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An Oral Dose of Interferon Influences Creatine Kinase in Cattle

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ABSTRACT

The purpose of a study was to determine the dose of natural bovine Interferon (IFN) given orally to calves to induce changes in the expression of genes associated with autoimmunity and inflammation as determined by Quantitative Polymerase Chain Reaction (qPCR) assays on RNAs isolated from Peripheral Blood Mononuclear Cells (PBMC). A study with IFN administered orally at 0, 50, 200 or 800 units per calf was conducted. The IFN was administered orally at 0 and 8 hours to four calves in each treatment group. The PBMC were collected before IFN administration (0 hour) and 8 and 24 hours after the first treatment was administered. Body weights, Complete Blood Counts (CBC), standard serum testing and rectal temperatures were also determined before and after treatment to monitor safety of treatments. The calves were restrained in a hydraulic chute for sampling. Surprisingly the Creatine Kinase (CK) in the sera of calves given oral IFN did not increase at 8 and 24 hours as much as the CK of controls. Within 8 hours, one dose of IFN significantly ($p < 0.05$) decreased CK expression from calves caught in a metal hydraulic chute.

INTRODUCTION

An attractive and inexpensive alternative to induction of endogenous IFN by chemical, biological or recombinant means is the administration of exogenous IFN to at-risk livestock populations. The action is immediate and does not take days to become effective. An important attribute of the IFNs, particularly IFNα, they are not species-specific. Bovine IFNα is active on primate cell cultures [1]. Porcine IFNα is active on human cell cultures [2]. Human IFNα is active on porcine [3], bovine [3,4], and feline [5] cell cultures.

MATERIALS AND METHODS

Interferon: Natural bovine IFN was obtained from Colorado Serum Company, Denver, CO. This product is a mixture of at least three IFN subspecies. The IFN was prepared so that only those IFN subspecies that resisted degradation at pH 2.0, for 60 min were utilized for treatment.

IFN assay

The IFN antiviral activity titer was determined by viral (vesicular stomatitis virus) plaque reduction assay on cell cultures of Madin Darby Bovine Kidney (MDBK) cells [6]. The titer was interpreted using the method described by Epstein [7].

Preparation of control and IFN solutions

The control solution was prepared by adding 10.0 ml of bovine Fetal Calf Serum (FCS) to a liter of normal saline. This 1.0% (v/v) FCS solution was also used as the diluent for three IFN doses used. An IFN concentrate (1,190 units/ml) was used to prepare each of three IFN treatments in final concentrations of 5, 20 and 800 units/ml.

Animals

Sixteen Holstein steer calves weighing between 129-193 kg were randomly allotted to control and treatment groups of 50, 200 or 800 units (4 calves per group). Calves in each group were given an individual placebo or IFN dose twice (t = 0 hr, 7:30 AM and t = 8 hr, 3:30 PM) on day one of the study. Each animal received a total of 10 ml, administered into the oral cavity with a sterile disposable 12 ml syringe. The calculated final amount of IFN given in each group were: 0, 0.3, 1.3 and 5.3 units/kg based on the mean weight per group. Body weights and rectal temperatures also were recorded. At t = 0 hr, 8 hrs and 24 hrs after the initial IFN dose, blood from each calf was collected in both a red-top BD Vacutainer tube and an EDTA tube for complete blood count (CBC) and other blood tests. Blood samples were transported to Texas A&M Veterinary Medical Diagnostic Laboratory (TVMDL; Amarillo, TX) immediately after collection.

Analysis of data and statistics

Data were analyzed as a complete randomized design by the model Yijk = μ +Trti + Timej + eijk: Means were separated by protected Least Significant Differences (LSD) for treatments within time and tested for significance at P≤ 0.05. The change difference at 8 and 24 hours was analyzed by Chi Square Analysis. Two-tailed t-tests were performed to determine the statistical significance (P<0.05).

Results

Within 8 hours of treatment with one oral dose of IFN, a significant (P < 0.05) decrease in CK expression was noted in calves caught in a hydraulic chute. The squeezing and bruising of muscles in the hydraulic chute was expected to increase CK in all groups of calves but all groups of calves given oral IFN had lower CK in their sera [8] (Figure 1).

