论著

西咪替丁对急性照射小鼠存活率及造血系统改变的影响

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[摘要] 目的 观察西咪替丁对急性照射小鼠存活率及造血系统改变的影响。方法 采用^{137}Cs γ射线全身照射小鼠，两次实验的照射剂量分别为6.0Gy和8.0Gy，剂量率均为1.01Gy/min。每次实验取健康雄性C57BL/6小鼠60只，按体重随机分为空白对照组、模型对照组、阳性药组(523)及33.3、100、300mg/kg西咪替丁组，每组10只。西咪替丁各剂量组于照射前5d灌胃给药，每天1次，照射后5h给药1次；阳性药组于照射前5d灌胃给药1次，照射后5h给药1次。检测8.0Gy照射后30d小鼠存活率，以及6.0Gy照射后30d小鼠外周血象、骨髓DNA含量和骨髓多染红细胞微核率。结果 8.0Gy照射后，模型对照组小鼠于第21天全部死亡，西咪替丁低、中、高剂量组30d存活率分别为50%、20%和30%；6.0Gy照射后第30天，与空白对照组比较，各照射组小鼠外周血白细胞明显降低(P<0.01)，骨髓多染红细胞微核率明显升高(P<0.05)。骨髓DNA含量明显降低(P<0.05)；与模型对照组比较，西咪替丁高剂量组外周血白细胞明显升高(P<0.01)，西咪替丁各剂量组骨髓DNA含量明显升高(P<0.01，P<0.05)，而骨髓多染红细胞微核率明显降低(P<0.01，P<0.05)趋于正常。结论 西咪替丁能提高急性照射小鼠30d存活率，且对其造血系统有较好的保护作用。

[关键词] 西咪替丁；辐射损伤，实验性；存活率；造血系统


Radioprotective effect of cimitidine on acutely irradiated mice survival and hematopoietic system

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[Abstract] Objective To investigate the radioprotective effect of cimetidine on survival rate and hematopoietic system in acutely irradiated mice. Methods The total body irradiation doses were 6.0Gy and 8.0Gy respectively at 1.01Gy/min rate. Thirty healthy male C57BL/6 mice were randomly divided into control group, model group, positive-drug (523) group and cimetidine groups (33.3mg/kg, 100mg/kg and 300mg/kg). Each group had ten mice. The mice were given intragastric administration of cimetidine for 5d before the irradiation in cimetidine groups, and 523 was administered before irradiation once a day in 523 group, and at 5h after irradiation, was given again. The 30d survival rate after 8.0Gy irradiation was recorded. The peripheral blood cells, bone marrow DNA content and frequency of micronucleated polychromatic erythrocytes (fMNPCE) were determined 30d after 6.0Gy irradiation. Results After 8.0Gy irradiation, all the mice died on 21th day in model control group. The survival rates in cimetidine groups were 50%, 20% and 30%, respectively. After 6.0Gy irradiation on 30th day, compared with control group, the peripheral white blood cells (WBC) and bone marrow DNA content were decreased significantly (P<0.01, P<0.05) in model group, and fMNPCE was increased significantly (P<0.05). Compared with model group, WBC was significantly increased in 300mg/kg cimetidine group (P<0.01). In cimetidine groups, the bone marrow DNA content was increased significantly after irradiation (P<0.01 or P<0.05), and the fMNPCE was decreased significantly (P<0.01 or P<0.05) and tended towards normal. Conclusion Cimetidine could improve 30d survival rate of acutely irradiated mice and has good protective effect on hematopoietic system.

[Key words] cimetidine; irradiation injuries, experimental; survival rate; hematopoietic system

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随着核技术的快速发展与广泛应用，电离辐射对人类健康的影响越来越受到重视。在现代战争和核武器的使用也使人类的生命受到极大威胁。科索沃战争中，美军大量使用贫铀弹，造成大量急性放射病，并使白血病的发病率急剧上升[1]。2011年日本福岛核电站发生核事故后，放射性物质大量泄漏，对现场工作人员及周边居民的健康造成严重影响，已有1名现场工作人员因遭受核辐射而罹患白血病[2]。据统计，电离辐射是继水、大气、噪音污染之后的第四大污染。为了有效防止电离辐射对人体的危害，除了采用必要的物理防护（距离防护、时间防护和屏蔽防护）外，还可采用安全有效的药物提高机体的抗辐射能力。


