

Ancillary Therapy For Bovine Respiratory Disease

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Abstract

Through ancillary therapy we attempt to improve response to antimicrobial drugs. Ameliorating the harmful effects of inflammation, blocking the activity of histamine, and improving immune function serve to alter the pathophysiology of the infectious process. We tend to assume that this alteration is consistently beneficial. But other possible effects include drug interactions and direct toxicity. This paper reviews the pharmacodynamics and pharmacokinetics of selected antiinflammatory, antihistamine, and immunomodulating drugs used in the therapy of bovine respiratory disease. Antiinflammatory drugs used in the therapy of bovine respiratory disease include glucocorticosteroids and non-steroidal antiinflammatory drugs (NSAIDs) such as aspirin, flunixin meglumine, and phenylbutazone. The glucocorticosteroids are potent antiinflammatories but also have deleterious effects on immune function with continued therapy. The NSAIDs have varying pharmacokinetics and also may produce toxicity through their potent prostaglandin-synthesis inhibition. An antihistamine labeled for use in cattle is available, but efficacy data has apparently not been published. Laboratory data supporting the use of vitamin C as an immunomodulator has been published, but clinical trial data is lacking. The literature concerning the immunomodulatory effects of levamisole indicates that results are variable at best.

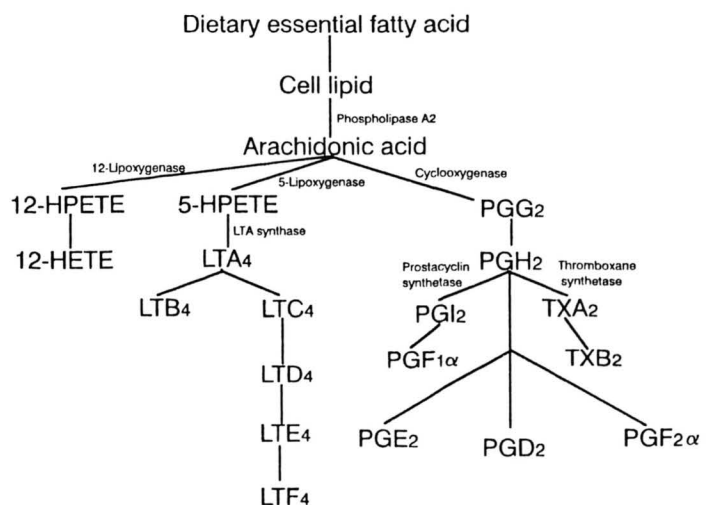
Through ancillary therapy we attempt to improve response to antimicrobial drugs. Ameliorating the harmful effects of inflammation, blocking the activity of histamine, and improving immune function serve to alter the pathophysiology of the infectious process. We tend to assume that this alteration is consistently beneficial. But other possible effects include drug interactions and direct toxicity. This paper reviews the pharmacodynamics and pharmacokinetics of selected antiinflammatory, anti-histamine, and immunomodulating drugs used in the therapy of bovine respiratory disease. Many of these drugs are not labeled for use in cattle, making a valid veterinary-client-patient relationship and an exaggerated withdrawal time necessary for their use. Additional criteria for extra-label use may be found in Food and Drug Administration Compliance Policy Guide 7125.06; Extra-Label Use of New Animal Drugs in Food-Producing Animals. Help in establishing exaggerated withdrawal times may be obtained from the Food Animal Residue Avoidance Databank (FARAD). Two FARAD locations are the University of California at Davis (916-752-7507) and the University of Florida, Gainesville, FL (904-392-4085).

