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Fenbendazole Stimulates Interferon Secretion in Calves during Viral Infection

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Abstract

A total of six trials (five with live animals and one *in vitro* study) were conducted to evaluate the effects of fenbendazole (FBZ) on the immune response in stressed feedlot cattle. FBZ was given to all treatment calves at the recommended label dosage of 2.3 mg/lb (5 mg/kg) body weight. In Trial 1, treatment with FBZ did not affect serum neutralizing (SN) virus titers or viral shedding following inoculation with live, avirulent bovine herpes virus (BHV-1), but did increase titers for interferon (IFN) in nasal secretions at one, four and seven days post-inoculation. In Trial 2, FBZ-treatment reduced viral shedding and increased IFN titer in nasal secretions on days 4, 7 and 11 following inoculation with live, virulent bovine viral diarrhea virus (BVDV). In Trial 3, treatment with FBZ increased average daily gain (P=0.11) and increased IFN titer in nasal secretions at two (P=0.12) and seven (P=0.07) days following intranasal vaccination with avirulent BHV-1. In naturally infected calves, control and FBZ-treated calves had greater nasal secretions of IFN compared to calves treated with morantel tartrate, levamisole, or thiabendazole (Trial 4). Treatment with FBZ did not increase weight gain or interferon secretions in response to vaccination with IBR and BVD viruses (Trial 5). In cell cultures treated with bluetongue virus, FBZ increased IFN titers. FBZ appears to stimulate IFN secretion in calves during experimental infection with either BHV-1 or BVDV (Trial 6).

Keywords: bovine, fenbendazole, immune response, interferon

Résumé

Six études ont été menées (cinq avec des sujets vivants et une étude in vitro) pour évaluer l'effet du fenbendazole (FBZ) sur la réaction immunitaire de bovins stressés provenant de parc d'engraissement. Le FBZ a été administré à tous les veaux traités à la dose recommandée de 5 mg/kg (2.3 mg/lb) de poids corporel. Dans l'étude 1, l'administration de FBZ n'a affecté ni les titres en anticorps neutralisant du sérum ni l'excrétion virale suivant l'inoculation avec le virus vivant atténué de l'herpès bovin (BHV-1) mais a augmenté les titres d'interféron dans les sécrétions nasales aux jours 1, 4 et 7 suivant l'inoculation. Dans l'étude 2, l'administration de FBZ a réduit l'excrétion virale et augmenté les titres d'interféron dans les sécrétions nasales aux jours 4, 7, et 11 suivant l'inoculation avec le virus vivant virulent de la diarrhée virale bovine (BVDV). Dans l'étude 3, l'administration de FBZ a accru le gain moyen quotidien (P=0.11) et les titres d'interféron dans les sécrétions nasales aux jours 2 (P=0.12) et 7 (P=0.07) suivant l'inoculation intranasale du virus atténué BHV-1. Parmi les veaux infectés naturellement, la sécrétion nasale d'interféron était plus élevée chez les veaux témoins et les veaux traités que chez les veaux traités avec du tartrate de morantel, du lévamisole ou du thiabendazole (étude 4). Dans des cultures cellulaires traitées avec le virus de la fièvre catarrhale (maladie de la langue bleue), l'administration de FBZ a augmenté les titres d'interféron. Le FBZ semble stimuler la sécrétion d'interféron chez les veaux durant l'infection expérimentale avec soit le BHV-1 ou soit le BVDV (étude 6).

Introduction

Broad spectrum anthelmintics are used almost universally in the livestock industry to control internal parasites. Fenbendazole[a] (FBZ) is a broad spectrum product that is a member of the benzimidazole group of anti-parasite medications.

Internal parasitism of feedlot cattle reduces performance and impairs immune function.[5,12,15] Specifically, sustained internal parasite infection has been shown to coincide with down-regulation of lymphocyte proliferation accompanied by dramatic decline in expression of interferon (IFN)-gamma.[6] During viral infection IFN is secreted from the infected cells, signaling nearby cells to initiate production of various antiviral proteins.[13] Treatment of

experimentally virus-infected calves with either oral[4] or injectable[10] IFN reduces clinical signs of disease.

In addition to their effects on parasites, some dewormers are reported to stimulate the bovine immune system. We tested FBZ to determine its effect on the bovine immune system, particularly the effect on IFN titers in nasal secretions of cattle when administered during experimental viral infections. An *in vitro* study was also conducted to ascertain the effect of various concentrations of FBZ on IFN induction by bluetongue virus in cell culture. The unusual properties of FBZ allow the anthelmintic to rid the animal of parasites and to enhance an immune response.

