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亚硒酸钠在低硒兔体内的药物动力学

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Pharmacokinetic study of sodium selenite in low-selenium rabbits

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ABSTRACT Sodium selenite has been used for prevention and treatment of Keshan disease and Kaschin-Beck's disease. The efficacious dosage regimens of sodium selenite in low-Se human body have not been clear. A single iv or ig of sodium selenite 2.0 mg/kg was given to rabbits. Selenium in whole blood was determined fluorophotomerically. The concentration-time curve following a single iv of sodium selenite in rabbits was found to be of 3-compartment open model. The pharmacokinetic parameters were: $T_{\frac{1}{2}\alpha}$ 0.11±0.03 h, $T_{\frac{1}{2}\alpha}$ 6.8±2.8 h, $T_{\frac{1}{2}\beta}$ 215±35 h, V_c 0.50±0.07 L/kg, Cl 19±5 ml/(kg·h), AUC 146±26 mg·h/L. The concentration-time curve following a single ig of sodium selenite showed a pattern of 2-compartment open model. The parameters were: $T_{\frac{1}{2}k_a}$ 13±6 h, $T_{\frac{1}{2}\alpha}$ 3.6±1.9 h, $T_{\frac{1}{2}\beta}$ 338±107 h, V_c 2.9±1.3 L/kg, AUC 78±29 mg·h/L, Cl 27±11 ml/(kg·h).

In low-Se rabbits the distribution in body was more rapid and more extensive, and the bioavailability was higher than that in normal-Se rabbits. Therefore, attention should be paid to the different levels of selenium during therapy with sodium selenite.

KEY WORDS selenium; nutrition disorders; pharmacokinetics

提要 低硒粮喂养兔两个月，全血硒从 148 ng/ml 降至 86 ng/ml，iv 或 ig 亚硒酸钠(Na_2SeO_3) 2.0 mg/kg。iv 血药-时曲线符合 3 室开放模型，ig 符合 2 室开放模型，其主要药物动力学参数：iv：$T_{\frac{1}{2}\alpha}$ 0.11 h，$T_{\frac{1}{2}\alpha}$ 6.8 h，$T_{\frac{1}{2}\beta}$ 215 h，V_c 0.5 L/kg，Cl 19 ml/(kg·h)，AUC 146 mg·h/L；ig：$T_{\frac{1}{2}k_a}$ 13 h，$T_{\frac{1}{2}\alpha}$ 3.6 h，$T_{\frac{1}{2}\beta}$ 338 h，V_c 2.9 L/kg，Cl 27 ml/(kg·h)，AUC 78 mg·h/L。

关键词 硒；营养障碍；药物动力学

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亚硒酸钠(Na_2SeO_3)防治克山病[1]和大骨节病[2]，已广泛用于临床。但其合理用药方案尚未解决，为此本室曾先后在正常硒水平的兔和人体内进行了亚硒酸钠的药物动力学研究[3,4]。因高发区接受亚硒酸钠防治的对象均为低硒人群，为探讨亚硒酸钠在低硒状态机体内的动力学行为，本文研究了亚硒酸钠在低硒兔体内的药物动力学。以便为低硒人群临床合理用药提供科学依据。

MATERIALS AND METHODS

大耳兔10只，♀♂各半，体重2.20±SD 0.23 kg，实验开始先用陕西省黄陵县双桥镇产的低硒粮（混合饲料硒含量平均低于13 ppb，其中玉米7.2 ppb，大豆16.2 ppb，小麦13.0 ppb)喂养两个月，使血硒水平由148±23降至86±17 ng/ml。

兔10只，匀分两组，A）组iv Na_2SeO_3水溶液(CP，北京化工厂，存干燥器中）2.0 mg/kg，给药后0，5，10，20，30 min，1，2，5，9，13，17，25，37，49，61，73 h，2，4，6，8，10，12，14 wk分别采血1.0 ml。B)组晨空腹ig Na_2SeO_3 2.0 mg/kg，后继续空腹8 h，给药后1，2，3，4，5，7，9，13，25，37，49，61，73，85，97 h，2，4，6，8，10 wk分别采血1.0 ml，肝素抗凝，-20℃保存。采血期间继续用低硒粮喂养。

