Corticosteroid Modulation of Interleukin-1 Hematopoietic Effects and Toxicity in a Murine System

By John Rinehart, Elizabeth W. Delamater, Lisa Keville, and John Measel

Interleukin-1 (IL-1) has been shown to ameliorate the hematopoietic toxicities of antitumor chemotherapeutic agents in both mice and humans. However, IL-1 toxicity in humans is considerable and is similar to the systemic inflammatory toxicities induced by IL-3, IL-6, and other cytokines with pleiotropic biologic activities, eg, fever, nausea, malaise, and hypotension. We hypothesized that corticosteroids may reduce IL-1 toxicity without reducing IL-1 hematopoietic effects in vivo. C3H/HeJ mice (female, 6 weeks) were treated for 7 days subcutaneously with cortisone acetate (CA), (0.1, 0.25, or 0.5 mg/d/mouse), intraperitoneally with IL-1 (1 or 2 µg/d/mouse), or both. As expected, IL-1 increased white blood cell counts, splenic granulocyte-macrophage colony-forming units, and spleen cell number, and protected mice from lethal doses of carboplatin (200 mg/kg). Paralatins, Bristol Laboratories, Evansville, IN) administered the day after completion of the 7 days of IL-1 administration. CA did not significantly block the hematopoietic effects of IL-1 or the ability of IL-1 to protect mice from the hematopoietic toxicity of carboplatin. IL-1 administered to mice at 8 µg/d/mouse for 5 days induced decreased activity, roughening of hair, diarrhea, pancytopenia, multiple metabolic abnormalities, and death in 60% of mice. IL-1 at the therapeutic doses (0.5 to 2 µg/d) was not toxic. CA in a dose-dependent manner blocked all of the above mentioned toxicities when administered 24 hours and 30 minutes before each IL-1 injection. CA also decreased IL-1-induced increase in plasma tumor necrosis factor levels at the time point examined.

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Materials and Methods

Mice. Female C3H/HeJ mice were obtained from the Animal Production Area, National Cancer Institute-Frederick Cancer Research and Development Center (Frederick, MD). Animals were anesthetized by Forane (isoflurane) inhaled anesthetic for 5 hours before treatment. Experiments were performed using mice at 5 to 8 weeks old.

Preparation of peripheral blood smears for differential counts. Animals were anesthetized by Forane (isoflurane) inhalant (Ana-quest, Madison, WI), then blood samples were obtained from the orbital venous plexus using a microcapillary tube coated with 5% EDTA in Hanks’ balanced salt solution (HBSS; Gibco-BRL, Gaithersburg, MD). Sixty microliters of the blood was diluted into 120 µL of EDTA solution and the white blood cell (WBC) and platelet counts were determined using a model S+IV B Coulter counter (Coulter Electronics, Hialeah, FL). Smears were made of the blood samples and stained with Wright’s stain (Sigma Chemical Co, St Louis, MO). These slides were examined by light microscopy and the percentages of lymphocytes, granulocytes, and monocytes were determined.

Preparation of spleen mononuclear cell suspensions and leukocyte-conditioned media (LCM). Animals were killed by cervical dislocation, their spleens removed and placed in cold isovole’s modified Dulbecco’s Eagle’s Medium (IMDM; Gibco). Spleens were dissociated by pressing through a Cellotex tissue sieve (PGC Sciences, Gaithersburg, MD) into 60-mm tissue culture dishes (Falcon 1007, Becton Dickinson Labware, Lincoln Park, NJ) containing IMDM supplemented with 20% fetal calf serum (FCS). Cells were layered on a ficoll-paque (Pharmacia Diagnostics, Silver Spring, MD) in 15-mL polypropylene tubes. These were centrifuged at 400g for 25 minutes and interface cells were harvested. Spleen mononuclear cells were washed three times by centrifugation at 200g. Spleen mononuclear cells from treated animals were cultured in a methylcellulose hematopoietic progenitor cell assays for CFU-GM (see below). To produce LCM, washed spleen mononuclear cells from normal, from untreated animals were suspended in IMDM + 20% FCS + 10 µg/mL phytohemagglutinin to a final concentration.
of 6 × 10^6/mL. The cell suspension was placed in 25-cm^2 tissue culture flasks, then incubated at 37°C for 5 days. After incubation, the cell supernatant (ie, LCM) was centrifuged and the resultant supernatant was passed through a 0.22-μm syringe filter (Gelman Sciences, Ann Arbor, MI), then stored in 2-mL aliquots at -80°C.