西咪替丁（cimetidine）是首个用于临床的H2受体拮抗药，常用于治疗胃溃疡、十二指肠溃疡及上消化道出血等疾病[20-23]。临床应用表明，西咪替丁不良反应轻微，安全可靠[24]。近年来研究发现，西咪替丁具有许多异于其他H2受体拮抗药的新用途。20世纪90年代，伊朗科学家Mozdarani等[24]研究发现，腹腔注射西咪替丁对0.25-1.0Gyγ射线诱导的骨髓细胞微核具有保护作用，之后陆续报道了腹腔注射西咪替丁可使低剂量中子一次照射后骨髓细胞核仁红细胞微核率降低，以及腹腔注射西咪替丁对大剂量γ射线致死性照射生存率的保护作用[25]。2002年，日本科学家Kojima等[27]通过离体人外周血淋巴细胞实验，证实了西咪替丁对大剂量X射线诱导的淋巴细胞微核发生和细胞凋亡具有保护作用。但腹腔注射的给药方式限制了西咪替丁在辐射防护领域的应用。本实验采用口服给药的方式，观察西咪替丁对33Cs γ射线一次性全身急性照射小鼠生存率的影响及造血系统损伤的保护作用。

1.1 仪器与试剂  759紫外可见光分光光度计购自上海奥普勒仪器有限公司，MEK-5216X血细胞分析仪购自日本Nihon Kohoden公司，流式细胞仪购自BD Biosciences公司。

1.2 动物分组及给药  CS7BL/6雄性小鼠(体重20-25g)饲养于上海思莱克实验动物有限公司(动物质量合格证号：2008001648541)，共120只，分两次随机，每次实验60只。将60只小鼠随机分为6组，每组10只：空白对照组(CMG)、模型对照组(MG)、阳性药523组(PG)、33.3mg/kg西咪替丁(CMTDL)、100mg/kg西咪替丁(CMTDM)、300mg/kg西咪替丁(CMTDH)。

西咪替丁各剂量组于照射前6d灌胃给药，每天1次，阳性药组于照射前1d灌胃给药1次，除空白对照组外，其余各组动物在末次给药2h内，于复旦大学放射医学研究所辐射中心进行33Cs γ射线一次性全身照射，两次实验照射剂量分别为6.0Gy和8.0Gy，剂量率为1.01Gy/min。照射后Shs西咪替丁各剂量组和阳性药组各给药1次。

1.3 30d存活率观察  8.0Gy照射后每天观察各组小鼠的生存状态及活动状况，记录各组小鼠死亡时间点和数量。连续30d，绘制存活曲线。

1.4 脏器指数  6.0Gy照射后30d，准确称量小鼠体重及脾脏、肝脏、胸腺重量，计算脏器指数。计算公式如下：脏器指数=脏器重量/小鼠体重。

1.5 外周血细胞计数  6.0Gy照射后30d，眼眶静脉从取血20μl，用血球计数仪检测外周血红细胞(RBC)、血小板(PLT)和白细胞(WBC)数量。

1.6 骨髓DNA含量检测  6.0Gy照射后30d，取血后脱颈处死致小鼠，解剖分离左右股骨，分别用PBS溶液洗滤骨髓细胞，用血球计数仪检测骨髓细胞DNA含量。

1.7 骨髓DNA含量检测  10cm2培养皿中加入1ml 0.2mol/L HClO4溶液，充分混匀，冷却至20℃。受照射小鼠尾静脉取血2ml，经0.22μm滤膜过滤后，加入0.2mol/L HClO4溶液，充分混匀，冷却至20℃。取上清液经离心处理，将上清稀释5倍后，于260nm处测定吸光度值。
2 结 果

2.1 西咪替丁对急性照射小鼠30d存活率的影响

8.0Gy照射后第13天，受照小鼠开始出现死亡，第21

天，模型对照组全部死亡。照射后30d内，空白对照

组和阳性药组无一例死亡，西咪替丁低、中、高剂

量组30d存活率分别为50%、20%和30%（图1），体

现了较好的保护作用，但不如阳性药的保护效果好。

![图1 小鼠30d存活率](image)

Fig. 1 The 30d survival rate of mice

表1 西咪替丁对照射后小鼠脾脏指数的影响（x±s，n=10）

<table>
<thead>
<tr>
<th>Group</th>
<th>Spleen index</th>
<th>Liver index</th>
<th>Thymus index</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG</td>
<td>0.2470</td>
<td>0.0006</td>
<td>0.1785</td>
</tr>
<tr>
<td>MG</td>
<td>0.2158</td>
<td>0.0003</td>
<td>0.1772</td>
</tr>
<tr>
<td>PG</td>
<td>0.2529</td>
<td>0.0005</td>
<td>0.1863</td>
</tr>
<tr>
<td>CMTDL</td>
<td>0.2594</td>
<td>0.0003</td>
<td>0.2348</td>
</tr>
<tr>
<td>CMTDM</td>
<td>0.2920</td>
<td>0.0006</td>
<td>0.1896</td>
</tr>
<tr>
<td>CMTDH</td>
<td>0.2358</td>
<td>0.0004</td>
<td>0.1908</td>
</tr>
</tbody>
</table>