Antiinflammatory Drugs

Physiology of inflammation

The majority of antiinflammatory drugs used in veterinary medicine target the lipid-derived autacoids, which include the eicosanoids. The eicosanoids include leukotrienes (LTs), thromboxane A₂ (TXA₂), prostacyclin (PGI₂), and other prostaglandins (PGs). Arachidonic acid is the primary precursor for the eicosanoids. It is either taken in directly through the diet or formed from linoleic acid of dietary origin and may be found in the mammalian cell membrane. Trauma, bacterial toxins, and other chemical insults directly or indirectly activate phospholipase A₂, releasing arachidonic acid from the cell membrane. The free arachidonic acid is then acted upon by either lipoxygenase or cyclooxygenase to form the eicosanoids (Fig. 1). The lungs are capable of synthesizing all of the eicosanoids, while some other tissues only synthesize selected products. An example is vascular endothelium, which primarily acts on PGH₂ with prostacyclin synthetase.

Figure 1. Synthesis pathway for eicosanoids



HPETEs - Hydroperoxyeicosatetraenoic acids, unstable intermediates

PG - Prostaglandins

LT - Leukotrienes

PGG₂, PGH₂ - Unstable prostaglandin intermediates

The eicosanoids have a wide variety of physiological effects.¹ PGI₂ (Prostacyclin) inhibits platelet aggregation, relaxes smooth muscle (bronchodilator in most species), inhibits gastric acid production, and may have a positive effect on renal blood flow. PGE₂ has similar effects on gastric acid production and renal blood flow, and also inhibits B-cell differentiation into plasma cells, T-cell proliferation, and release of lymphokines by T-cells. It also plays a major role in protecting the gastric mucosa. PGF₂α is a potent constrictor of smooth muscle in pulmonary vasculature and airways. TXA₂ (Thromboxane A₂) is thought to play a major role in platelet aggregation. It also is capable of bronchoconstriction and decreasing renal blood flow. Nerve endings are more sensitive to pain stimuli in the presence of PGE₂ and PGI₂.

Some of the leukotrienes were previously known as the slow reacting substance of anaphylaxis (SRS-A). LTC₄ and LTD₄ are approximately 1000 times more active than histamine in causing broncho-constriction and transudation from postcapillary venules. LTB₄ is a powerful leukocyte chemotactic agent.

Drugs which counteract the effects of the eicosanoids do so by inhibiting their synthesis. The eicosanoids are not stored, so this is an effective method of terminating their actions. These drugs may be divided into the glucocorticosteroids and the nonsteroidal anti-inflammatory drugs.

Glucocorticosteroids

Physiochemical properties

The basic endogenous glucocorticosteroid is hydrocortisone. All other glucocorticosteroids used in veterinary medicine are chemically altered forms of this compound. The glucocorticosteroids are 21 carbon compounds, which must have OH groups at carbons 11, 17, and 21 to have active antiinflammatory and glucogenic ability. This is called the alcohol form and is insoluble in water. The alcohol forms are transported in the blood attached to a carrier protein which serves as a reservoir from which the glucocorticosteroid is slowly released into the tissues. The alcohol forms are available as suspensions or solubilized in 40-50% polyethylene glycol.

Water-soluble glucocorticosteroids are synthetic and have various esters replacing the OH group on the 21 carbon. These forms are not attached to carrier proteins in the blood, making them more rapidly available to cells. Succinate and phosphate are common esters found in water-soluble forms.

Acetate and dipropionate esters are water-insoluble. They are used as "depo" agents for slow absorption. The synthetic glucocorticosteroids must be converted back to the alcohol form within the cell before they are active.

Pharmacokinetics

Addition of molecular alterations prolongs duration of action; dexamethasone > prednisolone > hydrocortisone. This relationship also holds true for antiinflammatory potency. Elimination half-time for dexamethasone in cattle is approximately 6 hours.

Pharmacodynamics

The glucocorticosteroids are extremely effective at preventing the synthesis of all the eicosanoids described above. This is done through membrane stabilization and by inducing synthesis of lipocortin, a protein which inhibits phospholipase A₂. These drugs also have substantial effects beyond eicosanoid synthesis inhibition. The glucocorticosteroids are protein catabolic, which leads to increased Ca⁺⁺ mobilization due to breakdown of the protein matrix in bone. Gluconeogenesis is also stimulated, using amino acids as a substrate. The increase in blood glucose is considered a short-term effect. Fatty acid and glycerol blood levels are also elevated. Some gluco-corticosteroids promote Na⁺ retention by the kidney (with increased K⁺ excretion), leading to increased extracellular fluid volume.