Preparation and culture of bone marrow (BM). Mice were killed by cervical dislocation, and tibias placed in chilled HBSS. BM cells were obtained by flushing cold HBSS through tibias with a 27-gauge needle. Cells were washed once in cold HBSS, then resuspended to 3 × 10^7 cells/mL in IMDMEM supplemented with 20% FCS. BM mononuclear cells (3 × 10^7) were incubated in methylcellulose at a final concentration of 1% supplemented with 20% FCS and 1% antibiotic-antimycotic solution. Positive control cultures had 10% LCM added. The cell cultures were plated in triplicate wells in 6-well tissue culture dishes and incubated at 37°C in a fully humidified atmosphere of 5% CO2 for 7 days. On the seventh day, the number of CFU-GM were determined by examination using an inverted microscope.

Administration of biologic response modifiers or chemotherapy. IL-1β was a gift from Syntex Discovery Research (Palo Alto, CA). IL-1β was dissolved in sterile saline containing 0.5% bovine serum albumin (BSA); injections (0.2 mL/mouse) were administered intraperitoneally (IP). Cortisone acetate (CA) (Cortone; Merck, Sharp and Dohme, West Point, PA) was dissolved in sterile IMDMEM; injections (0.2 mL/mouse) were administered subcutaneously (SQ). Carboplatin (Paraplatin, Bristol Laboratories, Evansville, IN) was dissolved in sterile 0.9% NaCl for injection according to package directions. Individual animals in an experimental group were administered an intravenous (IV) injection of Carboplatin (0.1 mL) in the lateral or dorsal tail vein.

Cell proliferation. Cells were prepared as described in previous sections, and resuspended to 1 × 10^7 cells/mL in RPMI-1640 containing 20% fetal bovine serum, supplemented with 100 μg/mL penicillin, 0.1 μg/mL streptomycin, 0.25 μg/mL amphotericin-B, and 0.2 mmol/L L-glutamine. The cell suspension was pipetted into quadruplicate wells of a 96-well round-bottomed tissue culture plate in 100 μL. Proliferation was induced by human recombinant IL-2. A two-fold serial dilution of IL-2 (10,000 to 156 Cetus U/mL) was prepared and 100 μL was added to the appropriate wells. The plates were incubated at 37°C, 5% CO2 for 72 hours. After incubation, the wells were pulsed with 0.5 μCi 3H-thymidine, for 4 hours. The cells were harvested using a PHD multiple automated sample harvester (Cambridge Technology Inc, Cambridge, MA) and the radioactivity on the glass filter discs obtained from the harvest was measured by liquid scintillation. The data were expressed as mean counts per minute (cpm) from quadruplicate wells of the 5,000 U/mL concentration that induced the highest cpm in all experiments.

Staining of BM or spleen for flow cytometry. BM cells and spleen mononuclear cells were obtained as described above. Cells were washed three times in HBSS and resuspended to 2 × 10^7 cells/mL in HBSS without phenol red containing 1% BSA (Fraction V, Sigma) (staining buffer). Ethidium bromide (5 mg/mL in 10 mmol/L TRIS, 1 mmol/L EDTA) was added to the cell suspension. After incubating 20 minutes in an ice bath, the cells were washed by adding 2 mL of staining buffer and pelleting at 300g for 6 minutes at 4°C. Stained cells were resuspended in 400 μL cold staining buffer and held on ice until quantitation by a flow cytometer.

Enzyme-linked immunosorbent assay (ELISA). ELISA was used to determine the concentration of putative inhibitors of hematopoiesis. Human TNFα was assayed using a commercially available kit (Predicta; Genzyme Corp, Cambridge, MA). The absorbance was measured at 450 nm. Concentration of TNFα was determined by comparing results of test samples with a standard curve generated by the same assay. The sensitivity of this assay is 10 pg/mL.

Statistical methods. Statistical analysis was performed using the appropriate test for each individual variable.
INTERACTIVE EFFECTS OF IL-1 AND CORTICOSTEROIDS

Table 1. Effect of CA and IL-1β on Hematopoietic Parameters in C3H/HeJ Murine Spleens

