Efficacy of sodium iodide for prevention of respiratory disease in preweaned dairy calves

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OBJECTIVE
To determine the pharmacokinetics of sodium iodide (NaI) following oral administration to preweaned dairy calves, and to assess the efficacy of NaI for prevention of bovine respiratory disease (BRD) in preweaned calves at a commercial calf-raising facility.

ANIMALS
434 healthy preweaned dairy calves.

PROCEDURES
In the first of 2 experimental trials, each of 7 calves received NaI (20 mg/kg, PO) once. Blood and nasal fluid samples were collected at predetermined times before (baseline) and for 72 hours after NaI administration for determination of iodine concentrations. Pharmacokinetic parameters were determined by noncompartmental analysis. In the second trial, 427 calves at a calf-raising facility were randomly assigned to receive NaI (20 mg/kg, PO, 2 doses 72 hours apart; n = 211) or serve as untreated controls (216). Health outcomes were compared between the 2 groups.

RESULTS
For all 7 calves in the pharmacokinetic trial, the iodine concentration in both serum and nasal fluid samples was significantly increased from the baseline concentration and exceeded the presumed therapeutic iodine concentration (6.35 μg/mL) throughout the sampling period. In the on-farm trial, the odds of being treated for BRD before weaning for NaI-treated calves were twice those for control calves (OR, 2.04; 95% CI, 1.38 to 3.00).

CONCLUSIONS AND CLINICAL RELEVANCE
Results suggested that, although oral administration of NaI (20 mg/kg) to preweaned dairy calves achieved iodine concentrations presumed to be effective in both serum and nasal fluid, it was not effective for prevention of BRD in preweaned calves at a commercial calf-raising facility. (*Am J Vet Res* 2020;81:673–680)

Bovine respiratory disease is the second leading cause of death in preweaned dairy calves, only exceeded by neonatal calf diarrhea.[1] The estimated annual cost of BRD in preweaned calves is $14.71/calf at risk of disease.[1] Calves are at greatest risk of developing BRD during stressful periods, such as processing (ie, vaccination, dehorning, and castrating) and weaning, and the number of weaned dairy calves that die because of BRD has been increasing.[2] Therefore, it is important to investigate options to enhance the immune system of calves prior to stressful events.

Such events (eg, weaning) can lead to immunosuppression, which makes calves more susceptible to viral respiratory pathogens, such as bovine respiratory syncytial virus, bovine herpesvirus 1, parainfluenza virus type 3, and bovine viral diarrhea virus. Viral infection can damage the respiratory tract mucosa and exacerbate immunosuppression, which facilitates the establishment of secondary bacterial infections caused by the migration of normal pharyngeal flora or other bacterial pathogens, such as *Mannheimia haemolytica*, *Pasteurella multocida*, *Mycoplasma bovis*, and *Histophilus somni*, into the lower portion of the respiratory tract.[3–5]

Antimicrobial resistance of bacteria is an emerging global issue that necessitates the development or identification of alternative strategies to prevent and treat bacterial infections.[6,7] Dairy heifers are commonly vaccinated against respiratory viral pathogens by a parenteral route prior to breeding, but parenteral administration of vaccines to young dairy calves may not be effective owing to the presence of maternal antibodies that interfere with processing of vaccine antigens by the immune system.[8,9] Vaccines against BRD pathogens that can be administered by the intranasal route have been developed for cattle. Intra-

ABBREVIATIONS

AUC	Area under the concentration-time curve
BRD	Bovine respiratory disease
C_{max}	Maximum concentration
NaI	Sodium iodide
$t_{1/2\lambda}$	Terminal half-life
t_{max}	Time to maximum concentration
TUS	Thoracic ultrasound score

nasal administration of vaccines stimulates primarily mucosal immunity rather than systemic immunity but typically avoids maternal antibody interference, which may be beneficial in young calves.