(1)P<0.05, (2)P<0.01 compared with model group (MG)

2.2 西咪替丁对急性照射小鼠脾脏指数的影响

6.0Gy照射后第30天，与空白对照组比较，各照射组

小鼠脾脏指数、肝脏指数和胸腺指数均无明显变化，
说明照射后第30天，受照小鼠受照射后已有不同程度

的恢复。与阳性药组相比较，仅西咪替丁各剂量组脾

脏指数明显升高(P<0.05，P<0.01)，提示西咪替丁对辐

射后机体造血功能有较强的促进作用(表1)。

表2 西咪替丁对辐照小鼠外周血细胞及骨髓红细胞微核率的影响（x±s，n=10）

<table>
<thead>
<tr>
<th>Group</th>
<th>WBC(10^9/L)</th>
<th>RBC(10^12/L)</th>
<th>PLT(10^9/L)</th>
<th>fMNPCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG</td>
<td>2.99</td>
<td>81.09</td>
<td>4.98</td>
<td>785.75</td>
</tr>
<tr>
<td>MG</td>
<td>1.83</td>
<td>45.92</td>
<td>5.43</td>
<td>630.3</td>
</tr>
<tr>
<td>PG</td>
<td>1.87</td>
<td>55.94</td>
<td>4.93</td>
<td>636.6</td>
</tr>
<tr>
<td>CMTDL</td>
<td>2.45</td>
<td>74.91</td>
<td>4.44</td>
<td>613.5</td>
</tr>
<tr>
<td>CMTDM</td>
<td>2.12</td>
<td>51.97</td>
<td>4.97</td>
<td>635.7</td>
</tr>
<tr>
<td>CMTDH</td>
<td>2.87</td>
<td>66.95</td>
<td>3.30</td>
<td>662.7</td>
</tr>
</tbody>
</table>

fMNPCE: Frequency of micronucleated polychromatic erythrocytes. (1)P<0.05, (2)P<0.01 compared with control group (CG); (3)P<0.05, (4)P<0.01 compared with model group (MG)

鼠骨髓DNA含量明显上升(P<0.05，P<0.01，图2)，
说明西咪替丁对骨髓DNA具有较好的保护作用，且
高剂量西咪替丁的保护效果明显优于阳性药。

![图2 西咪替丁对辐照小鼠骨髓DNA含量的影响(x±s，n=10)](image)

Fig. 2 Effect of cimitidine on the content of DNA in bone marrow of irradiated mice (x±s, n=10)

(1)P<0.05, (2)P<0.01 compared with control group (CG); (3)P<0.05, (4)P<0.01 compared with model group (MG)
2.5  West Nile virus effect on acute radiation exposure. 6.0 Gy irradiation for 30 days, with white background. Model of the normal group and the radiation-induced group, the survival rate of bone marrow cells was significantly higher than the control group (P<0.05, P<0.01). The radiosensitivity of the irradiated group was lower than the control group, and the white background group was significantly lower than the model group (P>0.05), indicating that the normal group has better protective effects.

3 Discussion

Large doses of electromagnetic radiation can cause significant damage to the body, leading to death. Protection measures are necessary to reduce the effects of radiation exposure. The study observed the survival rate of bone marrow cells, and found that the survival rate of bone marrow cells in the white background group was significantly higher than that in the model group (P>0.05). This indicates that the white background group has better protective effects.

Bone marrow is a tissue that is particularly sensitive to electromagnetic radiation. The survival rate of bone marrow cells is a measure of the protective effect. The study showed that the survival rate of bone marrow cells in the white background group was significantly higher than that in the model group (P>0.05). This indicates that the white background group has better protective effects.

DNA is a key to cell survival. It contains the genetic information necessary for the growth and development of cells. The role of DNA in cell survival is crucial. The study observed the survival rate of bone marrow cells and found that the survival rate in the white background group was significantly higher than that in the model group (P>0.05). This indicates that the white background group has better protective effects.

PLT numbers significantly decreased. These changes were consistent with the radiation dose and the clinical manifestation of the disease, indicating that the disease is caused by radiation exposure. The study observed the survival rate of bone marrow cells and found that the survival rate in the white background group was significantly higher than that in the model group (P>0.05). This indicates that the white background group has better protective effects.

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Abbreviations

DNA: Deoxyribonucleic acid
WBC: White blood cell
RBC: Red blood cell
PLT: Platelet

References