The glucocorticosteroids have a profound effect on the immune system, proving, as in life, there is no such thing as a free lunch in pharmacology. Numerous adverse effects on the immune system have been linked to the glucocorticosteroids.² They have been shown to inhibit interleukin-1 production by macrophages. Interleukin-1 acts as a chemo-tactic agent for leukocytes, activates T lymphocytes, and increases acute-phase protein production. Other effects of glucocorticosteroids include inhibition of macrophage migration-inhibition factor (this compound keeps macrophages from leaving the area of infection), interference with the actions of interferon-gamma, and interference of interleukin-2 production by activated T-cells. Glucocorticosteroids have also been shown to induce monocytes to produce a protein factor which inhibits neutrophil activity and to inhibit antibody responses to antigens.³ Cattle appear to be much more susceptible to the immunosuppressive effects of dexamethasone than swine. Two mg/kg of dexamethasone administered to swine does not have the immunosuppressive effects of 0.04 mg/kg administered to cattle.³ Dexamethasone administered at 0.04 mg/kg (0.9 mL/100 lbs. of a 2 mg/mL solution) daily for 3 days is used as an immunosuppression model in cattle.^{4,5}

The question becomes whether the anti-inflammatory or immunosuppressive effects are the most important clinically. A trial conducted in yearling feedlot cattle would indicate that the immunosuppressive effects predominate.⁶ Cattle were randomized into two groups, each of which received IV oxytetracycline (5 mg/lb) and IM Pyrilamine (250 mg) daily for three days as

the first-line treatment for respiratory disease. In addition, cattle in treatment 1 received 10 mL (20 mg) dexamethasone IM daily for the first three days, while those in treatment 2 received 10 mL of a placebo. Treatment of nonresponders was the same for both treatment groups.

	Treatment 1	Treatment 2
# treated	1113	1071
# responding	913 (82.0%)	916 (85.5%)
Death loss	77 (6.9%)	61 (5.7%)
Relapses	265 (23.8%)	193 (18.0%)

Response significantly different at $P \leq 0.05$

Relapses significantly different at $P \leq 0.01$

While it is possible the results would have been different with a different antibiotic, this study supports the observation that routine use of steroids in the therapy of bovine respiratory disease gives a short term improvement in visual appearance with a long term decrease in treatment response. Steroids still have a place in the therapy of inflammatory respiratory diseases such as diphtheria and tracheal edema, provided they are used reasonably. It is unlikely that a one-time administration of a glucocorticosteroid at a reasonable dose will have clinically significant effects on the immune system.

Bovine labels

Azium[®] powder and Azium[®] solution (Schering-Plough Animal Health, Kenilworth, NJ) are prescription products labeled for the treatment of bovine ketosis and use as an antiinflammatory agent in the bovine. Azium[®] solution is the alcohol form of dexamethasone solubilized in an alcohol/polyethylene glycol solution. Label dose of Azium[®] solution is 5 to 20 mg IM or IV with no slaughter withdrawal. Generic dexamethasone products are available, but all are labeled for horses only (not for use in horses intended for food). An exaggerated withdrawal time is necessary for use of these products.

Predef[®] 2X (Upjohn, Animal Health Division, Kalamazoo, MI) is an aqueous suspension of isoflupredone acetate labeled for IM or intrasynovial use in cattle for treatment of bovine ketosis, musculoskeletal conditions, allergic reactions, overwhelming infections with severe toxicity, shock, and other conditions. It is a prescription product, and requires a 7 day slaughter withdrawal. Isoflupredone acetate has 50 times the antiinflammatory potency of hydrocortisone (compared to 70-80X for dexamethasone). Label dose is 10 to 20 mg, repeated in 12-24 hours if needed.