Augmentation of the host's immune system is another alternative for prevention of BRD. The upper portion of the respiratory tract (nose, nasal cavity, paranasal sinuses, pharynx, and larynx; upper respiratory tract) of cattle has multiple innate defense mechanisms, one of which is dependent on the presence of peroxidases in airway surface liquid.[10,11] Lactoperoxidase is produced in epithelial submucosal glands, and hydrogen peroxide is produced by dual oxidase enzymes on the respiratory epithelium.[10,11] The substrate for the reaction is either a halide or a pseudohalide ion.[10,11] In the natural system, lactoperoxidase catalyzes a reaction between hydrogen peroxide and thiocyanate, a pseudohalide secreted by the NaI symporter in the basolateral plasma membrane, resulting in the formation of hypothiocyanite within the airway surface liquid.[10,11] Hypothiocyanite has antibacterial properties.[12,13] If iodine is available during that reaction, hypoiodous acid will be produced, which has potent antibacterial and antiviral properties.[10,11]

Results of an experimental study[14] indicate that the lactoperoxidase-hydrogen peroxide-iodide reaction inactivates or inhibits bovine herpesvirus 1, parainfluenza virus type 3, *M haemolytica*, and *Bibersteinia trehalosi* in vitro, and oral administration of NaI (70 mg/kg) to weaned beef calves causes a marked increase in the iodine concentration of nasal secretions for at least 72 hours. In fact, the iodine concentration achieved in the nasal secretions of the treated calves exceeded the minimal iodine concentration necessary for inactivation of respiratory pathogens in vitro (6.35 µg/mL).[14] In cattle, NaI is commonly administered IV for the treatment of infections caused by *Actinomyces bovis* and *Actinobacillus lignieresii* at a dose of 70 mg/kg. In the United States, NaI has a legacy label for these indications, which does not include withdrawal times for meat and milk.

Scientific evidence that supports the use of NaI to enhance the innate immunity of calves against respiratory tract pathogens would be beneficial to the cattle industry for many reasons, including the improved health and production of the animals as well as a decrease in antimicrobial use and treatment costs for BRD. The study reported here had 2 primary objectives. The first was to determine the pharmacokinetics of NaI following oral administration of a single dose (20 mg/kg) of the compound to preweaned dairy calves. The second objective was to assess the efficacy of NaI (20 mg/kg, PO, 2 doses 72 hours apart) for prevention of BRD in preweaned dairy calves at a large calf-raising facility. Our hypotheses were that high concentrations of iodine would be secreted in the respiratory fluids of preweaned dairy calves following oral administration of NaI and that preweaned dairy calves orally administered NaI would have lower thoracic ultrasound and respiratory scores and be less likely to require treatment for BRD, compared with similar calves that did not receive NaI.

Materials and Methods

The study consisted of 2 experimental trials. The first trial was conducted to determine the pharmacokinetics of NaI following oral administration to preweaned dairy calves. It involved the use of university-owned calves and was conducted at the University of California-Davis William R. Pritchard Veterinary Medical Teaching Hospital. The second trial was conducted to assess the efficacy of NaI for controlling BRD in preweaned dairy calves and was performed at a commercial calf-raising facility in the Central Valley of California. The owner of the calf-raising facility consented to the trial prior to its initiation. All study procedures were reviewed and approved by the University of California-Davis Institutional Animal Care and Use Committee.

Trial 1 (Pharmacokinetic trial)

Animals—Seven university-owned preweaned female Holstein calves (age range, 14 to 26 days) were used for this study. Each calf was considered healthy on the basis of results of a physical examination. The calves were transported to the veterinary teaching hospital and individually housed in pens (approx 1 × 2 m) within a barn such that they did not have nose-to-nose contact with each other for the duration of the trial. The calves were fed 3 L of milk replacer[a] twice daily and had free access to water and a commercial starter ration for the duration of the trial. Following a 2-day acclimation period, each calf received 1 dose of NaI (20 mg/kg, PO); the compound was provided as a 20% solution[b] (200 mg/mL) that was added to the morning milk replacer feeding on day 1. Appetite, urination, and defecation of each calf were monitored throughout the duration of the trial. Following NaI administration, calves were also monitored for signs of iodism, such as hypersalivation, epiphora, and coughing, as well as other adverse effects twice daily.

