BOVINE RECOMBINANT INTERLEUKIN-2 ENHANCES RESISTANCE TO BOVINE HERPESVIRUS-1: DOSE RESPONSE TRIAL

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Summary

Twenty-five calves were allotted to five groups: controls that did not receive bovine recombinant interleukin-2 (rIL-2) and four groups that received 5 daily injections of rIL-2 at 11.4, 1.1, 0.11, or 0.011 μg/lb/day. On day 0 of the experiment, all calves received bovine herpesvirus-1 (BHV-1) vaccine and the first of the 5 daily injections of bovine rIL-2. All calves were infected with BHV-1 on day 21 of the experiment. Calves treated with 11.4 μg/lb/day had elevated rectal temperatures and mild diarrhea during administration of rIL-2. All other calves were normal. Compared to control calves, those treated with 11.4, 1.1, and 0.11 μg/lb/day had higher ($P<0.05$) serum antibody titers to BHV-1 and following challenge lower ($P<0.05$) BHV-1 titers in nasal secretions. Additionally, clinical disease as evidenced by nasal and ocular discharge was less severe. Cytotoxic responses against BHV-1-infected bovine kidney cells were increased ($P<0.05$) in calves treated with rIL-2 in a dose dependent manner. These data suggest that bovine rIL-2 at doses of 0.11 to 1.1 μg/lb/day for 5 days may enhance immunity against BHV-1 without causing adverse side effects.

Introduction

Interleukin-2 (IL-2) is a glycoprotein secreted by a subset of T cells and large granular lymphocytes after stimulation with mitogen or antigen. This lymphokine induces the clonal expansion of activated T cells and B cells and activates natural killer cells.

Recently, we evaluated the use of bovine rIL-2 in bovine herpesvirus-1 (BHV-1)-vaccinated and -challenged calves. Our data indicated that bovine rIL-2 (11.4 μg/lb body weight) used in conjunction with BHV-1 vaccination enabled calves to withstand a challenge with virulent BHV-1 better than a vaccination alone, suggesting that bovine rIL-2 may be an effective adjuvant to immunization against viral diseases. However, the dose of bovine rIL-2 used in that study caused mild fever and diarrhea, which abated immediately after rIL-2 treatment was stopped.

The objective of the present study was to determine if a lower dose of bovine rIL-2 would enhance resistance to BHV-1 without causing adverse side effects.

Procedures

Twenty-five Holstein or crossbred beef calves, 4 to 6 months old and seronegative for BHV-1, were used. The calves were allotted by weight to one of five treatment groups; controls that did not receive rIL-2 and four groups that received intramuscular injections of bovine rIL-2 at 11.4, 1.1, 0.11, or 0.011 μg/lb/day for 5 days.

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At the start of the experiment (day 0), calves were vaccinated with a modified-live BHV-1 vaccine (Norden Laboratories, Lincoln, NE) and their respective doses of bovine rIL-2 were administered intramuscularly. Bovine rIL-2 was administered daily for 4 subsequent days. Calves that did not receive bovine rIL-2 were injected intramuscularly with an equivalent volume of saline for 5 consecutive days. On day 21, all calves were inoculated intranasally (2 ml) and conjunctivally (1 ml) with 10^7 PFU/ml of BHV-1.

Results and Discussion

Treatment of calves with 11.4 μg/lb/day of bovine rIL-2 resulted in elevated rectal temperatures and mild diarrhea, but these signs subsided immediately after the last injection of bovine rIL-2. Calves in other rIL-2 treatment groups remained normal and healthy during the administration of rIL-2.

Following challenge with virulent BHV-1, calves that received 11.4, 1.1, and 0.11 μg/lb/day showed significantly lower ($P<0.05$) rectal temperatures on days 2 to 5 postinfection than control calves There was a similar trend with regard to clinical signs of BHV-1 infection, with nasal and occular discharges from rIL-2-treated calves being significantly less severe ($P<0.05$) than those from control calves.

Cytotoxic responses against BHV-1-infected bovine kidney cells by peripheral blood mononuclear cells (PBMC) from control calves remained low at all sampling times, whereas the cytotoxic response by PBMC from calves treated with rIL-2 increased in a dose dependent manner. Following rIL-2 injections, cytotoxic responses were significantly higher for PBMC from calves receiving 11.4, 1.1, and 0.11 μg/lb/day at all sampling times than for PBMC from control calves.

Calves treated with rIL-2 at 11.4 and 1.1 μg/lb/day had higher titers of ($P<0.05$) serum neutralizing antibodies to BHV-1 on days 10, 15, 21, and 25, and calves treated with 0.11 μg/lb/day had higher titers on days 15 and 21 ($P<0.05$), compared to control calves.

Shedding of BHV-1 in nasal secretions was significantly lower on days 1 to 6 postinfection in calves treated with 11.4 and 1.1 μg/lb/day and on days 3 and 4 postinfection in calves treated with 0.25 μg/lb/day, compared to control calves.

Discussion

Interleukin-2 augmentation of antiviral immunity has been demonstrated by adoptive transfer of immune lymphocytes from IL-2-treated animals and treatment of cattle with bovine rIL-2. The present study, while indicating a dose response of calves to bovine rIL-2 administered in conjunction with BHV-1 vaccine, also demonstrated that augmentation of immunity is possible with a dose that would not cause any visible adverse side effects. Although the optimum dose required should be confirmed by field trials, this study and our earlier study clearly demonstrate the potential benefit of bovine rIL-2 as an immunoadjuvant to vaccines against the bovine respiratory disease complex (BRD).

Some concern has been expressed about the effectiveness of vaccines alone as a means to combat BRD, which according to current estimates is causing an annual economic loss in the range of $250 million to $1 billion. The efficacy of vaccines may often be compromised by colostrally acquired maternal antibodies and certain states of stress-induced immunosuppression. This suggests the need for additional ways to modulate the immunity of cattle to resist BRD, and our study indicates the practical value of immunotherapeutic use of bovine rIL-2.