<table>
<thead>
<tr>
<th>Dose (mouse/d × 7 d)*</th>
<th>Control</th>
<th>CA 0.25 mg</th>
<th>IL-1 2 µg</th>
<th>IL-1 2 µg + CA 0.25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen weight (mg)</td>
<td>153 ± 10t</td>
<td>52 ± 33</td>
<td>416 ± 153</td>
<td>391 ± 368</td>
</tr>
<tr>
<td>No. mononuclear cells/spleen (×10⁶)</td>
<td>16.3 ± 3.7</td>
<td>8.1 ± 0.6</td>
<td>137 ± 12.4g</td>
<td>128.5 ± 0.2g</td>
</tr>
<tr>
<td>Spleen CFU-GM</td>
<td>807 ± 119</td>
<td>61 ± 24f</td>
<td>36,696 ± 6,414f</td>
<td>74,422 ± 16,663f</td>
</tr>
<tr>
<td>% Spleen leukocytes in S-phase</td>
<td>2.5 ± 0.4</td>
<td>0.7 ± 0.15</td>
<td>14.9 ± 1.65</td>
<td>18.3 ± 0.85</td>
</tr>
<tr>
<td>Spleen leukocyte proliferation in response to IL-2</td>
<td>1,745 ± 417</td>
<td>455 ± 46</td>
<td>16,312 ± 1,832f</td>
<td>14,672 ± 8,414f</td>
</tr>
</tbody>
</table>

* Mice were killed on day 8 after 7 days of SQ CA, IP IL-1β, or both at doses indicated.
† Data presented as mean ± SD (n = 15 to 17 mice, three experiments).
‡ Numbers are total CFU-GM/spleen.
§ P < .01 compared with control.
∥ Data presented as mean cpm ± SD; IL-2 concentration = 5,000 Cetus U/mL.

RESULTS

In initial experiments, we administered IL-1 either at 1.0 or 2.0 µg/d/mouse IP, CA at 0.1 or 0.25 mg/d/mouse SQ or both IL-1 and CA for 7 days. Controls received injections both IP and SQ of appropriate carriers. Peripheral blood counts were determined the day before, during, and after treatment as indicated in Fig 1. IL-1 alone suppressed the absolute lymphocyte count (ALC), the absolute granulocyte count (AGC), and platelet count during treatment, but the values of these parameters increased above baseline and control levels by day 12. CA alone at 0.1 mg/d/mouse had no significant effects on these parameters, but CA administered in combination with IL-1 attenuated the decrease in AGC, ALC, and platelet count seen during IL-1 administration alone, and attenuated the rebound in these parameters seen when IL-1 was administered alone. The effect of these treatments on splenic parameters is seen in Table 1. Mice were killed the day after completing the treatments as described above and in Table 1. IL-1 alone increased splenic weight, cell number, CFU-GM, the fraction of cells in S-phase, and proliferative response to IL-2. CA decreased all of these parameters when administered alone. However, when CA was administered with IL-1, splenic CFU-GM increased in number compared with IL-1 alone. The effect of these treatments on BM parameters is presented in Table 2; CA, IL-1, and the combination did not significantly change the number of cells or CFU-GM/femur or the fraction of cells in S-phase.

In the next series of experiments, we examined the protective effects of IL-1 alone (2 µg/d/mouse), CA alone (0.1, 0.25, or 0.5 mg/d/mouse), and IL-1 plus CA when given for 7 days before carboplatin, 200 mg/kg; 20/24 control mice died compared with 0/20 mice after receiving IL-1 alone (P < .01) (Fig 2). IL-1 plus CA was as effective as IL-1 alone in rescuing mice from carboplatin toxicity when all three doses of CA administered with IL-1 were analyzed together (1/28 died) and compared with IL-1 alone, or when the three IL-1 plus CA groups were separately compared with IL-1 alone (see Fig 2). Interestingly, CA alone at 0.5 mg/d/mouse also improved post-carboplatin survival (P < .01). IL-1 and IL-1 plus CA reduced, but did not eliminate, the marked decrease in AGC, ALC, and platelet counts induced by Carboplatin, 200 mg/kg (Fig 3).

To determine if CA reduced toxicity of IL-1, we examined the toxicity of increasing doses of IL-1: 2 µg/d/mouse induced no apparent toxicity by inspection of mice; 4 and 6 µg/d/mouse induced weight loss, roughened fur, diarrhea, and decreased activity, but no deaths (data not shown). Mice treated with 8 µg/d/mouse for 5 days died (6/10) or were moribund by day 6 (Table 3). Administration of CA 24 hours and then 30 to 60 minutes before each IL-1 injection reduced mortality in a dose-dependent manner; no deaths were ob-

Table 2. Effect of CA and IL-1β on Hematopoietic Parameters in C3H/HeJ Murine Bone Marrow