Sample collection and analysis—For each calf, a brief physical examination, which included evaluation of respiration and assessment for coughing and the presence of nasal and ocular discharges, was performed immediately before sample collection at each predetermined sample acquisition time. A blood sample (10 mL) and nasal secretion specimen were collected at 0 (immediately before; baseline), 1, 3, 6, 12, 24, 36, 48, and 72 hours after NaI administration. Blood samples were collected by jugular venipuncture into 10-mL blood collection tubes[c] without any additives to obtain serum for determination of serum iodine concentration. Blood samples were centrifuged at 1,000 × *g* for 10 minutes at room temperature (approx 22°C). Serum was harvested from each sample, placed in a clean cryovial, and stored frozen at –80°C until analyzed.

Nasal secretion specimens were obtained by placing a dental cotton roll[d] into each nasal cavity for approximately 20 seconds. The rolls were then removed and placed into a 15-mL conical tube[e] that contained a plunger from a 1-mL syringe to ensure space at the bottom of the tube for fluid to collect during centrifugation. The tubes were centrifuged at 400 × *g* for 15 minutes at room temperature. The resulting fluid was pipetted into clean 2-mL cryovials. If < 1 mL of fluid was recovered, the recovered fluid was diluted 1:2, in an equal volume of Dulbecco PBS solution.[f] The nasal fluid samples were then stored frozen at –80°C until analyzed.

All blood and nasal fluid samples were submitted to the Michigan State University Veterinary Diagnostic Laboratory in Lansing, Mich, for determination of iodine concentration by inductively coupled plasma mass spectroscopy as described.[15] Briefly, each serum or nasal fluid sample was mixed with 10% trichloroacetic acid at a 1:4 dilution to precipitate the proteins from the sample. Following centrifugation, the supernatant was removed for analysis. The sample was diluted 20-fold with a solution containing a mixture of 0.5% EDTA and Triton X-100, 1% ammonium hydroxide, 2% butanol, and 20 ppb of scandium, rhodium, indium, and bismuth as internal standards.[g] The inductively coupled plasma mass spectroscopy system was tuned to yield a minimum sensitivity of 7,500 counts/s for 1 ppb yttrium (molecular weight, 89 g/mol), < 1.0% oxide as determined by the 156:140 mass ratio, and < 2.0% double-charged ions as determined by the 70:140 mass ratio. Concentration was calibrated with a 4-point linear curve of the iodine-to-internal standard response ratio.

Trial 2 (on-farm trial)

Animals—Four hundred twenty-seven apparently healthy Holstein and Jersey calves (age range, 11 to 17 days) maintained at a commercial calf-raising facility in the Central Valley of California were enrolled in a blinded randomized clinical trial. All calves were born off-site at 1 of 7 local dairy farms and were transported to the calf-raising facility within 24 hours after birth. Colostrum was administered at the farm of origin, and information regarding colostrum intake was not available to investigators. Upon arrival at the calf-raising facility, each calf was individually weighed and received a modified-live virus vaccine[h] that contained a temperature-sensitive strain of bovine herpesvirus 1, bovine respiratory syncytial virus, and parainfluenza virus type 3 (2 mL, intranasal) and a live-culture bacterin[i] containing avirulent *Salmonella dublin* (2 mL, SC).

At 5 days of age, each calf received a live-culture bacterin[j] containing avirulent *P multocida* and *M haemolytica*. Additional vaccines were administered to each calf at > 35 days of age after the trial was completed. All calves were individually housed in hutches and fed and cared for in accordance with the standard operating procedures for the facility. The study was conducted in November when ambient temperatures were moderate (range, 7.2°C to 18.3°C).

