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双苯氟嗪的急性毒性及其对离体血管平滑肌的作用

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提要 双苯氟嗪(Dip)为桂利嗪(Cin)的新衍生物。Dip抑制NE和KCl所致兔主动脉环收缩，抑制KCl所致收缩显著强于抑制NE，抑制KCl所致猪基底动脉、冠脉及桡动脉收缩的pD_2'值分别为5.7±0.6，5.4±0.4和4.6±0.5，对基底动脉选择性最高，且显著强于Cin，Dip iv LD_{50}与Cin相近，分别为37和36 mg/kg。

关键词 双苯氟嗪；桂利嗪；胸主动脉；基底动脉；冠状血管；钙通道阻滞剂；血管平滑肌

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冰片促进四甲基吡嗪的吸收

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Enhancement of absorption of tetramethylpyrazine by syntbetic borneol

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ABSTRACT Sprague-Dawley rats were given ig tetramethylpyrazine phosphate (TMP) 5 mg/kg with or without previous borneol 5 mg/kg. The plasma TMP concentrations were analysed by GC method, and the data were treated by NONLIN program. The C_{max} were 931 and 562 ng/ml, respectively, ($P<0.01$); while the AUC were 68 849 and 37 174, respectively, ($P<0.05$). It is suggested that the borneol enhances the absorption of the TMP but not in elimination.

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KEY WORDS borneol; tetramethylpyrazine; absorption; pharmacokinetics; gas chromatography; pyrazines; combination drug therapy

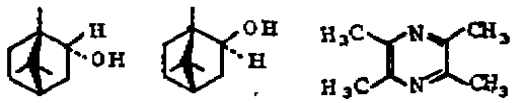
提要 本文研究冰片对四甲基吡嗪(TMP)药物动力学的影响，大鼠分为单用 TMP 和合用冰片 TMP 二组，ig 给药后不同时间的血药浓度用气相色谱法测定，并用 NONLIN 程度处理求出药物动力学参数。两组比较，C_{max} 为 562:931 ng/ml ($P<0.001$)；AUC 为 37 174:68 849($P<0.05$)表明冰片能促进 TMP 的吸收从而提高其血药浓度。对其清除无影响。

关键词 冰片；四甲基吡嗪；吸收；药物动力学；气相色谱法；吡嗪类；联合药物治疗

"药引"是中医长期实践总结的一种经验，其临床上冰片经常作为药引与当归川芎等药联用，以增强药效[1]。对脑心血管特别是治疗中风偏瘫有显著疗效的华陀再造丸其组方就是例子，在对其进行开发性研究中，本文就冰片与诸药的相互作用研究冰片对四甲基吡嗪药物动力学的影响，以探索药引的科学性及机制。

冰片有"通诸窍，散郁火"等作用，主要由龙脑(camphol)和异龙脑(isocamphol)两个异构体组成天然冰片与合成冰片的差异是两个异构体比例不同[2]，其药动学证实冰片经口服 30 min 后中枢药浓度达最高峰[3]。

四甲基吡嗪(tetramethylpyrazine, TMP)是中药川芎的主要有效成份[4]，对心脑血管系统疾病有效，用于治疗急性闭塞性脑血管等疾患[5-7]。



Camphol　Isocamphol　Tetramethylpyrazine

MATERIALS AND METHODS

合成冰片(龙脑 59.9%，异龙脑 37.5%，广州化工厂生产)，用 1%羧甲基纤维素钠(NaCMC)胶体溶液配成含冰片 2 mg/ml 的混悬液。磷酸四甲基吡嗪(TMP)由广东利民药厂生产，用 1% NaCMC 胶体溶液配成含 TMP 2 mg/ml 的药液。实验药液均置于 4 ℃。

Sprague-Dawley 大鼠 20 只，体重 212±SD 16 g，随机分为冰片加 TMP 组(合用组)及单用 TMP(单用组)各 10 只。冰片及 TMP 剂量均为 5 mg/kg，大鼠于实验前禁食 12-14 h，于 09:00-10:00 ig。合用组先 ig 冰片，25 min 后再 ig TMP；单用组先 ig 1% NaCMC 5 ml/kg 作为对照，25 min 后再 ig TMP。ig TMP 后 2, 5, 10, 15, 20, 25, 30 和 60 min 分别从尾静脉取血 120 μl，肝素抗凝，2000×g 离心 5 min 分取 50 μl 血浆。用气相色谱法[8]测定血浆 TMP 浓度。此法表明 TMP 的测定不受冰片等常用药物的干扰，灵敏度较高，最低检测限为 10 ng/ml，线性范围 20-800 ng/ml，样品测定的日间和日内误差均在 10%以下。

