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8-(*N*,*N*-二乙胺)-*n*-辛基-3,4,5-三甲氧基苯甲酸酯在血管平滑肌细胞培养液中的作用

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关键词 TMB-8；血管平滑肌；钙通道阻滞剂；培养的细胞；钙放射性同位素

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Effects of isolation housing and timing of drug administration on amikacin kinetics in mice

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KEY WORDS social isolation; animal housing; drug administration schedule; amikacin; chronobiology; pharmacokinetics

AIM: To study the influences of social condition and drug administration time on amikacin metabolism in mice. **METHODS**: Forty ♂ ICR mice were randomly assigned into 4 groups according to 1) housing condition: individual housing (I, one mouse in a cage) or aggregated housing (A, 10 mice in a cage) and 2) drug administration time: at midday (D) or at midnight (N), ie I - D, I - N, A - D, and A - N groups. Amikacin was injected sc 15 $mg \cdot kg^{-1}$ after 4 wk of raising at D or N. Blood samples were taken at 5, 10, 15, 20, 30, and 60 min after medication in each mouse. Plasma amikacin was measured by enzyme immunoassay. The concentration-time data were fitted with one-compartment open model in each mouse and data were analyzed with group *t* test. **RESULTS**: The clearance (*Cl*) of amikacin

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was larger and the half-life ($T_{\frac{1}{2}}$) was shorter in A − N group than in A − D or I − N groups respectively. $AUC_{(0-t)}$ in A − N group was less than in I − N group. No differences of kinetic parameters between 2 isolated housing (I − D and I − N) groups were found. CONCLUSION: Aggregated housing and midnight drug administration increased the disposition of amikacin.

The effects of drugs can be changed according to housing condition[1], and there are circadian rhythms both in drug effects and drug disposition[2-4]. In this study the kinetics of amikacin known to be excreted from the kidney were studied in mice under different social conditions. Social isolation can also cause physiological, biochemical and even structural changes in animals or human[5-9]. Under social isolation, cerebral spinal fluid monoamine metabolism can be changed in monkeys and human, and brain catecholamines, plasma corticosterone, hypothalamic serotonin metabolites can be changed in rats.

MATERIALS AND METHODS

Forty ♀ ICR mice, aged 5 wk were randomly assigned into 4 groups according to 1) housing condition: individual housing (I) or aggregated housing (A) and 2) drug administration time: at midday (D, 13:00) or at midnight (N, 01:00), ie I − D, I − N, A − D, and A − N groups. In I groups the mice were individually raised in cages (16 cm × 16 cm × 25 cm) on light (day, 07:00 − 19:00)-dark (night, 19:00 − 07:00) cycle. Room temperature was kept at 25 ± 1 ℃. In A groups the mice were raised under the same condition as those in I groups except for 10 mice per cage. Amikacin dissolved in saline was subcutaneously injected 15 $mg \cdot kg^{-1}$ at midday (13:00) or midnight (01:00) after 4 wk of raising. Blood sampling was from orbital *sinus*, using heparinized micropipette aspirator tubes, 5, 10, 15, 20, 30, and 60 min after medication in each mouse. Plasma amikacin concentrations were measured by enzyme immunoassay. Kinetic parameters of each mouse were calculated using one-compartment open model and area under the concentration-time curve (AUC) was calculated by trapezoidal method. The kinetic data of different groups were analyzed using group *t* test.

RESULTS

There were no *significant* differences in body weight between socially isolated ($n = 20$) and aggregated ($n = 20$) groups both before ($\bar{x} \pm s$; 31.4 ± 0.9 *vs* 31.2 ± 0.7 g) and after 4 wk of raising (38.6 ± 2.8 *vs* 40.0 ± 2.2 g). The clearance (Cl) of amikacin in A − N group was larger than that in A − D and I − N groups. The half-life ($T_{\frac{1}{2}}$) in A − N group was shorter than that in A − D and I − N groups. $AUC_{(0-t)}$ in A − N group was less than in I − N group. No differences of kinetic parameters between I − D and I − N groups were found (Fig 1, Tab 1).