采用荧光比色法测定[5]全血硒含量。以混合酸消化，使其中硒化物转变为无机的Se^{4+}，在酸性条件下Se^{4+}与2,3-二氨基萘（DAN)生成4,5-苯并苤硒脑(4，5-benzopiaselenol)，此化合物具有较强的荧光，并可用环已烷萃取，在一定条件下苤硒脑生成的荧光强度与Se^{4+}的浓度成正比。用RF-520型岛津荧光分光光度仪测定全血硒浓度，最小检出量为环已烷中Se^{4+} 1 ng/ml。本实验测定0.1 μg标准硒的变异系数为2.8%，回收率为93-100%。

血药浓度-时间数据用IBM-PC-XT型计算机，3P87程序处理。用房室法及统计矩法计算药物动力学参数。

RESULTS

房室模型的选择 根据8种房室模型判定标准[6-8]，选择最佳房室模型。结果见Fig1。

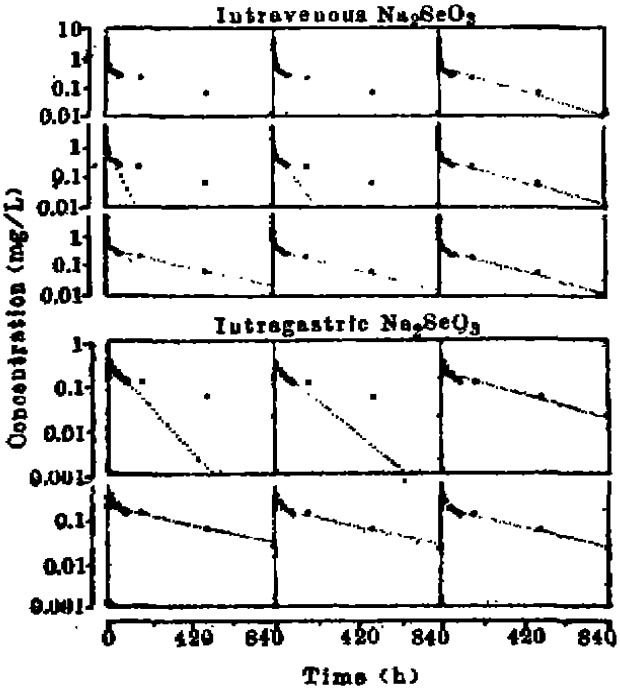

Fig 1. Concentration of selenium in whole blood 3or 2 compartments and $1/C$ or 1 weights after iv or ig sodium selenite 2.0 mg/kg in low-Se rabbits.

上述多种房室模型判定结果表明：低硒兔iv Na_2SeO_3时3室模型较其它模型更契合本实验曲线(权重$1/C$)，ig时则2室模型更契合本实验曲线(权重1)。

动力学参数 根据上述房室模型判定，A组和B组分别按3室及2室开放模型计算药物动力学参数，结果见Tab 1。

用统计矩方法计算Na_2SeO_3的动力学参数，结果见Tab 2。

上述两种方法计算药物动力学参数结果基本一致。

Tab 1. Pharmacokinetic parameters after iv or ig sodium selenite 2.0 mg/kg in normal and low-Se rabbits[3]. $n=5$, $\bar{x}\pm SD$. *$P>0.05$, ***$P<0.01$ *vs* normal-Se rabbits.

Parameter		Intravenous		Intragastric	
		Normal	Low-Se	Normal	Low-Se
P	(mg/L)		2.98±0.45		
π	(1/h)		6.85±1.97		
A	(mg/L)		0.79±0.25		1.77±0.47
α	(1/h)		0.12±0.05		0.21±0.05
B	(mg/L)		0.33±0.09		0.15±0.04
β	(1/h)		0.0033±0.0006		0.0022±0.0007
N	(mg/L)				−0.77±0.47
K_a	(1/h)				0.06±0.03
K_{12}	(1/h)		4.67±1.30		0.16±0.04
K_{21}	(1/h)		1.98±0.74		0.02±0.01
K_{13}	(1/h)		0.26±0.12		
K_{31}	(1/h)		0.04±0.01		
K_{10}	(1/h)		0.04±0.01		0.03±0.01
T_p	(h)				11.2±4.3
C_p	(mg/L)				0.36±0.09
$T_{\frac{1}{2}\pi}$	(h)	0.16±0.09	0.11±0.03*		
$T_{\frac{1}{2}\alpha}$	(h)	5.3±2.4	6.6±2.6*	13.7±1.7	3.6±1.1***
$T_{\frac{1}{2}\beta}$	(h)	238±60	215±35*	223±61	338±107*
$T_{\frac{1}{2}k_a}$	(h)			2.7±0.6	13.3±6.2***
V_c	(L/kg)	0.23±0.03	0.50±0.07***	4.3±1.2	2.9±1.3*
Cl	[ml/(kg·h)]	6.0±2.0	19.1±4.9***	37±13	27±11*
AUC	(mg·h/L)	262±53	146±26***	56±14	79±29*

