

快 报

一种新型的肿瘤定位辐射增敏 药物(CM)的合成与作用研究

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Misonidazole 和甲硝羟乙唑(灭滴灵)等硝基化合物是目前提高实体瘤中乏氧细胞辐射敏感较好的一类亲电子化合物, 由于其对神经系统毒副作用较大, 因而限制了该类药物的临床应用。为了提高其辐射增敏疗效而降低其神经毒性, 我们合成了一种具有亲肿瘤和辐射增敏的新型的双功能化合物——甲硝羟乙唑衍生物(CM)。经元素分析、mp 测定、TLC、纸电泳、紫外及红外光谱扫描等一系列分析证明为 CM, 其分子式为 $C_{18}H_{23}O_{10}N_7 \cdot 1/2 H_2O$ 。先后共合成 12 批, 产品纯度达 98%, 合成方法稳定。CM 与 ^{99m}Tc 螯合后, 在带 S_{180} 小鼠中进行分布试验证明: CM 有浓集于肿瘤组织的作用。iv 后 24 小时内, 在瘤中始终维持在较高的水平, 肿瘤与脑和肌肉组织的放射强度比值分别在 10~16 及 5~7 左右, 有肿瘤定位作用; 在脑内含量低, 降低了神经毒副作用。这与其脂水分配系数小有关。LD₅₀ 试验表明: 其毒性较小, 比原化合物灭滴灵低。若将 CM 与 Ca^{++} 螯合成 CMCa ip 荷 S_{180} 小鼠, 然后在肉瘤 180 局部缺氧下合并照射后, 则 CMCa 合并照射组比单独照射组(R)对 S_{180} 生长有明显的抑制作用, 10 天的抑制率可达 77.4%, 比 R 组抑瘤明显 ($P < 0.05$), 其辐射致敏增强比(SER)值为 1.89, 也比灭滴灵致敏效果强, 故 CM 具有明显的辐射增敏作用。

上述初步结果表明: 我们合成的 CM 是一种具有肿瘤定位和提高肿瘤乏氧细胞辐射增敏效果颇有希望的双功能的新型药物, 其合成原料来源丰富, 合成方法简便, 可能对临床诊治肿瘤有一定的实用价值。有关合成方法及药理的详细报道将在第二军医大学学报等刊物上陆续发表。

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THE STUDIES OF SYNTHESIS OF A NEW TYPE TUMOR LOCALIZING RADIOSENSITIZER AND ITS ACTION

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The compound containing nitro group(e. g. misonidazole and metronidazole or flagyl) is a electron-affinic sensitizer which now improve better radiosensitiveness of hypoxic cell in solid tumor. However, neurotoxicity has limited its clinical use. In order to enhance its radiosensitizing effectiveness and reduce its neurotoxicity, a bifunctional compound-metronidazole derivative(CM) had been synthesized which had a tumor-affinic property and radiosensitize hypoxic cells. A series of analyses (e. g. m. p determination, TLC, paper electrophoresis and UV, IR)proved this synthetic compound to be a metronidazole derivative(CM). Its molecular formula is $C_{18}H_{23}O_{10}N_7 \cdot 1/2 H_2O$. Twelve batches of this compound has been synthesized, and its purity was 98%, the synthetic method was stable. when labeled with ^{99m}Tc , it produced ^{99m}Tc -CM which could concentrate and maintain a high concentration in tumor in mice bearing S_{180} within 24 hours after iv injection. The radioactivity ratio of ^{99m}Tc retained in tumor with that of brain and muscle was 10~16 and 5~7 respectively, suggesting that ^{99m}Tc -CM had a strong tumor-affinic property. Because of its lower concentration in the brain, its neurotoxicity was decreased. In LD_{50} experimments, it indicated that its toxicity was lower than that of the original compound "flagyl". when CM was chelated with Ca^{++} to form CMCa and ip into S_{180} bearing mice, after which the mice were locally irradiated with γ -ray under tumor acute local hypoxic condition, then the results indicated that the growth inhibiting effect on S_{180} in irradiated group with CMCa was strronger than irradiated (R) group alone. The tumor was inhibited by 77.4% within 10 days and higher than that of R group ($p < 0.05$). Its radiosensitizing enhancement ratio (SER) was 1.89 and its radiosensitizing effect was stronger than that of metronidazole. Therefore, CM had a obvioug radiosensitizing action.

The above preliminary results indicated that CM might be a new promising real bifunctional drug which had a tumor localizing action and enhanced radiosensitizing effect to hypoxic cells in tumor. In addition, its synthetic raw material was abundant and the synthetic method was simple, thus CM might be a practical useful drug in clinical diagnosis and therapy of tumor.