Non-Steroidal Antiinflammatory Drugs (NSAIDs)

Aspirin (acetylsalicylic acid)

Physiochemical properties

Aspirin is a weak acid with a pKa of 3.5. In the relatively alkaline environment of the rumen, at a pH of 6.5, approximately 1000 times as much aspirin is in the ionized form compared to the more diffusible nonionized form. This results in a slow absorption rate in cattle. Aspirin is also highly protein bound (70-90%), a characteristic shared by all NSAIDs discussed here. Administration of 2 NSAIDs at one time or a NSAID in conjunction with another highly protein bound drug (sulfas) will result in higher concentrations of free drug in the plasma due to competition for binding sites.

Pharmacokinetics

There are large differences in elimination half-times between species. Values range from ≈ 4.0 hours after oral administration in cattle to ≈ 38 hours in cats. The pharmacokinetics of aspirin have been studied in adult cows of dairy breeding.⁷ The slow absorption rate after oral administration is evident in the difference between elimination half-times ($T_{1/2\beta}$) for IV sodium salicylate and oral acetylsalicylic acid in the table below. The $T_{1/2\beta}$ is longer after oral administration due to the rumen acting as a slow release reservoir for aspirin absorption into the blood. The low volume of distribution (Vd) indicates limited distribution to tissues.

$T_{1/2\beta}$ (hrs) - IV	0.54 ± 0.04
$T_{1/2\beta}$ (hrs) - oral	3.70 ± 0.44
Vd (L/kg)	0.24 ± 0.02
Absorption $T_{1/2}$ (hrs)	2.91 ± 0.37
Bioavailability	70%

An oral dose of 100 mg/kg (70 grains/100 lbs) maintained serum concentrations in excess of 30 $\mu\text{g/mL}$ between approximately 1 hour and 5 hours after administration. The mean peak serum concentration was close to 50 $\mu\text{g/mL}$. An oral dose of 50 mg/kg failed to reach serum concentrations of 30 $\mu\text{g/mL}$. The authors used 30 $\mu\text{g/mL}$ as the minimum concentration for pain relief based on human serum concentrations required for relief of headaches, aches, and pains. Serum concentrations near 100 $\mu\text{g/mL}$ are necessary in man to relieve severe arthritic pain. The authors noted clinical improvement in two cows with nonsuppurative tarsitis at 100 mg/kg orally, but noted no improvement at this dose in a bull with suppurative tarsitis. These data cast doubts on the ability of a reasonable dose of aspirin to control severe pleural pain. However, the 100 mg/kg

dose might be expected to have a significant effect on fever.

Pharmacodynamics

Aspirin is a cyclooxygenase inhibitor. It relieves pain and controls inflammation through peripheral actions by inhibiting the synthesis of numerous inflammatory mediators. Antipyretic effects are both central (temperature control center in the hypothalamus) and peripheral (vasodilation and redistribution of body water).

Bovine labels

Numerous aspirin boluses (60 and 240 grain) are available for use in cattle. Introduction of the 240 grain boluses into an atonic rumen may result in prolonged contact between the bolus and the ventral wall of the rumen. Severe tissue damage or a penetrating ulcer are possibilities.

Phenylbutazone

Physiochemical properties

Phenylbutazone is a weak acid, $pK_a = 4.4$. It is highly protein bound (up to 99% in horses) and may displace other highly bound drugs such as sulfas. It has produced fatal blood dyscrasias in man. IM injection of phenylbutazone is not appropriate due to the irritating nature of the solution.

Pharmacokinetics

As for aspirin, there are large species differences in $T_{1/2\beta}$. Values range from 2.5-6.0 hours in the dog to 55-65 hours in cattle. The pharmacokinetics of phenylbutazone have been determined in adult cows.⁸

$T_{1/2\beta}$ -oral	54.7 ± 4.2 hrs
$T_{1/2\beta}$ -IV	55.1 ± 5.6 hrs
Vd β	0.09 ± 0.01 L/kg
Bioavailability (oral)	67.5% (41.9-95.5)
Tmax (oral, 5 mg/kg)	8 hrs
Cmax (oral, 5 mg/kg)	32.1 ± 1.0 µg/mL