<table>
<thead>
<tr>
<th>Dose (mouse/d × 7 d)*</th>
<th>Control</th>
<th>CA 0.25 mg</th>
<th>IL-1 2 µg</th>
<th>IL-1 2 µg + CA 0.25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. bone marrow cells/femur (×10⁶)</td>
<td>6.9 ± 0.9t</td>
<td>7.3 ± 0.6</td>
<td>6.4 ± 0.6</td>
<td>5.6 ± 0.6</td>
</tr>
<tr>
<td>Bone marrow CFU-GM</td>
<td>581 ± 96t</td>
<td>526 ± 150</td>
<td>618 ± 51</td>
<td>532 ± 146</td>
</tr>
<tr>
<td>% Bone marrow cells in S-phase</td>
<td>12.7 ± 0.3</td>
<td>10.9 ± 0.4</td>
<td>14.6 ± 0.8</td>
<td>13.3 ± 0.8</td>
</tr>
<tr>
<td>Bone marrow cell proliferation in response to IL-2</td>
<td>9,391 ± 1,068</td>
<td>13,627 ± 1,114</td>
<td>10,378 ± 2,148</td>
<td>8,302 ± 452</td>
</tr>
</tbody>
</table>

* Mice were killed on day 8 after 7 days of SQ CA, IP IL-1β, or both at doses indicated.
† Data presented as mean ± SD (n = 15 to 17 mice, three experiments).
‡ Numbers are total CFU-GM/femur.
§ Data presented as mean cpm ± SD; IL-2 concentration = 5,000 Cetus U/mL.
A 100
80 - - I
2 60
40 -
20 -
0 -

Control (24)
CA 0.1mg (10)
CA 0.25 mg (10)
CA 0.5 mg (8)

0 2 4 6 8 10 12 14 16 Days

Fig 2. In three separate experiments, 8-week-old female C3H/HeJ mice were injected with IL-1 (IP at 2 μg/d/mouse), CA (SC at 0.10, 0.25, or 0.5 mg/d/mouse) or both IL-1 and CA or carrier only SC and IP for 7 days ("7 through "1). On day zero, mice were administered 200 mg/kg carboplatin IV. Mice were then followed daily for survival without further manipulation. The number of mice/group are as indicated in parenthesis. (In Fig 2B, all of the lines except IL-1 2 μg+CA 0.5 mg are superimposed.)

Discussion

The data presented here support the hypothesis we developed; in vivo corticosteroids may block the toxic effects, observed in animals receiving CA 0.5 mg/d/mouse plus IL-1. Preadministration of CA also reduced weight loss induced by IL-1 and improved activity levels in surviving mice. IL-1 at this toxic dose induced multiple hematologic and biochemical abnormalities (Figs 4 and 5); by day 6, total WBC count, AGC, ALC, and platelet count were all markedly reduced. (Compare the "zero", i.e., no cortisone control mice between Fig 4A (no IL-1, no CA) and Fig 4B (IL-1, no CA). CA partially reversed IL-1-induced thrombocytopenia and neutropenia and, in fact, increased AGC above control levels. As expected, this schedule of IL-1 also increased plasma serum glutamic oxaloacetic transaminase, and blood urea nitrogen (BUN) and markedly decreased plasma glucose, iron, and cholesterol. Mice pretreated with CA showed amelioration of these IL-1-induced hematologic and biochemical abnormalities in a dose-dependent manner. IL-1 administration at 8 μg/d/mouse (Table 3), but not 2 μg/d/mouse, induced high plasma TNF which were decreased by pretreat-
but not the hematopoietic effects of IL-1. Thus, this study surprisingly showed that CA blocks some immunologic effects of IL-1 while sparing the examined hematologic effects in vivo, and therefore, supports our previously reported in vitro observations. Corticosteroids induce multiple metabolic and immunologic effects when administered in pharmacologic doses to mice and men. Just as complex are the proenin effects induced by administration of IL-1. Although our present work may provide some clues, the mechanisms of these interactions are of undoubted complexity and will require additional studies to elucidate. IL-1 and CA blocked development of IL-1 toxicity and reduced the observed levels of TNF below our assay level of detection. TNF may induce many of the toxicities associated with IL-1 administration in mice and men. However, in our studies, the lowest dose of CA used completely eliminated the increased TNF levels at the single time point examined, but not all IL-1 toxicity. Several possibilities may explain this paradox: local TNF release and action may be important in TNF toxicity and measurement of plasma levels may underestimate TNF effects. Furthermore, we only obtained TNF levels in plasma at one time point that may not have been optimal in reflecting TNF release. Thus, TNF may have been released but undetected at the time point examined. Finally, other cytokines may play a role and may act alone or synergistically with TNF at levels below our levels of detection to induce toxicity observed. For example, IL-6 and interferons may induce inflammatory-related systemic effects as well as TNF. IL-1 may induce toxicity unrelated to induced release of cytokines; IL-1 may directly enhance margination of oxidant-releasing granulocytes and macrophages into sensitive tissues. The decreased WBC counts observed with toxic doses of IL-1 supports this possibility. Finally, IL-1 may directly

induce alteration in vascular endothelial cells to ultimately induce tissue hypoperfusion.