The purpose of the studies described herein was to determine the effects of fenbendazole administration on immune function in beef calves.

Material and Methods

Cell Cultures

Bovine fetal kidneys (BFK) obtained at an abattoir were used to prepare BFK cell cultures. Growth medium for cells consisted of Eagle's Minimal Essential Medium (MEM) prepared in deionized water with 0.11% $NaHCO_3$ and 10% fetal bovine serum (FBS). Growth medium for cells used in the bovine viral diarrhea virus (BVDV) study consisted of the aforementioned MEM with 0.11% $NaHCO_3$ and 10% horse serum (HS). Maintenance medium consisted of MEM with 10% FBS and 0.11% $NaHCO_3$. Maintenance medium for the BVD study consisted of MEM with 10% HS and 0.11% $NaHCO_3$. Potassium penicillin G, streptomycin sulfate and amphotericin B were included in all media. Cultures were incubated at 98.6°F (37°C) under CO_2 (1 to 2%).

Serum Neutralization Tests

Serum antibody titers for bovine herpes virus-1 (BHV-1) and BVDV were determined by microtitration in BFK cells, essentially as described by others but with the addition of the microtransfer technique.[3,11] Four microtiter wells per serum dilution were used, and the titer was recorded as the reciprocal of the highest final dilution of serum completely protecting at least three of four wells. Serum samples were inactivated by heating at 133°F (56°C) for 30 minutes.

Viruses

The BHV-1 virus used in two studies was an avirulent vaccine strain provided by Dr. Dale Bordt (Beecham Laboratory, Whitehall, IL). Vaccine (Resbo BHV-1-PI_3 [parainfluenza type 3]) for intramuscular (IM) administration used in one of the studies was obtained from Norden Laboratories, Lincoln, NE. The BVDV was the virulent NY-1 strain obtained from Dr. Don Croghan (National Veterinary Services Laboratory, USDA, Ames, IA); bluetongue virus (BTV) was provided by Colorado Serum Company (Denver, CO); vesicular stomatitis virus (VSV), Indiana Strain, was obtained from B.D. Rosenquist (University of Missouri, Columbia, MO).

Fenbendazole

FBZ (10% suspension; 100 mg/mL) was dosed according to label instructions (2.3 mg/lb, 2.3 mL/100 lb BW; 5 mg/kg, 5.0 mL/kg BW) and given orally to cattle at the time of virus inoculation. For the *in vitro* tests, FBZ was diluted in MEM to concentrations of 1, 10 and 100 mg/mL and 1 and 10 nanograms/mL.

Experimental Design

Ten calves (four heifers and six steers) were purchased from a Tennessee farm and transported to the Texas Agricultural Experimental Station in Bushland, TX. Average arrival weight was 499 lb (227 kg) and 543 lb (247 kg) for heifers and steers, respectively. Upon arrival, the calves were administered a 4-way clostridial bacterin-toxoid and placed in a pen with a Pinpointer®[b] device that allowed for individual monitoring of feed consumption. Trials 1 and 2 were conducted with these calves.

In Trial 1, calves were inoculated intranasally with avirulent BHV-1 virus (2 mL dose of $10^{7.2}$ plaque-forming units [PFU]/mL), at which time five of the calves were given the label dose of FBZ. Weight and rectal temperature were recorded, and blood samples for complete blood counts (CBC) and serum IFN determinations were collected at 0, 1, 2, 4, 7, 11 and 14 days post-inoculation. Nasal secretions for IFN assay were obtained by inserting a tampon into the nasal passage for 20-30 minutes.[8] Serum samples for antibody determinations were collected immediately prior to, and 14 and 21 days after, BHV-1 virus inoculation. Nasal swabs for viral isolation were collected on the same days as the weight and temperature. Nasal swabs were expressed immediately into vials of transport media (MEM with 2% HS and antibiotics) and stored at –94°F (–70°C) until tested.

Fecal samples were tested for parasite ova before and after each trial by the Texas A&M Veterinary Medical Diagnostic Laboratory (TVMDL) in Amarillo, TX. A flotation technique was used to detect ova.