Values reported ± standard deviation or (range)

Tmax = Time of maximal serum concentration

Cmax = Maximal serum concentration

The authors extrapolated a therapeutic serum concentration of 60-90 µg/mL from human literature. They proposed an oral loading dose of 10-20 mg/kg and daily maintenance doses of 2.5-5.0 mg/kg. The pharmacokinetics of phenylbutazone in adult Holstein bulls have also been investigated.⁹

$T_{1/2\beta}$ -oral	62.6 ± 12.9 hrs
$T_{1/2\beta}$ -IV	61.6 ± 7.2 hrs

VdSS	0.14 ± 0.02 L/kg
Bioavailability (oral)	73.0 ± 2.0 %
Tmax (oral, 10 mg/kg)	8.99 ± 0.72 hrs
Cmax (oral, 10 mg/kg)	47.3 ± 2.5 µg/mL

Values reported ± standard deviation

An IV dose of 10 mg/kg maintained serum concentrations above 65 µg/mL for 10 hours and above 55 µg/mL for 20 hours. Serum concentrations at 30 hours were near 50 µg/mL. The volumes of distribution from both studies indicate limited distribution to tissues. Caution should be used in extrapolating these pharmacokinetic values to younger cattle with pneumonia due to age and disease dependent changes in pharmacokinetics. It is also important to remember that antiinflammatory activity of phenylbutazone may persist much longer than serum concentrations due to irreversible binding to the cyclooxygenase enzyme.

Pharmacodynamics

Phenylbutazone is a cyclooxygenase inhibitor with anti-inflammatory, antipyretic, and analgesic properties. The potent antiprostaglandin activity may lead to gastric ulceration with repeated high doses.

Bovine labels

No products with a bovine label are marketed in the United States. Use of an injectable or oral product in an extra-label-manner requires an exaggerated withdrawal time.

Flunixin meglumine

Physiochemical properties

Flunixin meglumine is a highly substituted derivative of nicotinic acid. It is highly protein bound in the horse. Flunixin meglumine may persist in inflammatory exudates for extended periods beyond serum concentrations.¹⁰

Pharmacokinetics

Flunixin meglumine is rapidly absorbed from IM injection sites. Peak plasma concentrations of 3.4 ng/mL are obtained within 15 minutes. Plasma concentration remains near 3.1 ng/mL at 24 hours. $T_{1/2\beta}$ is reported as 3.7 hours.¹¹

Pharmacodynamics

Flunixin meglumine is considered an effective analgesic, antiinflammatory, and antipyretic. The mechanism of action is cyclooxygenase inhibition. The efficacy of flunixin meglumine in the therapy of experimental *Pasteurella haemolytica* pneumonia has been investigated in 12 week old dairy calves.¹² Calves were allocated to 4 groups: no treatment, oxytetracycline (10 mg/

kg IM SID for 3 days), flunixin meglumine (2.2 mg/kg IV SID for 3 days), and both oxytetracycline and flunixin meglumine. Oxytetracycline alone reduced the number of calves with fevers and tachypnea and reduced the extent and severity of fibrinous pneumonia as compared to the controls. Flunixin meglumine alone produced no antipyretic effect and no reduction in severity of *Pasteurella* pneumonia compared to the control calves. Fewer calves were noted with tachypnea. One of the 8 flunixin meglumine calves died, compared with none in the other two positive treatment groups. When oxytetracycline and flunixin meglumine were combined, no macroscopic consolidation was evident in the lungs, and rectal temperature dropped more quickly than in any of the other three groups.

Another study induced pneumonia in 12-week-old calves by administering PI3 virus into the upper airways.¹³ Flunixin meglumine (2.2 mg/kg IV SID for 3 days) reduced the number of calves coughing, the number of calves with fever (> 39.7° C), and the number of calves with tachypnea as compared to untreated controls. The treated group had a marked decrease in pulmonary consolidation.