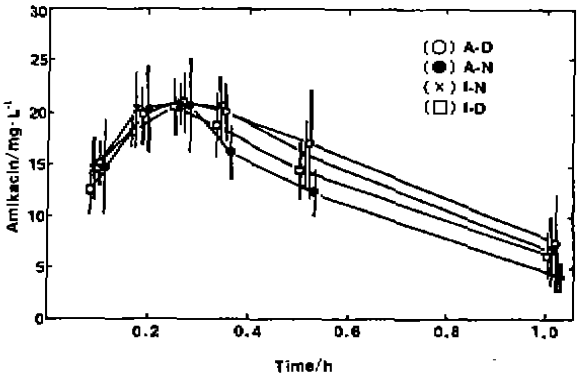

Fig 1. Amikacin concentrations in plasma. I: individual, A: aggregated, D: midday, N: midnight. $n = 10$, $\bar{x} \pm s$.

DISCUSSION

Experimental studies in mice showed that under

Tab 1. Kinetic parameters of sc amikacin 15 $mg \cdot kg^{-1}$. $n = 10$ in each group. $^bP < 0.05$ *vs* A − D; $^eP < 0.05$ *vs* I − N.

	I − D	I − N	A − D	A − N
K_a/h^{-1}	8.1 ± 3.2	7.3 ± 1.7	7.7 ± 1.9	8.8 ± 3.8
$Cl/L \cdot h^{-1} \cdot kg^{-1}$	0.96 ± 0.16	0.89 ± 0.19	0.86 ± 0.29	1.13 ± 0.19^{be}
$T_{\frac{1}{2}}$/min	21.4 ± 4.6	21.7 ± 7.4	25.7 ± 10.5	16.0 ± 3.2^{be}
$V_d/L \cdot kg^{-1}$	0.49 ± 0.11	0.44 ± 0.10	0.44 ± 0.04	0.44 ± 0.11
$AUC_{(0-t)}/\mu g \cdot h \cdot L^{-1}$	16 041 ± 3 370	17 810 ± 4 900	20 260 ± 13 360	13 790 ± 2 900^e

social isolation the time of pentobarbital-induced sleep was longer[1], and haloperidol had a shorter $T_{\frac{1}{2}}$ than under social condition[10]. Besides, circadian variations of the response and the kinetics of drugs have been reported both in human[11] and animals[2-4]. From the pharmacokinetic point of view, we investigated the effects of social environment and drug administration time on the kinetics of amikacin in mice. The results of this study showed that in aggregated housing mice Cl was larger and $T_{\frac{1}{2}}$ shorter, when amikacin was administered at midnight than at midday, which was different from the reported result of haloperidol[10].

Amikacin is a drug known to be eliminated from the body through the excretion by the kidney. Studies have shown that the glomerular filtration rate is highest in midnight time. This may account for the larger Cl and shorter $T_{\frac{1}{2}}$ of amikacin administered at midnight than at midday. This study also showed that when administered at midnight, amikacin Cl was larger, $T_{\frac{1}{2}}$ shorter and $AUC_{(0-t)}$ less in mice under aggregated housing than in group under isolated housing condition. No differences of kinetic data were found between two groups under isolated housing condition. These indicated that changing social condition could change amikacin disposition. Although the exact underlying mechanism of the above phenomenon is not known, this study does suggest that non-drug factors such as drug administration time and housing condition should be considered in pharmacological and toxicological studies with experimental animals.

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隔离饲养及给药时刻对小鼠阿米卡星药物动力学的影响

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关键词 社会隔绝；动物住房；给药计划表；阿米卡星；时间生物学；药物动力学；

目的：研究社会环境及给药时刻对小鼠阿米卡星代谢的影响. 方法：小鼠按饲养环境：隔离饲养(I)或集体饲养(A)及给药时间：日中(D)及午夜(N)随机分为：I-D, I-N, A-D, A-N 4组. 饲养4周后于D (13:00)或N (01:00) sc阿米卡星15 mg·kg^{-1}，测定给药后其血浆浓度，以开放一室模型拟合并计算有关药代动力学参数. 结果：A-N组阿米卡星清除率较A-D及I-N组增大，血浆半衰期变短，0-1小时血浆浓度-时间曲线下面积($AUC_{(0-t)}$)较I-N组减少. 隔离饲养两组(I-D, I-N)间药代动力学参数无显著差异. 结论：社会环境及给药时刻均显著影响小鼠阿米卡星代谢动力学.