Experimental design—Calves were individually identified by means of a unique ear tag. Each calf was randomly assigned to receive NaI (20 mg/kg, PO in milk on day 1 and again on day 4; n = 211) or serve as an untreated control (216) by randomization of the calves' ear tag numbers, with blocking for farm of origin and age. The calves in the NaI-treatment group received 2 doses of NaI 72 hours apart to ensure that the serum and nasal fluid iodine concentrations remained above the minimum effective iodine concentration required for in vitro inactivation of bovine respiratory tract pathogens (6.35 µg/mL; presumed effective concentration) reported in a previous study.[14]

A subgroup of 140 calves (70 NaI-treated calves and 70 control calves) were randomly selected by randomization of ear tag numbers and blocking by age to undergo a thoracic ultrasonographic examination and be assigned a TUS and clinical respiratory score immediately before NaI administration on day 1 and again on day 7. The individual responsible for administering NaI to the designated calves was not involved with the thoracic ultrasonographic examinations or score assignments. Each treatment group was assigned a color, and the hutches of study calves were marked with the appropriate color so the individuals performing the thoracic ultrasonographic examinations and clinical scoring remained unaware of (were blinded to) the treatment group assignment.

Clinical respiratory score—Each calf of the subset of 140 calves selected for additional evaluation was assigned a clinical respiratory score as described[16] prior to the ultrasonographic examination on days 1 and 7. Briefly, 4 variables (rectal temperature, cough, nasal discharge, and ocular discharge and ear position) were assessed and assigned a score on a scale of 0 (clinically normal) to 3 (severely abnormal; BRD likely). Thus, 12 was the maximum clinical respiratory score that could be assigned to a calf during an assessment. All clinical respiratory scores were assigned by the same investigator (MCH).

TUS—Following assignment of the clinical respiratory score, each calf of the subset of 140 calves selected for additional evaluation underwent a thoracic ultrasonographic examination on days 1 and 7. All examinations were performed by 3 veterinarians with a portable ultrasound unit[k] and a 5- to 7.5-mHz variable frequency rectal probe as described.[17] Briefly, the hair was clipped from both sides of the thorax from the fourth to tenth intercostal spaces.[17] The skin was soaked with isopropyl alcohol, and the ultrasound probe was applied to each intercostal space where the hair had been clipped and moved in a dorsal to ventral direction.[17] The entire lung field was scanned,

and the calf was assigned a TUS on a 4-point scale, where 1 = ultrasonographically normal lung tissue, 2 = presence of diffuse comet tails without evidence of lung tissue consolidation, 3 = evidence of lung tissue consolidation ≥ 1 cm in 1 or more areas, and 4 = evidence of extensive lung tissue consolidation (ie, ≥ 6 cm) in 1 or more areas.[17]

Treatment records and weaning weights—Calves were monitored and treated for disease by calf-raising personnel in accordance with the standard operating procedures for the facility. All health events and treatments were recorded daily. One trained facility employee was responsible for making treatment decisions for the study calves (ie, calf treater). Calves with a fever (> 38.6°C) in addition to signs of depression, coughing, nasal discharge, or ocular discharge were treated for BRD. Calves with a head tilt alone or in conjunction with a fever were treated for otitis. Calves with feces of watery or bloody consistency or with signs of depression and dehydration were treated for diarrhea. Calves were individually weighed by facility personnel at weaning. All health (including weights) and treatment records were maintained in and extracted from a record management software program.[l]

Data analysis

During the pharmacokinetic trial, serum samples were successfully obtained at all 9 sample acquisition times for all 7 calves. However, a complete set of nasal fluid samples was successfully obtained from only 5 of the 7 calves. Thus, 2 calves were excluded from the nasal fluid sample analysis: one because of contamination of the baseline sample, and the other because an insufficient volume of nasal secretions was obtained at 2 of the 9 sample acquisition times. Repeated-measures ANOVA was used to compare serum and nasal fluid iodine concentrations among various sample acquisition times (times). The iodine concentrations over time in serum and nasal fluid samples were plotted, and the C_{max} and t_{max} were determined by visual examination of the plots. Noncompartmental analysis[m] was used to estimate other pharmacokinetic parameters for NaI. The $t_{1/2\lambda}$ was calculated as 0.693/terminal rate constant, and the AUC was calculated by use of the log-linear trapezoidal method.