Bovine labels

There is not currently a bovine label for flunixin meglumine in the United States. It is marketed as a combination product with oxytetracycline in England and France. Use of flunixin meglumine in food animals requires an extended withdrawal period.

Antihistamines

Histamine

Histamine is released primarily from mast cells in response to antigenic stimulation and cellular insult. The mucosa of the bronchial tree and intestine have high concentrations of mast cells. Histamine causes bronchoconstriction, vasodilation, and increased capillary permeability through the activation of H1 receptors (although H2 receptors may play a role in vasodilation). The antihistamines used in food animal medicine are primarily H1 blockers.

Pharmacodynamics

The H1 blockers are competitive antagonists at the H1 receptor. Some H1 blockers also have prominent anti-cholinergic activity, although this is not so for the ethylenediamine antihistamines discussed here. Pyrilamine maleate and tripeleminamine hydrochloride are two ethylenediamine H1 blockers used in veterinary medicine. There has apparently been very little work done in the form of clinical trials to validate the efficacy of these drugs in the treatment of bovine respiratory

disease. Their primary application may be respiratory syndromes where a hyperimmune component is suspected, as in atypical interstitial pneumonia. In regard to airway constriction, it is interesting to note that antihistamines are ineffective in the treatment of human asthma, as are cyclooxygenase inhibitors. It is felt that leukotrienes are predominantly responsible for allergic bronchoconstriction, as evidenced by protection provided by lipoxigenase inhibitors.¹

Pharmacokinetics

As for clinical trials, the pharmacokinetics of these drugs in the bovine have apparently not been investigated. The label for tripeleminamine HCL calls for administration Q6-12 h, as needed. This is consistent with the rapid elimination of this class of antihistamines shown in other species. The efficacy of once daily administration of an antihistamine in the feedlot environment should be critically evaluated in light of the short duration of action of these compounds.

Bovine labels

Tripeleminamine HCL (Re-covr[®], Solvay Animal Health, Inc., Mendota Heights, MN) is labeled for use in cattle. Label dose is 1.1 mg/kg (2.5 mL/100 lbs.) IV or IM, repeated in 6 to 12 hours if needed, with a 4 day withdrawal period. Pyrilamine maleate is approved only for use in horses not intended for food.

Immunomodulators

Two immunomodulators which have received recent attention in food animal medicine are vitamin C and levamisole. A good rule for evaluating these compounds is to remember the term "modulator" includes both stimulators and inhibitors. An excellent reference on the current status of immunomodulation in food animals has been published.¹⁴

Vitamin C (ascorbic acid)

A review of the literature by Reddy and Frey indicates that vitamin C concentrations in leukocytes are higher than other tissues and are decreased by viral infections and stress. Interferon production, antigen clearance, and lymphocyte proliferation are affected by vitamin C concentrations.¹⁵ Most animals synthesize their own vitamin C, notable exceptions being Man, non-human primates, and guinea pigs.

Physiochemical properties

Vitamin C is a water soluble vitamin. The generic preparations currently available contain 250 mg/mL of sodium ascorbate in water.

Pharmacokinetics

The pharmaco-kinetics of the injectable products have apparently not been studied in the bovine.

Pharmacodynamics

Forty-two steers of various breeding, weighing between 350 and 500 kg, were used to determine the effect of vitamin C on normal and dexamethasone altered bovine neutrophil function.⁴ Dexamethasone, 0.04 mg/kg IM SID for 3 days, was used to depress neutrophil function. Treatment groups consisted of untreated controls, dexamethasone daily for 3 days, vitamin C (20 mg/kg, SC) daily for 3 days, and vitamin C (10, 20, or 40 mg/kg, SC) daily in conjunction with daily dexamethasone administration. Administration of vitamin C in the absence of dexamethasone resulted in increased neutrophil oxidative metabolism. The ability of neutrophils to mediate antibody-dependent cell-mediated cytotoxicity (ADCC) was also enhanced. Dexamethasone administration decreased neutrophil oxidative metabolism and ADCC. Ascorbic acid tended to reverse these effects in a dose dependent fashion. No effect was noted at the lowest dose (10 mg/kg). Vitamin C also tended to increase the ability of bovine neutrophils to phagocytize *Staphylococcus aureus*. Clinical trials showing the link between these neutrophil responses and treatment response have not been published.

