

用整体放射自显影术研究¹⁴C 标记于哌嗪二酮或甲基吗啉基团吗丙嗪的分布卢大用¹, 胥彬, 章辛, 陈瑞婷 (中国科学院上海药物研究所, 上海 200031, 中国)

Distribution of ¹⁴C labeled at dioxopiperazine or methyl morpholine group of probimane by whole body autoradiography

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ABSTRACT Probimane (AT-2153) is a new anticancer compound. It was first developed in this Institute. It is effective against mouse tumors S37, S180, Lewis lung carcinoma, L1210 and human pulmonary adenocarcinoma heterotransplanted into nude mice. In the present work, ¹⁴C was labeled at central dioxopiperazine or methyl morpholine group of probimane 120 mg · kg⁻¹ was injected iv in mice bearing Lewis lung carcinoma by whole body autoradiography. The results showed that probimane was broken into at least two parts: a central part and a methyl morpholine group. The central part of compound hardly penetrated through the blood-brain barrier, but accumulated in the urinary bladder. The methyl morpholine group showed a high affinity to tumor tissue and accumulated in spleen, bone and liver.

KEY WORDS lung neoplasms; probimane; antineoplastic agents; autoradiography; carbon radioisotopes; tissue distribution; pharmacokinetics

摘要 吗丙嗪是一新的抗癌化合物。本实验用 ¹⁴C 分别标记于吗丙嗪的哌嗪二酮母体结构和外接甲基吗啉基团上进行带 Lewis 肺癌小鼠的整体放射自显影术研究。结果显示吗丙嗪在体内会断裂, 中间部分的哌嗪二酮母体结构难以通过血脑屏障, 而在膀胱中积蓄。甲基吗啉基团对 Lewis 肺癌有高亲和性和蓄积性。同时在脾, 骨和肝中蓄积。

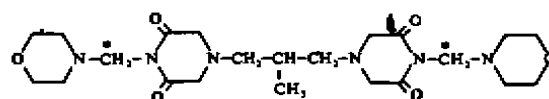
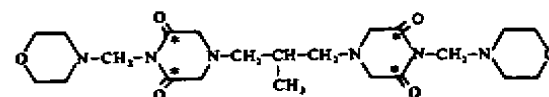
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关键词 肺肿瘤; 吗丙嗪; 抗肿瘤药; 放射自显影术; 碳放射性同位素; 组织分布; 药物动力学

吗丙嗪[probimane; 1,2-bis(*N*⁴-morpholine-3,5-dioxopiperazine-1-yl)propane]是丙亚胺^(1,2)衍生物。由本所首先合成。丙亚胺为常用的抗癌药物⁽¹⁻³⁾, 且具放射增敏作用^(4,5), 可降低阿霉素毒性⁽⁶⁾, 治疗 psoriasis⁽⁷⁾。吗丙嗪是在丙亚胺外接上两个甲基吗啉基团, 对许多小鼠肿瘤如 Lewis 肺癌、L1210 有抑制生长作用和增加化合物在水中的溶解度及增加对人体肿瘤株的抑制作用⁽⁸⁾。本文在吗丙嗪的哌嗪二酮母体结构和外部甲基吗啉基团上标记 ¹⁴C 进行小鼠整体放射自显影, 以了解该化全物的哌嗪二酮结构和外部甲基吗啉基团在体内的分布情况。

¹⁴C probimane A¹⁴C probimane B

MATERIALS AND METHODS

[¹⁴C]Probimane A (Pro A)是¹⁴C 标记于甲基吗啉部分的甲基上, 放射活度为 73.3 kBq · mg⁻¹。[¹⁴C]Probimane B (Pro B)是¹⁴C 标记于哌嗪二酮母体结构的碳原子上, 放射活度为 130 kBq · mg⁻¹。Lewis 肺癌系本所药室保种, C₅₇BL 小鼠由中国科学院上海实验动物中心提供。己烷、羟甲基纤维素(CMC)均为 CP。X 光胶片为上海感光胶片厂生产(医疗 II 型)。

本实验操作参照⁽⁹⁾。Pro A 和 Pro B 用生理盐水配成 120 mg · kg⁻¹ iv 于接种 Lewis 肺癌后 d 8 的小鼠, 分别在给药后 15 min, 2 h 和 24 h 进行小鼠的整

体放射自显影实验。小鼠轻握手中，浸入混有干冰的己烷溶液中 5 min。取出后用 5% CMC (混有干冰) 包埋，用 LKB-2250 型整体切片在 -20℃ 切成 20 μm 片，经冷冻干燥后，将膜面贴在 X 光胶片上，2.5 月后显影及定影。胶片用测微光度计(Carl Zeiss, JENA II 型)测定相对黑度(缝宽 30 μm, 缝高 10 mm)。