The data for the on-farm trial were coded so that the person (BVL) who analyzed it remained blinded as to which group was the NaI-treated group and which group was the untreated control group. General linear models were used to assess the effect of NaI treatment on the following continuous and ordinal outcome variables: TUS on day 1, TUS on day 7, change in TUS between days 1 and 7 (ΔTUS), clinical respiratory score on day 1, clinical respiratory score on day 7, average daily gain, number of diarrhea events, number of BRD events, and number of otitis events. Logistic regression was used to assess the effect of NaI administration on whether a calf was treated for diarrhea, BRD, and otitis. The outcome of interest (dependent variable) in those models was whether a calf was treated for the disease in question (yes or no). Both the general linear models and logistic regression models included fixed effects for treatment group (NaI or control), breed, sex, herd of origin, birthdate, and all possible 2-way interactions involving treatment

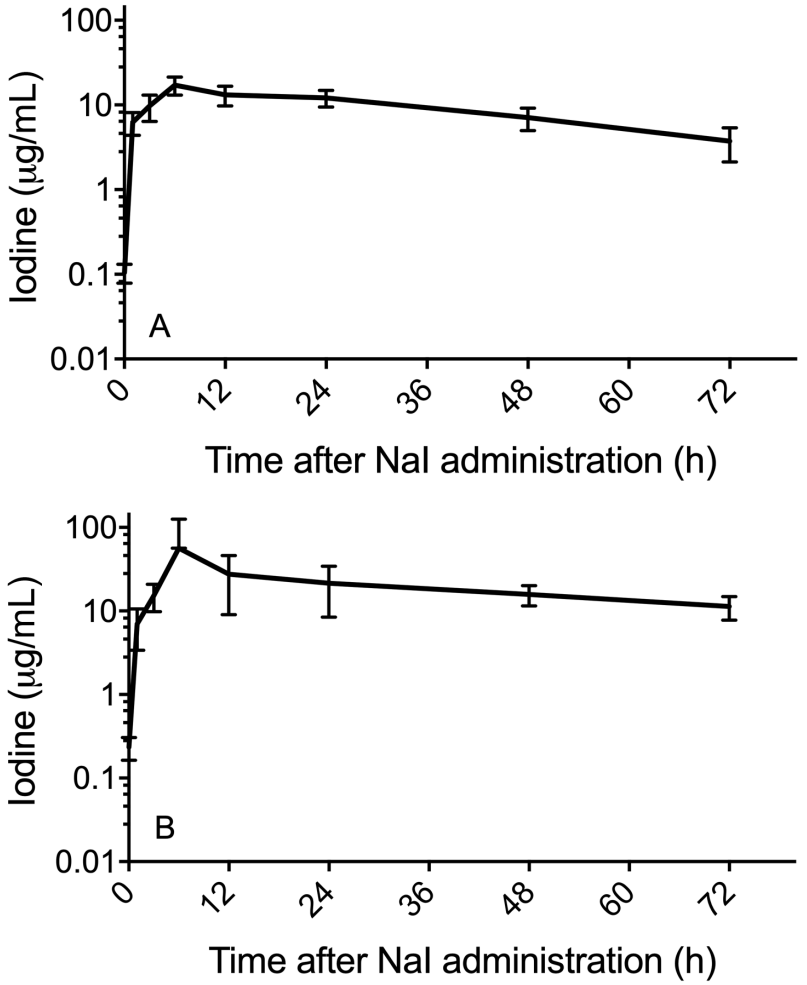

Figure 1—Mean ± SD iodine concentration over time in serum (A) and nasal fluid (B) samples obtained from 7 healthy preweaned female Holstein calves (age range, 14 to 26 days) that received a single dose of NaI (20 mg/kg, PO; pharmacokinetic trial). Values for nasal fluid samples represent the mean for only 5 of the 7 calves; 1 calf was excluded from the analysis because the baseline nasal secretion specimen was contaminated, and 1 calf was excluded because a sufficient volume of nasal secretions for analysis was not obtained at 2 of the 9 sample acquisition times.