Bovine labels

The generic products currently available are labeled for use in non-human primates and guinea pigs. Their extra-label use in cattle requires an extended withdrawal time.

Levamisole

Physiochemical properties

Levamisole is an imidazothiazole compound. The HCL salt is water soluble. The injectable forms are composed of the phosphate salt.

Pharmacokinetics

Levamisole is highly metabolized in the liver, with only $\approx 6\%$ excreted unchanged. Elimination half-time in cattle is $\approx 4-6$ hours.

Pharmacodynamics

The anthelmintic activity of levamisole is mediated through a nicotine-like action at autonomic ganglia of the parasites. Higher concentrations interfere with parasite energy metabolism. Levamisole is effective against a wide range of gastrointestinal and pulmonary parasites but is generally ineffective against immature and inhibited forms in cattle.

The effect of levamisole on the immune system is

thought to be an alteration of the function of T lymphocytes, monocytes, and neutrophils. The effects are time- and dose-dependent. Immunostimulatory benefits occur at doses in the 2 to 3 mg/kg range, compared to an anthelmintic label dose of 6 mg/kg.¹⁶ Cattle receiving levamisole (8 mg/kg, SC) at the time of vaccination for IBR-PI3 had a decreased immune response as compared to controls by serum neutralization.¹⁷ Ten, 4-5 month old, Holstein steers were used to evaluate the efficacy of levamisole on induced BVD infection.¹⁸ The calves were treated with penicillin and streptomycin for 3 days following appearance of clinical signs. One group also received levamisole (2 mg/kg, SC) 3 days of each week for 7 weeks. The levamisole treated calves did not develop the marked lymphopenia displayed by the control calves. Speed of recovery and severity of infection did not differ between the treatment and control group. A study using the dexamethasone immuno-suppression model described for vitamin C above showed that levamisole did not enhance neutrophil function in dexamethasone treated calves.⁵ The efficacy of levamisole in the treatment of respiratory disease needs to be investigated in the feedlot environment via a clinical trial utilizing negative controls and a rigid protocol. Some of the inconsistent trial results in the literature may be attributed to trial design.

Bovine labels

Levamisole phosphate is labeled for use in cattle (Levasole[®] injectable solution, 13.65%, Tramisol[®] injectable solution, 13.65%, Pitman-Moore, Mundelein, IL, Tramisol[®], RX Veterinary products, Porterville, CA). Levamisole HCL is available in bolus and powder forms.

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Abstract

Associations between viral infections and respiratory disease in artificially reared calves

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Market-purchased, week-old, dairy bred calves entering a commercial calf-rearing unit were blood sampled at six-week intervals until three months old. Viral infections were monitored by ELISA for antibodies to bovine herpesvirus 1, bovine respiratory syncytial virus, parainfluenzavirus-3, bovine adenovirus subgroup 1 and bovine viral diarrhoea virus (BVDV). The immunoperoxidase test was used to detect BVDV in serum. The total immunoglobulin concentration in the initial blood sample was measured by the zinc sulphate turbidity test. The relationship between clinical respiratory disease, viral sero-conversion and the initial concentration of serum immunoglobulin was investigated by the use of the relative risk statistic, Fisher's exact test, χ^2 techniques and the correlation coefficient. Treat-

ment rates for respiratory disease of 45 per cent were observed during the first period of the study and 19 per cent during the second period. During the first period there was a significant positive association between clinical respiratory disease and seroconversion for all the viruses except parainfluenzavirus-3 and BVDV but in the second period there was no such relationship. Similarly, in the first period, but not in the second, there was a significant negative association between clinical respiratory disease and both antiviral immunoglobulin as measured by ELISA and total immunoglobulin as measured by the zinc sulphate turbidity test. Two of the 536 calves that survived to three months of age were found to be persistently infected with BVDV.