Tab 2. Parameters of statistical moment algorithm after iv or ig sodium selenite 2.0 mg/kg in low-Se rabbits. Area 0-T(n), $\bar{x}\pm SD$.

Parameter	Intravenous	Intragastric
AUC(S_0)(mg·h/L)	145±16	65±19
AUMC(S_1)	27 335±6 984	17 746±8 022
S_2	0.1283 E+08±0.2240 E+07	0.6085 E+07±0.4076 E+07
MRT(h)	275±33	264±52
VRT(h)	44 903±1 701	46 908±7 659

DISCUSSION

将本实验求得的低硒状态兔 Na_2SeO_3 药物动力学参数与正常硒水平兔的药物动力学参数[3]进行比较(Tab 1)表明：

Na_2SeO_3 ig 后，低硒兔吸收相半衰期($T_{\frac{1}{2}k_a}$)明显长于非低硒兔，表明低硒动物对硒的吸收较缓慢。其分布相半衰期($T_{\frac{1}{2}\alpha}$)显著短于非低硒兔，可能是由于机体处于低硒状态时，硒从血液向组织的转运速度加快的结果。由于低硒兔对硒的吸收速度较慢，加之原血硒水平较低，因而达峰时间(T_p)表现后移的趋势。消除相半衰期($T_{\frac{1}{2}\beta}$)在两种动物身上没有明显的差别，说明低硒兔补硒后，硒从组织向血液的转运过程是基本正常的。

iv Na_2SeO_3 后，表观分布容积(V_c)，在低硒兔明显大于非低硒兔，表明低硒兔补硒后，硒在组织内分布较广泛。给低硒兔 iv Na_2SeO_3 药-时曲线下面积(AUC)明显小于非低硒兔，这可能是由于低硒动物给硒后，硒迅速大量向组织内转移而血硒浓度增加不多的缘故，也可能与低硒兔的血浆清除率(Cl)较非低硒兔明显

加快有关。

此外，低硒兔与非低硒兔对亚硒酸钠的生物利用度分别为54±13%和21±6%，差异非常显著($P<0.01$)，说明低硒动物对硒的吸收利用大大提高。

上述对比结果表明：低硒兔对亚硒酸钠的体内分布速度快且范围广，生物利用度高，提示低硒人群补硒给药方案设计，用低硒人群亚硒酸钠的药物动力学参数比正常人的药物动力学参数更为适宜。低硒人群的药物动力学特点有待研究。

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一个用 logistic 模型分析量-效关系的程序

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A program for analysis of dose-response relationship with logistic model

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ABSTRACT In order to avoid the defects in common methods for analysis of dose-response curves, we fit groups of dose-response curves simultaneously or separately on computer by using logistic model, with the EC_{50} and slope factor as the basic parameters. The pD_2 and pA_2 values were calculated from the best estimated EC_{50}s. This method shows a good compatibility with the original experimental data. The BASIC program can be conveniently run on microcomputers.

KEY WORDS drug dose-response relationship; biometry; software

提要 为了避免拟合量-效曲线常用方法中的缺点，我们用 logistic 方程，以 EC_{50} 及斜率因子为基本参数，在计算机上对成族量-效曲线进行同步拟合或单独拟合。由得到的最佳 EC_{50} 值及其误差，可计算出 pD_2 及 pA_2 值及其误差。此方法对原始数据可容性高，使用方便。用 BASIC 语言编制的程序可在微型计算机上运行。

关键词 药物剂量-效应关系；生物统计学；软件

拟合量-效曲线在许多药理学研究中，特别在受体研究中，是不可缺少的基本工具。用直

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