group. All models were built by backward elimination such that all fixed effects were included in the model and then variables with values of $P > 0.1$ were removed one by one in a stepwise manner to produce the model that described the relationship between treatment and outcome most appropriately. For the logistic regression models, confounding was assessed by evaluation of the change in the OR for treatment group between models with and without the potential confounder included. If the OR changed by > 20%, the variable in question was identified as a confounder and forced back into the model regardless of its *P* value. Results for the logistic regression models were reported as the ORs and their associated 95% CIs. All analyses were performed by use of a commercial statistical software program.[n]

Results

Pharmacokinetic trial

All 7 calves tolerated oral administration of NaI well, and no adverse effects were observed including signs of iodism, such as abnormally increased lacrimation, ptyalism, coughing, or diarrhea. The mean iodine concentration over time in serum and nasal fluid samples was plotted **(Figure 1)**. For both serum and nasal fluid samples, the mean ± SD iodine concentration was increased from baseline (before NaI administration; 0 hours) at all other sample acquisition times. The pharmacokinetic parameters for NaI as estimated from serum iodine concentration data were summarized **(Table 1)**. In serum, the iodine concentration increased quickly following oral administration of NaI, achieving a mean ± SD C_{max} of 17.2 ± 4.0 µg/mL at a mean ± SD t_{max} of 7.7 ± 2.9 hours. The mean serum iodine concentration remained above the presumed therapeutic concentration (6.35 µg/mL) for the duration of the sampling period. The mean ± SD $t_{1/2\lambda}$ of NaI in serum was 26.7 ± 6.5 hours. In nasal fluid samples, the iodine concentration achieved a mean ± SD C_{max} of 59.0 ± 66.8 µg/mL (median, 30 µg/mL; range, 19.7 to 177.4 µg/mL) at a mean ± SD t_{max} of 7.2 ± 2.7 hours (median, 6 hours; range, 6 to 12 hours). The mean nasal fluid iodine concentration exceeded the presumed effective concentration beginning 1 hour after NaI administration and remained above that concentration for the remainder of the sampling period. The fact that the C_{max} for nasal fluid iodine concentration was approximately 3.5 times the C_{max} for serum iodine concentration indicated iodine was actively excreted into nasal secretions following oral administration of NaI.

On-farm trial

The mean rectal temperature, clinical respiratory score **(Figure 2)**, and TUS **(Figure 3)** did not differ significantly between the NaI-treated calves and control calves at the start of the trial. On day 7, the mean clinical respiratory score for the NaI-treated calves (1.9) was significantly ($P = 0.024$) greater than that for the control calves (1.5). There was a significant association between treatment group and birthdate and herd of origin for calves. When controlling for the effects of birthdate and herd of origin, NaI-treat-

Table 1—Pharmacokinetic parameters for NaI following oral administration of a single dose (20 mg/kg) to 7 healthy preweaned female Holstein calves (age range, 14 to 26 days) as estimated by noncompartmental analysis.

Parameter	Mean ± SD	Median (range)
C_{max} (µg/mL)	17.2 ± 4.0	18.7 (12.1–23.4)
t_{max} (h)	7.7 ± 2.9	6 (6–12)
$t_{1/2\lambda}$ (h)	26.7 ± 6.5*	27.6 (17.9–39.6)
$AUC_{0-\infty}$ (h•µg/mL)	802.1 ± 256.8	774.1 (534.9–1,253)
$AUC_{\%extrap}$ (%)	18.2 ± 6.4	19.4 (8.5–29.6)

*Harmonic mean.

$AUC_{0-\infty}$ = AUC from time 0 to infinity. $AUC_{\%extrap}$ = AUC from the last measured time extrapolated to infinity and expressed as a percentage of the total AUC.