In Trial 2, 10 calves seronegative for BVDV were intranasally administered virulent BVDV (10^7 tissue culture infectious dose $[TCID]_{50}$/mL, 2 mL dose), at which time five of the calves were given the label dose of FBZ. Weight and rectal temperatures were recorded on days 0, 1, 2, 4, 7, 8, 11 and 13 after challenge. Nasal samples for BVDV excretion, nasal secretions for IFN determinations and blood samples for CBC and serum IFN determinations were collected on days 0, 2, 4, 7, 11 and 13. Serum samples for antibody determinations

were collected before and 13 days after virus inoculation. Virus isolations from nasal samples were coded on a qualitative rather than quantitative score.

Trial 3 was conducted to determine the effect of FBZ on the response to a modified-live BHV-1 virus vaccine (Beecham Laboratory, Whitehall, IL) given at the same time as the dewormer. Cattle were screened to determine serum neutralization antibody titers for BHV-1 virus. Thirty (30) steer calves were given an intranasal modified-live BHV-1 vaccine and 15 of these calves were administered the label dose of FBZ. Cattle were allotted to six pens of five head each. Variables measured were serum antibody titers at 0 and 21 days, IFN in the nasal secretions at 0, 2 and 7 days after vaccination, and weights at 0 and 28 days. Mean initial weights were 618 lb (281 kg) and 601 lb (273 kg) for control and FBZ-treated calves, respectively. Fecal samples were taken at 0 and 7 days for detection of parasite ova.

In Trial 4, IFN production was measured in the nasal secretions of cattle given FBZ, thiabendazole (TBZ), morantel tartrate (MOT) or levamisole (LVS). One-hundred male calves were purchased from six auction markets in Virginia, Tennessee or South Carolina during a three-day period and transported to an order buyer facility in Newport, Tennessee. The calves were allotted to treatment groups or a control group by auction market of origin and by sale weight. Twenty calves each received FBZ, TBZ, MOT, or LVS at the respective label dosage and route of administration while 20 calves served as untreated controls. Calves were ear tagged, fecal samples and nasal secretions were collected, and rectal temperatures were taken and recorded.

After commingling for an additional day, calves were shipped from Tennessee to Texas, a distance of 1180 miles (2596 km). At arrival in Texas they were immediately unloaded, weighed and offered feed and water. Shrink determined from pay weight to arrival was calculated. On the day after arrival, calves were administered a clostridial bacterin-toxoid, a spot-on insecticide, a vitamin A injection, and ear tagged with a Pinpointer® tag to allow monitoring of individual feed intake. Blood samples were collected for serology, and the weight and rectal temperature of each calf were recorded.

Two days after arrival, calves were inspected at dawn and scored for clinical illness using a 7-point system: two points for temperature ≥104°F (40°C); two points for anorexia (less than 1 lb [0.45 kg] consumption for 24 hours); and one point each for depression or mucopurulent nasal or ocular discharge. Calves with five points or more were treated with penicillin/streptomycin[c] injectable for three consecutive days. If a calf did not respond favorably to treatment, it was treated with a combination of sulfamethazine and penicillin for three additional days. Nasal secretions were collected at two and six days after arrival. Body weight for each calf was recorded 51 days after arrival; calves were bled again for serology at 50 days after arrival.

Fifteen healthy feedlot steers in Trial 5 were assigned to a 28-day study to determine the effect of FBZ on IFN concentration in nasal secretions of calves given an IM modified-live IBR-PI_3 vaccine. Individual body weights were determined on days 0 and 28. Feed intake was determined by Pinpointer®. IFN concentrations in nasal secretions were determined at 0, 3 and 7 days after vaccination. Antibody to BHV-1 virus was determined before and 28 days after vaccination. Ten calves were administered vaccine, and five of the 10 also received FBZ. Five control calves were not vaccinated and received only FBZ at day 0.

In an *in vitro* study (Trial 6), samples from cell cultures treated with each dosage of FBZ were screened for IFN at FBZ concentrations of 10 and 100 ng/mL and 1, 10 and 100 µg/mL of culture media. Cell cultures were grown until each flask of BFK cells had a confluent monolayer. FBZ dilutions were then made. FBZ was added to the flasks at concentrations of 10 or 100 ng/mL or 1, 10 or 100 µg/mL either 24 hours before, 24 hours after, or both 24 hours before and after inoculation with $10^{5.9}$ $TCID_{50}$ of BTV. Control cultures were given MEM only.

After 24 hours, flasks were harvested by freezing. Flasks were subsequently thawed and combined at respective dilutions. Samples were then dialyzed for 24 hours in a KCl-HCl buffer of pH 2.0 obtained by dissolving 16.66 grams KCl and 3.33 mL concentrated HCl in sufficient water to make 5,000 mL total buffer. Dialysis for another 24 hours was conducted in phosphate buffered saline (PBS) with a pH of approximately 7.4. Dialysis tubing with a molecular weight of 12,000 to 14,000 kDal was used in the dialysis.