样品测定值用 C-R 1 B 数据处理机按峰面积计算，数值在 IBM 微机上用修改后的 NONLIN 程序(夏文江等编。西北农业大学)拟药时曲线，进行房室模型和药物动力学参数的计算。各参数采用两样本均数比较的 t 检验方法进行统计学处理。

RESULTS

TMP 血药浓度时间的拟合曲线及药物动

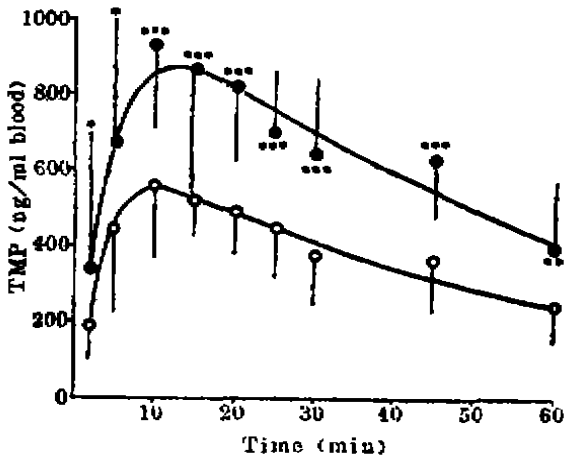


Fig 1. Tetramethylpyrazine (TMP) concentrations in blood of rats after intragastric gavage of tetramethylpyrazine phosphate 5 mg/kg with (●) or without (○) ig (25 min previously) borneol 5 mg/kg. $n=10$, $\bar{x}\pm SD$. *$P>0.05$, **$P<0.05$, ***$P<0.01$.

力学参数分别见 Fig 1 与 Tab 1。大鼠预先 ig 冰片后，合用组 TMP 的血药浓度比单用组明显提高，尤其是给药早期。给药后 10，15 和 20 min 的数值分别为 931:562，871:525，828:494(ng/ml)，P 值均<0.001。曲线下面积(AUC)合用组亦明显增加，为 68 849:37 174，$P<0.05$。两组 TMP 的吸收均快速，达峰时间，消除常数均无明显差异。两组的药物动力学特点呈开放一室模型。

Tab 1. Pharmacokinetic parameters after ig tetramethylpyrazine phosphate (TMP 5 mg/kg) with or without ig (25 min previously) borneol 5 mg/kg. $n=10$. $\bar{x}\pm SD$. *$P>0.05$, **$P<0.05$, ***$P<0.01$.

Parameter	Borneol + TMPP	TMPP
K (min^{-1})	0.0217±0.018	0.0196±0.007*
K_a (min^{-1})	0.362±0.275	0.614±0.67*
$T_{\frac{1}{2}}$ (min)	46.8±33.3	39.2±14.0*
T_p (min)	12.1±5.1	10.1±4.1*
C_{max} (ng/ml)	937±221	555±166**
AUC ng/(ml·min)	68 849±37 651	37 174±17 739***

DISCUSSION

实验表明，大鼠合用冰片后明显地提高 TMP 的血药浓度，增加 AUC。推测冰片促进 TMP 的胃肠吸收，由于 AUC = FX_0/VX，因此，亦未能排除冰片减少 TMP 的体内分布(即 V 值减少)所致。但在排泄方面无太大的关系。

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山茛菪碱对兔血凝、纤维蛋白及血栓形成的影响

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Effects of anisodamine on blood coagulation, fibrin and thrombosis in rabbits

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ABSTRACT Anisodamine at dose of iv 10 and 20 mg/kg prolonged plasma prothrombin time, bleeding time and coagulation time, and showed positive reaction of plasma protamine paracoagulation test in conscious rabbits. The drug prolonged the thrombin time and reduced the contend of plasma fibrin. Anisodamine markedly inhibited blood platelet aggregation both *in vitro* and *in vivo*, dose-dependently. The extracorporeal thrombosis time was prolonged, the length and weight of thrombus was decreased after iv anisodamine 20 mg/kg. These results suggest that anisodamine has inhibitory action thrombosis and blood coagulation.

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