RESULTS

Pro A iv 后 15 min 已在各脏器中测出放射性脑及脊髓中也有分布，其中肝、骨骼、脾、肾、颌下腺、胃肠道壁和 Lewis 肺癌内放射性较高。2 h 后，多数组织的放射性有所降低，但肝、颌下腺、骨骼和肠壁的放射性与 15 min 时基本相同。Lewis 肺癌及脾的放射性明显增强。24 h 后，肝、颌下腺、骨骼和肠壁内的放射性已经降低，其它几种组织下降更明显，而 Lewis 肺癌和脾内放射性进一步增加(Fig 1, plate 2)。

Pro B iv 后 15 min, 2 h, 24 h, 小鼠脑及脊髓中几乎没有放射性；膀胱内放射性始终很强；在 Lewis 肺癌中的放射性强度与多数组织相似，无特殊高亲和性。给药 15 min 后，除脑及脊髓外，各组织中放射性都很高，其强度顺序为膀胱 > 肾 > 肝 > 脾 > 肺 > 肌肉 > 骨骼 > 胃肠道。2 h 后，多数组织放射性迅速下降，肾及肝放射性略高于其它组织，肠内容物中放射性增高。给药 24 h 后，除膀胱外，体内放射性大部分消失，本底很淡。

Pro A 在体内的排泄速度明显低于 Pro B。由于 Pro B 的放射活度高于 Pro A，给药 15 min 后，带 Lewis 肺癌小鼠体内放射性明显高于给同剂量的 Pro A 的小鼠(Fig 1 A 和 C)，但分布情况相似而给药 2 h 后，Pro A 和 Pro B 在小鼠体内总的放射性强度已相近(Fig 1 B 和 D)。24 h 后，给 Pro B 的小鼠体内的放

Tab 1. Comparative densities of autoradiographic films on mice bearing tumor given [¹⁴C]probimane (A).

Tissues	15 min	2 h	24 h
muscle	60	48	49
tumor	61	93	120
liver	122	118	62

射性远低于给 Pro A 的小鼠。

用测微光度计测定结果(Tab 1, Tab 2), 亦显示上述趋势(胶片本底 27.5)。

Tab 2. The comparative densities of autoradiographic films on mice bearing tumor given [¹⁴C]probimane (B).

Tissues	15 min	2 h	24 h
muscle	120	59	39
tumor	120	60	43
liver	140	71	52
urinary bladder	130	180	170

DISCUSSION

由于 probimane 分子比较复杂，我们只进行了两个部位的定位标记，因此只能了解吗啉基甲基与二氧化咪唑母体结构间的单键。

本实验显示，不同标记部位的 probimane 和不同时间放射自显影结果不相同，说明 probimane 在体内代谢时会发生断裂，其断裂部位可能在吗啉基甲基与二氧化咪唑基间的单键上。作为咪唑二酮母体结构(中间基团)在体内的排泄很快，iv 24 h 后，咪唑二酮母体结构大部分已从体内排出。由于小鼠膀胱内放射性始终很高，推测咪唑二酮母体结构从尿中排泄率很高。此外，在前 2 h 肠内容物放射性也较高，说明开始时咪唑二酮母体结构还从粪中排出。

当 ¹⁴C 标记于咪唑二酮母体结构以外的甲基吗啉基团时，放射性自体内排出较慢，Lewis 肺癌中放射性蓄积最明显，这和 Mückter 等的报道^[10]相一致，即推测甲基吗啉能与肿瘤细胞(其 pH 值较低)结合，起阻止细胞生长的作用。

除 Lewis 肺癌外，脾、肝、骨骼中放射性也较高，提示甲基吗啉基团对脾、肝、骨骼等也可能产生一定的直接影响。

Pro B iv 后，脑中放射性非常低，提示完整的 probimane 和分解后的咪唑二酮母体结构都难以通过血脑屏障。根据 Greig 等报道^[11]，ip 丙亚胺后，脑髓液中原药含量很低。这一结果与本实验结果相似，说明丙亚胺的结构改变为 probimane 后，虽水溶性增加，

并不能增加哌嗪二酮母体结构进入血脑屏障。由此推测当肿瘤转移到脑或脊髓后, probimane 可能无效。

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蝙蝠葛碱的首次通过效应

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First-pass effect of dauricine

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ABSTRACT The first-pass effect of dauricine (Dau) was compared with that of lidocaine (Lid) by measuring the ventricular fibrillation threshold (VFT) and dauricine plasma concentration in rats or rabbits.

After forelimb or mesenteric vein (imv) infusion of Dau at a rate of 1 mg · kg⁻¹ · min⁻¹ in rats, the VFT were 1.64-3.17 or 1.60-2.11 V, respectively. In the case of Lid at 2.5 mg · kg⁻¹ · min⁻¹, the VFT were 1.69-4.79 or 1.67-2.80 V, respectively, after ear vein (iev) or imv infusion of Dau at a rate of 0.5 mg · kg⁻¹ · min⁻¹ in rabbits, the VFT were 6.50-12.14 or 5.81-7.43 V, respectively. Plasma Dau concentration through iev infusion was significantly higher than that through imv route. As the dose of imv infusion increased, AUC of Dau showed a nonlinear increase.

The results suggested that Dau showed a considerable first-pass effect, which was dose-dependent.

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