METHYLPREDNISOLONE REDUCES THE NEPHROTOXICITY CAUSED BY CISPLATIN

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Male Sprague-Dawley rats were given either 6.5 or 8.5 mg/kg of iv cisplatin combined with three injections of sc methylprednisolone in doses of either 50, 100 or 250 mg/kg at -4, 0 and 4 h after the cisplatin injection. Blood urea nitrogen and serum creatinine levels were determined on day 5 following the cisplatin injection. The protective effects of methylprednisolone on cisplatin-induced nephrotoxicity were clearly demonstrated. Our preliminary results suggest that a much higher dose of cisplatin could be injected in cancer chemotherapy, if it was combined with methylprednisolone.

KEYWORDS cisplatin; methylprednisolone; rat; nephrotoxicity

INTRODUCTION

Cisplatin is an effective anticancer drug against a variety of malignant tumors. Its dose-limiting factor is nephrotoxicity. Many attempts have been made to reduce the nephrotoxicity caused by cisplatin. Aggressive hydration during chemotherapy with cisplatin is a clinically useful modality (1). Diethyldithiocarbamate (2), probenecid (3), and WR-2721 (4) are all well known as antidotes against cisplatin nephrotoxicity. However, the clinical use of these agents is limited, because their protective effects against cisplatin toxicity have not been well evaluated. Borch et al. (2) and Yuhas et al. (4) evaluated the renal function by blood urea nitrogen (BUN) levels alone, which were elevated not only by renal
dysfunction but also by metabolic disorder. Ross et al. (3) demonstrated that the combination of 100 mg/kg probenecid reduced the creatinine levels in F344 rats injected with 7.5 mg/kg of cisplatin. However, the peak creatinine levels of the probenecid-treated rats was 64% of the controls given cisplatin alone. Umeki et al. (5) reported that fosfomycin and glucocorticoids reduced cisplatin-induced nephrotoxicity, however, the effects of glucocorticoids on cisplatin nephrotoxicity were not well investigated in their clinical study. Our preliminary experiment was conducted to evaluate the protective effects of methylprednisolone against cisplatin nephrotoxicity.

MATERIALS AND METHODS

Male Sprague-Dawley rats, weighing 200-250 g, were obtained from the Animal Center, Kyushu University. Cisplatin and methylprednisolone (MP) were purchased from Nippon Kayaku Co. Ltd. and Upjohn Japan Co. Ltd., respectively. The rats were injected with either 6.5 or 8.5 mg/kg of cisplatin intravenously (iv). These doses were chosen as LD$_{10}$ or LD$_{50}$ for Sprague-Dawley rats based on our previous experiments (6). The rats were also given three injections of either 50, 100 or 250 mg/kg of MP, subcutaneously (sc), at -4, 0, and 4 h after the cisplatin injection. BUN and serum creatinine levels were determined on day 5 following the cisplatin injection, because, BUN and serum creatinine are conventional indicators for renal function in animal experiments using rats and these values show their peaks on day 4 or 5 after cisplatin injection. Statistical analysis was performed by Student's t-test.

RESULTS

Tables I and II show BUN and serum creatinine levels in rats injected with either 6.5 or 8.5 mg/kg of iv cisplatin, respectively, with several doses of sc MP. BUN and serum creatinine levels in the rats given cisplatin with sc MP in doses of 100×3 or 250×3 mg/kg were significantly lower than those in the control animals injected with 6.5 mg/kg of iv cisplatin alone (Table I).
Significant differences in BUN and serum creatinine levels were indicated between the control rats which received 8.5 mg/kg of iv cisplatin alone and the MP-treated rats injected with 250x3 mg/kg of MP (Table II).

**Table I.** BUN and Serum Creatinine Levels in Rats Injected with 6.5 mg/kg of Cisplatin with Various Doses of Methylprednisolone (MP)

<table>
<thead>
<tr>
<th>MP (mg/kg)</th>
<th>BUN (mg/dl)</th>
<th>p Value vs control</th>
<th>Creatinine (mg/dl)</th>
<th>p Value vs control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>60±23</td>
<td>-</td>
<td>1.2±0.5</td>
<td>-</td>
</tr>
<tr>
<td>50x3</td>
<td>33±23</td>
<td>NS</td>
<td>0.7±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>100x3</td>
<td>22±6</td>
<td>&lt;0.01</td>
<td>0.5±0.2</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>250x3</td>
<td>27±6</td>
<td>&lt;0.02</td>
<td>0.5±0.1</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

Data represent mean±SD of 5 rats. BUN and serum creatinine levels in normal control (untreated rats) were 18±2 mg/dl and 0.5±0.1 mg/dl, respectively. MP (250x3 mg/kg) alone did not affect BUN or serum creatinine levels in rats.

**Table II.** BUN and Serum Creatinine Levels in Rats Injected with 8.5 mg/kg of Cisplatin with Various Doses of Methylprednisolone (MP)

<table>
<thead>
<tr>
<th>MP (mg/kg)</th>
<th>BUN (mg/dl)</th>
<th>p Value vs control</th>
<th>Creatinine (mg/dl)</th>
<th>p Value vs control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>83±18</td>
<td>-</td>
<td>1.2±0.3</td>
<td>-</td>
</tr>
<tr>
<td>50x3</td>
<td>41±36</td>
<td>NS</td>
<td>0.7±0.7</td>
<td>NS</td>
</tr>
<tr>
<td>100x3</td>
<td>56±34</td>
<td>NS</td>
<td>0.8±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>250x3</td>
<td>45±15</td>
<td>&lt;0.01</td>
<td>0.6±0.1</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data represent mean±SD of 5 rats. BUN and serum creatinine levels in normal control (untreated rats) were 18±2 mg/dl and 0.5±0.1 mg/dl, respectively. MP (250x3 mg/kg) alone did not affect BUN or serum creatinine levels in rats.
DISCUSSION

Glucocorticoids have a variety of biological actions. The antiemetic effects of dexamethasone (7) and MP (8) during chemotherapy with cisplatin have been reported. However, there have been few reports concerning the protective effects of glucocorticoids on nephrotoxicity caused by cisplatin. Galpin et al. (9) investigated whether glucocorticoids decreased the elevated serum creatinine levels to base line levels in patients with drug-induced interstitial nephritis. Based on this report, Umeki et al. (5) clinically studied the effects of fosfomycin and MP on cisplatin nephrotoxicity. They found that the elevation in urinary N-acetyl-β-D-glucosaminidase (NAG) levels was inhibited in patients treated with fosfomycin and MP. In clinical studies, the dose of cisplatin is usually limited to a level which does not cause any increases in BUN or serum creatinine levels. Our previous experiment demonstrated that urinary NAG was one of the most sensitive markers for cisplatin nephrotoxicity, however, the deviation of the data was too large to enable any statistical analysis to be made (10). The present experiments using animals were conducted to confirm the protective effects of MP against cisplatin nephrotoxicity. MP in a dose of 250x3 mg/kg reduced the serum creatinine levels almost to the normal range, while clear dose-related effects of MP on BUN or serum creatinine levels were not shown. Another in vitro study using cultured bladder cancer cell lines demonstrated that MP did not affect the antitumor effect of cisplatin (data not shown). Our preliminary results suggest that a much higher dose of cisplatin could be injected if it was combined with MP in cancer chemotherapy. More studies are required to elucidate the mechanism of the protective action of MP against the nephrotoxicity induced by cisplatin.

REFERENCES


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