}为（110.5±100.8）ng/mL，$t_{1/2}$为（3.4±1.4）h，t_{max}为（2.2 ±0.7）h，36 h内有（1.7±1.2）%的Oxo以原型方式从尿中排出；多次给药后，稳态平均血药浓度$c_{ss\text{-}av}$为（36.89±29.35）ng/mL，稳态血药浓度波动度(DF)为2.4±0.8，经统计分析，多次给药28 d后Oxo在胃癌患者体内药代动力学特征与单次给药相比并未发生变化，多次给药后未产生药物蓄积现象。与文献数据对照，Oxo在中国晚期胃癌患者与国外患者体内的药代动力学参数基本一致。

中文关键词:奥替拉西钾 药代动力学 药物蓄积评价 固相萃取 LC-MS/MS 替吉奥胶囊

Determination of potassium oxonate in human plasma and urine and its pharmacokinetics and accumulation evaluation in human

Abstract: An LC-MS/MS method was established for the determination of potassium oxonate (Oxo) in human plasma and urine,the pharmacokinetics of Oxo was investigated in advanced gastric cancer patients after single and multiple administration of tegafur,gimeracil and oteracil potassium capsule (S-1),and the situation of drug accumulation after multiple administration was evaluated.For multiple administration,12 gastric cancer patients were treated with S-1 according to the body surface area (BSA) as follows:for single administration,patients were treated with 60mg S-1 after breakfast;for 28-day consecutive administration,a dose of 60mg S-1 was treated after breakfast,and the dose of 60mg after supper for BSA≥ 1.5 m ^{2} or 40mg for 1.25m ^{2} 2 respectively.Then the Oxo concentration in human plasma and urine was determined,and the pharmacokinetic characteristics and drug accumulation were evaluated.The calibration curves of Oxo were linear over the concentration ranges of 2-400 ng/mL in plasma and 0.02-10 μg/mL in urine.After single-dose administration of S-1,(1.7±1.2)% of Oxo was excreted in the form of prototype in urine within 36 h.The main pharmacokinetic parameters were as follows:the c_{max} was (110.5±100.8)ng/mL,$t_{1/2}$ was (3.4±1.4)h,t_{max} was(2.2 ±0.7) h,respectively.For the multiple administration,the $c_{ss\text{-}av}$ *and degree of fluctuation (DF) of Oxo were (110.8±108.0) ng/mL and 2.4±0.8,respectively.In the 28-day consecutive regimen,no significant chang in pharmacokinetic characteristics or drug accumulation of Oxo was observed,the safty of that multiple administration of S-1 in clinical application was confirmed.Compared with the data in literatures,the main pharmacokinetic parameters of Oxo in Chinese patients proved to be similar with those in other races.*

keywords:potassium oxonate;pharmacokinetics;accumulation evaluation;solid phase extraction;LC-MS/MS;tegafur gimeracil and oteracil potassium capsule

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