CA did not block the hematopoietic effects of IL-1 in these studies and, in fact, appeared to enhance IL-1 induction of splenic CFU-GM. We have not explained as yet the mechanism of this latter effect. Moreover, these results must be regarded with caution because we examined only one time point and one dose of CA (Table 1). Nevertheless, we did examine multiple doses of CA in combination with IL-1 in regard to the effect on carboplatin-induced mortality; doses of CA that failed to block carboplatin-induced mortality did not block IL-1 reversal of carboplatin-induced mortality (Fig 2). We hypothesize that (1) IL-1 induces production of inflammatory mediators (eg, TNF, interferons, α, β, and γ, macrophage inflammatory proteins, prostaglandins, and others) that inhibit hematopoiesis, and (2) that IL-1 induces production of hematopoietic growth factors when given at nontoxic doses (0.5 to 2 μg/d/mouse). We further hypothe-

\begin{table}[h]
\centering
\caption{Survival and Plasma TNF Levels After High-Dose IL-1β in C3H/HeJ Mice: Effect of Treatment With Cortisone Acetate}
\begin{tabular}{|l|c|c|c|c|c|}
\hline
No. Deaths/Total & Plasma TNF Levels (pg/mL) \\
\hline
Control & 0/6 & 0 \\
CA 0.25 mg & 0/3 & 0 \\
CA 0.5 mg & 0/3 & 0 \\
IL-1 & 6/10 & 420 ± 153 \\
IL-1 + CA 0.1 mg & 2/6 & 0 \\
IL-1 + CA 0.25 mg & 2/10 & 0 \\
IL-1 + CA 0.5 mg & 0/10 & 0 \\
\hline
\end{tabular}
\end{table}

\* C3H/HeJ mice received no IL-1/β or IL-1β at 8 μg/mouse/d on days 2, 3, 4, and 5 without or with CA, SQ on days 1, 2, 3, 4, and 5. CA was given 30 to 60 minutes before IL-1/β.

† Treated animals died on day 5; on day 6 surviving animals were exsanguinated by cardiac puncture and TNFα levels determined by ELISA.

‡ Data presented as mean ± SD of the mean. Two separate experiments were performed.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig4}
\caption{In two separate experiments, 6-week-old C3H/HeJ mice were given IL-1 (IP at 8 μg/mouse), CA (SQ at 0.1, 0.25, 0.5 mg/mouse), or both IL-1 and CA for 5 days. Mice surviving were bled on day 6 by cardiac puncture for determination of peripheral blood counts illustrated in Fig 4 and plasma parameters illustrated in Fig 5. The number of animals surviving to day 6 and plasma TNF levels are shown in Table 3.}
\end{figure}
We have also observed that at high doses, CA (0.5 mg/d/mouse) blocked carboplatin-induced death in our murine model. We chose carboplatin for use in these studies because its only observed toxicity at the doses used are hematologic: mice died at the nadir of their peripheral blood counts and bacterial peritonitis was present at death. Furthermore, biochemical profiles obtained 24 hours before death in mice receiving carboplatin alone showed no decrease in renal or hepatic function (data not presented). We have now shown that high-dose cortisone acetate does ameliorate the hematopoietic toxicity of carboplatin. It is likely that the mechanisms by which CA and IL-1 protect mice from the hematopoietic toxicities of carboplatin are different because IL-1 increases the number of hematopoietic precursors in spleen (CFU-GM), whereas at high doses, CA reduces hematopoietic precursors. CA may act by increasing the number of hematopoietic precursors in G1 or induction of other protective mechanisms (eg, induction of elevated levels of glutathione or metallothiones). IL-1 may provide hematopoietic protection by increasing the total number of hematopoietic precursors.

These observations may have clinical utility. It may be possible to reduce toxicity of IL-1, IL-3, IL-6, or GM-CSF by concomitant administration of corticosteroids. We have shown in vitro that hydrocortisone succinate, prednisone, and dexamethasone enhance IL-1, IL-3, and GM-CSF induction of human CFU-GM proliferation at concentrations readily obtainable clinically with modest doses of these corticosteroids. Furthermore, we have shown that GM-CSF and IL-1 induce human mononuclear release of TNF and this release is blocked by the same concentrations of corticosteroids that enhance CFU-GM induction. These observations may have clinical utility. It may be possible to reduce toxicity of IL-1, IL-3, IL-6, or GM-CSF by concomitant administration of corticosteroids. 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