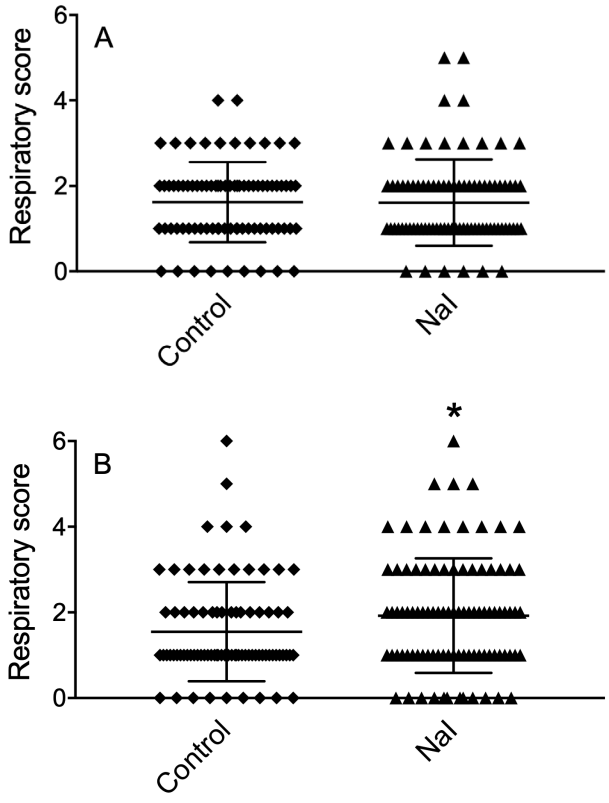

Figure 2—Plots of the clinical respiratory scores for preweaned dairy calves that did (NaI; triangles; n = 70) and did not (control; diamonds; 70) receive NaI (20 mg/kg, PO, on days 1 and 4) before (A) and 7 days after (B) administration of the first dose of the compound (ie, on-farm trial). Each of 4 variables (rectal temperature, cough, nasal discharge, and ocular discharge and ear position) was assigned a score from 0 (clinically normal) to 3 (severely abnormal), then the 4 scores were summed together and recorded as the clinical respiratory score. Thus, 12 was the maximum clinical respiratory score that could be assigned to a calf. For each plot, the long horizontal line represents the mean and the short horizontal lines represent the SD. *Mean value differs significantly ($P < 0.05$) from that for the control group.

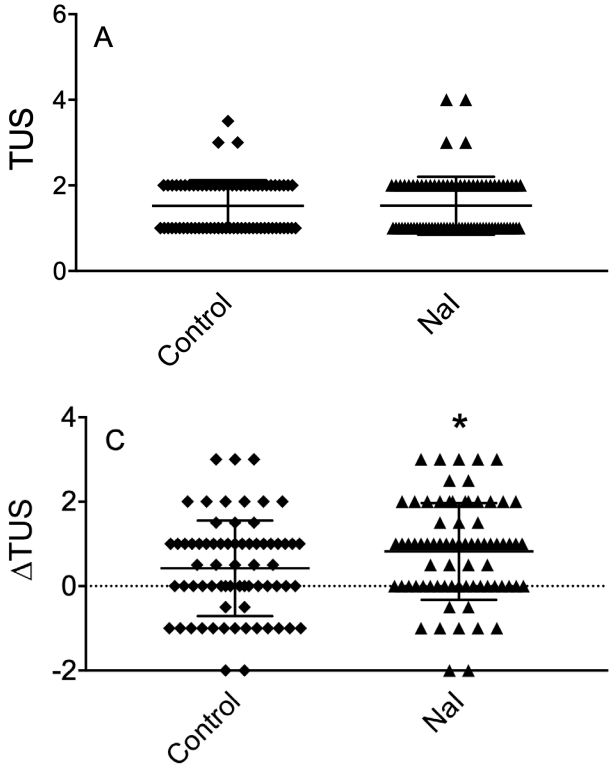

Figure 3—Plots of the TUSs for the calves of Figure 2 before (A) and 7 days after (B) administration of the first dose of NaI and the difference in TUS (ΔTUS) between days 1 and 7 (C). The TUS was assigned on a 4-point scale, where 1 = ultrasonographically normal lung tissue, 2 = presence of diffuse comet tails without evidence of lung tissue consolidation, 3 = evidence of lung tissue consolidation ≥ 1 cm in 1 or more areas, and 4 = evidence of extensive lung tissue consolidation (ie, ≥ 6 cm) in 1 or more areas. In panel C, positive values indicate that the TUS increased from day 1 to day 7, and negative values indicate that the TUS decreased from day 1 to day 7. ***See*** Figure 2 for remainder of key.

ed calves also had a significantly (P = 0.001) greater mean TUS on day 7 (2.79), compared with control calves (2.32). The mean ΔTUS was significantly (P = 0.013) greater for the NaI-treated calves (0.98) than for the control calves (0.51), when controlling for the effects of birthdate and herd of origin.