Viral Isolation

Nasal excretion of BHV-1 virus was detected and quantified in BFK six-well culture plates. Serial dilutions were made from the nasal swab transport medium and 0.5 mL of the dilution was incubated on BFK cell cultures at 98.6°F (37°C) for one hour. Viral fluids were aspirated and the overlay medium was added. Plates were stained after seven days to detect BHV-1 viral activity through plaque formation. Nasal excretion of BVDV in Trial 2 was detected by fluorescent antibody testing performed by Dr. Richard Mock (TVMDL).

IFN Assay

Before the IFN assay, nasal secretions were dialyzed overnight in a KCl-HCl pH 2.0 buffer and dialyzed in PBS solution of pH 7.2 for 24 additional hours. The plaque reduction IFN assay method as modified was used.[9] Serial dilutions of the prepared sample were made in maintenance medium, and 0.1 mL amounts

of these dilutions were applied to microtiter plates of BFK cells and allowed to remain overnight at 98.6°F (37°C). Control cultures were treated overnight with 0.1 mL maintenance medium. After the incubation period, fluids were aspirated and washed with 0.05 mL of Hanks' balanced salt solution (BSS). The VSV (calculated to contain 50 PFU) was added to each plate. After absorption at 98.6°F (37°C) for one hour, excess viral fluids were aspirated and the soft agar overlay medium was added. After 24 hours, plates were fixed with an alcohol-formaldehyde fixative. IFN titers were determined by the probit method[7] and were expressed as the reciprocals of the dilutions which produced 50% reduction in the number of VSV plaques, as compared with the number in control cultures.

Statistical Analysis

An analysis of variance system[1] was used to compare experimental data. A *P*-value of <0.05 was considered significant.

Results

In Trial 1, seven calves seronegative to BHV-1 virus at the time of virus inoculation developed antibody to BHV-1 virus by 14 days post-inoculation. The geometric mean titers (GMT) of antibody to BHV-1 virus were not different between treatment groups. Four of the seven calves had IFN in their nasal secretions at the time of virus BHV-1 inoculation and all calves developed IFN in their nasal secretions after virus inoculation. Calves had nasal secretion IFN from 1-7 days after inoculation, but serum IFN was detected in one calf. The nasal secretion GMT-IFN titers were higher at 1, 4 and 7 days after BHV-1 virus inoculation in the FBZ-treated group. Virus excretion in the nasal secretions was similar in both groups of calves. The mean average daily gain and feed efficiency were numerically improved in FBZ-treated calves compared to control calves, but the differences were not significant. Calves did not develop fever after avirulent BHV-1 virus inoculation.

In Trial 2, seven calves seronegative to BVDV at the time of virus inoculation developed BVDV neutralizing antibodies by 13 days post-inoculation. IFN was detected in the nasal secretions of six of seven calves after BVDV inoculation, and IFN titers were similar to those reported for Trial 1. The GMT-IFN titers of FBZ-treated calves were higher than controls at 4, 7 and 11 days after virus inoculation. Serum IFN was detected in one calf at one sampling after BVDV inoculation. Virus excretion of BVDV, as evidenced by duration and amount of BVDV excretion in the nasal secretions, suggested that the most severe BVDV infections occurred in control calves at 2, 4, 7 and 11 days after virus inoculation. BVDV was detected at 13 of 15 sampling times in control calves, and 9 of 20 sampling times in FBZ-treated calves ($P<0.01$).

Calves consumed less feed after inoculation with BVDV. Feed consumption declined to a third or less of normal consumption by seven days, and generally returned to normal by 11 days after inoculation. On average, FBZ-treated calves had higher mean daily gain and better feed efficiency than controls. The mean feed-to-gain for FBZ and controls were 5.67 and 7.36, respectively, but no statistical procedures were conducted due to lack of replication for this variable. All calves developed fever by seven or eight days after BVDV inoculation.

Four calves administered FBZ but not inoculated with a virus did not have detectable IFN in their NS at 0, 3 or 7 days after FBZ administration. One calf given FBZ had IFN detected in the serum on days 0 and 3, but not on day 7 after FBZ administration.