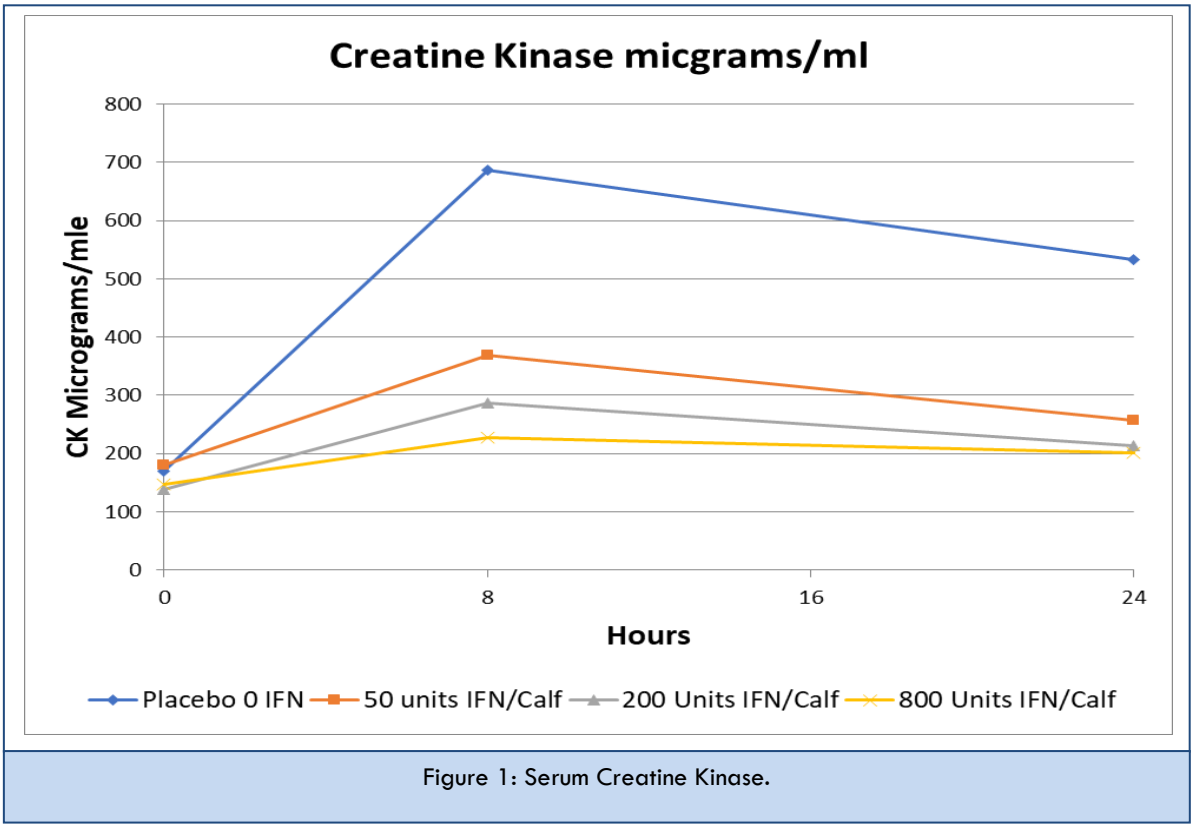

Figure 1: Serum Creatine Kinase.

DISCUSSION

Oral IFNα is beneficial when used in cattle with shipping fever. Cattle inoculated with virulent Infectious Bovine Rhinotracheitis (IBR) virus [9,10] or challenged with the protozoan parasite, Theileria parva [11] respond with milder disease when treated with low-dose oral IFNα. In studies of 7,000 feeder cattle, a single dose of orally administered human IFNα (0.7 international units (IU)/Kg) when given with antibiotics at the time of diagnosis of respiratory disease significantly ($p<0.001$) reduced mortality rates when compared to calves given diluent and antibiotics alone [12]. Data suggests that orally administered IFNα is bound to the tonsils and associated lymphoid and dendritic cells in the oropharyngeal cavity [13]. From here, a cascade of secondary cytokine and chemokine signals are released which have different systemic effects. For example, IFNα or IFNβ given orally up-regulates Mx gene activity in the murine splenocytes and human peripheral blood mononuclear cells [14]. Collectively, these *in vitro* and *in vivo* data demonstrate that orally administered IFN has rapid and systemic biological effects. Low-dose oral IFN may exert systemic and beneficial effects, including anti-viral effects by altering (up- or down-regulating) genes and their products likely needed for recovery from any systemic viral disease [15].

Alteration of more than 6000 genes out of 8000 tested was reported in cattle given low-dose oral human IFNα once daily for 5 days. The change in gene regulation was noted 4 hours after the last oral dose of human IFNα [16]. The authors are unaware that expression of CK has been reported to be influenced by IFNα. However, the authors report herein that within 8 hours, one dose of oral IFNα significantly ($p < 0.05$) decreased CK expression from calves in a hydraulic chute. Besides beneficial immunological effects, perhaps low-dose oral IFNα can help reduce the pain of animals bruised in handling.

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