Average daily gain was higher in FBZ-treated calves (3.92 lb [1.78 kg]/day) compared to control cattle (3.51 lb [1.60 kg]/day; $P=0.11$; Table 1). Feed intake was similar for both groups. Serum neutralization test results indicate that 11 of the 15 vaccinated cattle in each group were seronegative to BHV-1 virus at baseline, and all calves seroconverted by day 21. The antibody GMT was numerically higher in the FBZ-treated calves, but the difference was not significant (Table 2). Calves given FBZ and BHV-1 virus produced more IFN in nasal

Table 1. Effect of oral administration of fenbendazole on weight gain and feed consumption of calves inoculated intranasally with a virulent BHV-1 virus.

Treatment	No. of steers	Mean weight (lb; ± standard deviation [SD])		Average feed consumption (lb/day)	Average daily gain (lb)[a]
		0 day	28 day		
BHV-1	15	617.3 ± 45.9	715.5 ± 50.0	23.0	3.51 ± 0.73
BHV-1 + FBZ	15	601.6 ± 55.7	711.3 ± 56.2	23.0	3.92 ± 0.63

secretions at 2 (P=0.12) and 7 (P=0.07) days after vaccination (Table 3).

In Trial 4, a natural respiratory disease outbreak occurred. Overall morbidity rate was 64% and mortality rate was 10%. By 51 days after processing, all groups of calves were gaining approximately 2.0 lb (0.91 kg)/day or better, and all calves treated with dewormer had daily gains equal or better than controls; however, differences were not statistically significant. Weight gain and feed intake were not significantly different between treatment groups.

Ten calves died of bacterial pneumonia. *Mannheimia haemolytica* was isolated from eight of 10 dead calves and *Arcanobacterium pyogenes* was isolated from the remaining two. BVDV was also isolated from two calves. Deaths occurred in all five treatment groups; no significant difference in morbidity or mortality was observed between treatments. Quantitative fecal floatation was conducted at arrival and no differences in fecal egg counts were found between the groups. Various parasites were identified: strongylid type (93.0%), strongylids (3.0%), trichuris (2.0%), cestode (32.0%) and coccidia oocysts (66.0%).

After arrival in Texas, IFN concentrations were higher in control calves and FBZ-treated calves than in other groups (TBZ, MOT, or LVS). FBZ-treated calves and controls had significantly more IFN than LVS-treated calves two days after arrival. TBZ-treated calves and MOT-treated calves had less than half the IFN concentration of FBZ or control calves, but the difference was not significant (Table 4). At six days after arrival, GMT-IFN concentrations were ≤21, and treatment means were not significantly different.

Ten calves in Trial 5 were administered IBR-PI_3 vaccine intramuscularly, and five of those calves were also given FBZ at the time of vaccination. Interferon was detected in the NS of one of 10 vaccinated calves (vaccine-only group) at the time of vaccination. Interferon was not detected in the NS of any of the 10 vaccinated calves three days after vaccination, but was detected in three (one FBZ-only and two FBZ + vaccine) of 10 calves seven days after vaccination. On average, calves given FBZ gained numerically more weight than control calves (Table 5), but these differences were not significant.

In the *in vitro* test (Trial 6) where FBZ was added to cell cultures after the virus (MEM/FBZ), all IFN titers were higher in FBZ-treated cells than in control cells. The 10 ng/mL concentration of FBZ resulted in the highest IFN titer. When FBZ was on cell culture before and after BTV (FBZ/FBZ), the 100 µg/mL concentration produced the lowest IFN titer, compared to the 10 ng/mL concentration of FBZ which had the highest IFN titer. Except for the 100 µg/mL concentration, IFN titers from all FBZ-treated cultures were significantly higher (P<0.05) than the control IFN titer.

Table 2. Geometric mean titers (GMT) of BHV-1 virus neutralizing antibody of steer calves given BHV-1 virus vaccine, with or without fenbendazole (FBZ). Eleven of 15 steers in each group were seronegative at baseline.

Treatment	GMT at day	
	0	21
BHV-1	<4	9.1
BHV-1 + FBZ	<4	11.7

Table 3. Geometric mean titers of IFN in the nasal secretions of calves given intranasal BHV-1 virus vaccine, with or without oral fenbendazole (FBZ; 2.3 mg/lb BW).

Treatment	GMT (± SD) IFN at day		
	0	2	7
BHV-1	0	37.1 ± 5.3[a]	112.7 ± 6.9[b]
BHV-1 + FBZ	0	150.6 ± 13.0[b]	441.6 ± 7.2[c]
P-value		0.12	0.065

[a] 14 calves
[b] 11 calves
[c] 13 calves

Table 4. Geometric mean titers of IFN, measured at 2 and 6 days post-arrival, in the nasal secretions of calves treated pre-shipment with thiabendazole, fenbendazole, morantel tartrate, levamisole or no treatment.

Treatment Groups	Days after arrival	
	2	6
Thiabendazole	106[a,b]	9
Fenbendazole	239[a]	15
Morantel tartrate	86[a,b]	14
Levamisole	43[b]	21
Control	289[a]	8

[a,b] GMT with different superscripts are significantly different (P<0.05). No significant differences were observed on day 6 post-arrival.

Table 5. Weight gain (lb) of calves given fenbendazole with or without intramuscular modified-live IBR-PI_3 vaccine.

Treatment	Mean weight at day 0	Mean weight at day 28	Mean weight gain (± SD)	Percent BW gain
FBZ only	561.2	644.0	82.8 ± 28.8	14.8
Vaccine only	606.8	668.2	61.4 ± 36.7	10.1
FBZ + vaccine	628.8	702.6	73.8 ± 18.2	11.8

In the *in vitro* (FBZ/MEM) study where FBZ was added to cell cultures before virus, and then removed when virus was added, the 100 µg/mL concentration was the only concentration of FBZ that provided an IFN titer higher than the control. IFN titers in the lower FBZ concentrations were all lower than the control, and IFN titers decreased as FBZ concentrations decreased. However, no statistical procedures were conducted as there were five dilutions of FBZ before and after virus addition.

There were significant ($P<0.05$) differences in IFN titers among FBZ/MEM, FBZ/FBZ and MEM/FBZ treatments using total means and logarithmic means. The MEM/FBZ test resulted in the highest IFN titers compared to the other two tests.

Discussion

FBZ treatment in these studies resulted in enhancement of the IFN response in controlled studies with BHV-1 virus. In a field trial, FBZ treatment resulted in an enhanced IFN response during a natural mixed viral infection compared to treatment with other anthelmintics (but not controls). The IFN suppression noted in LVS-, MOT- and TBZ-treated calves was a surprising result. Very little is known about the immune modulating effects of morantel tartrate, but there has been considerable interest in levamisole and TBZ as immune stimulators.[2] Similarly, calves given FBZ produced a higher GMT of IFN two days after arrival in the feedlot compared to unvaccinated calves given TBZ, MOT, or LVS. The IFN detected was not in response to intranasal vaccination, but was instead the response to viral or other IFN inducers naturally occurring in the pneumonia outbreak.

In the studies reported here, FBZ has shown consistent effects on nasal secretion IFN. Dosage, frequency and timing of FBZ administration relative to the time and severity of viral infection are probably critical to whether the enhancement of the IFN response provides a benefit to the calf.

FBZ-treated calves gained more weight and utilized feed more efficiently than control calves after infection with BVDV or BHV-1 virus, but differences were not significant. Notably, less virus was excreted from FBZ-treated calves after BVDV inoculation. IFN production persisted longer in FBZ-treated calves after BVDV inoculation, but BVDV excretion did not.

Calves given intranasal BHV-1 virus vaccine and FBZ gained more weight than calves only given BHV-1 virus vaccine. Calves given intranasal BHV-1 virus vaccine and FBZ produced significantly more nasal secretion IFN and had a higher mean neutralizing antibody titer (not significant) compared to BHV-1 vaccinated calves not given FBZ. In contrast, FBZ did not enhance the IFN response in the nasal secretions of calves given IM IBR-PI_3 vaccine, presumably because the viruses from the IM vaccine did not replicate in the nasal passages.

In the *in vitro* tests, the 10 ng/mL concentration of FBZ in the MEM/FBZ and FBZ/FBZ studies induced the highest IFN titers in BFK cells inoculated with BTV. This low dose was the best dosage for enhancing the IFN response induced by BTV *in vitro*.

What would be the practical value of having additional interferon in the nasal secretions? Interferon has a profound effect on the immune system because interferon activates many immune response genes.

Conclusion

These data support the concept that FBZ enhances the IFN response and may function as an immune stimulator.

Endnote

[a]Safe-Guard® Beef and Dairy Dewormer, Intervet, Inc., Millsboro, DE

[b]Agricultural Identification Systems Corp., Cookeville, TN 38501

[c]Penicillin-streptomycin combination is no longer approved by the FDA for use in cattle

Acknowledgements

Partial support for these trials was provided by Hoechst-Roussel, Inc. and Pfizer, Inc.

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