Analysis of the health records indicated that 137 of the 211 (65%) NaI-treated calves and 104 of the 216 (48%) control calves were treated for BRD at least once. Sodium iodide–treated calves were approximately twice (OR, 2.04; 95% CI, 1.38 to 3.00) as likely to be treated for BRD as were control calves. Herd of origin also had a significant effect on treatment for BRD. Among calves from 2 of the 7 herds of origin, the frequency of treatment for BRD was significantly greater for NaI-treated calves than for control calves. Treatment group had no effect on average daily gain, number of diarrhea events, or number of otitis events.

Discussion

Results of the present study indicated that oral administration of NaI (20 mg/kg) to preweaned dairy calves significantly increased the iodine concentration in nasal secretions; however, it did not appear to be an effective strategy for the prevention of BRD. In fact, results of the on-farm trial suggested that preweaned dairy calves that were orally administered 2 doses of NaI (20 mg/kg) 72 hours apart had greater (more severe) clinical respiratory scores and greater changes in TUSs within the 7 days after initiation of treatment and were approximately twice as likely to be treated for BRD, compared with untreated control calves.

Findings of an experimental study[14] suggest that the lactoperoxidase-hydrogen peroxide-iodide reaction inactivates or inhibits bovine herpesvirus 1, parainfluenza virus type 3, *M haemolytica*, and *B trehalosi* in vitro. Therefore, the results of the on-farm trial of the present study were unexpected. The reason NaI-treated calves appeared to be at greater risk for treatment of BRD than control calves is unknown. However, BRD is a multifactorial disease, and iodine may not effectively inactivate or inhibit all BRD pathogens, such as atypical bacteria like *Mycoplasma* spp. Herd of origin also had a significant effect on the risk of treatment for BRD in the on-farm trial, which highlighted the importance of considering the epidemiological triad (host, agent, and environment) when studying BRD. Unfortunately, data for potential confounders, such as genetics, dam vaccination history, colostrum quality, and transfer of immunity via colostrum, were not available for the calves of the present study and could not be controlled for even though they would likely have had an effect on the outcomes of interest. The on-farm trial was conducted in late fall (November) when the ambient temperature was moderate. Environmental conditions could have influenced the pharmacokinetics of NaI as well as the clinical outcomes for the calves. Therefore, the external validity of our results in calves exposed to more or less environmental stress is unknown. It is also important to note that the incidence of BRD at this calf-raising facility was fairly high; 104 of 216 (48%) control calves and 137 of 211 (65%) NaI-treated calves were treated for BRD. The results may have been different had the BRD incidence been lower. Additionally, no attempt was made to identify respiratory tract pathogens in the calves of the on-farm trial, so it was unknown whether the fairly high incidence

of BRD was caused by a single pathogen or a group of pathogens.

The NaI dose (20 mg/kg) used in the pharmacokinetic trial was selected to avoid adverse effects associated with iodism. Results of the pharmacokinetic study indicated that dose was adequate to achieve iodine concentrations that exceeded the minimum iodine concentration necessary to inactivate bovine respiratory pathogens in vitro (6.35 µg/mL)[14] in both serum and nasal secretions. Thus, we chose to administer the same dose to the designated calves of the on-farm trial. A second dose was administered 3 days after the first in an attempt to maintain high concentrations of iodine in nasal secretions for the duration of the 7-day observation period.

Signs of iodism include lacrimation, nasal discharge, and cough, all of which are also associated with BRD. It is possible that the higher frequency of treatment for BRD and higher clinical respiratory scores for the NaI-treated calves of the on-farm trial might have been caused, at least in part, by iodism. However, that seems unlikely because of the low dose of NaI administered, the fact that the same dose did not cause similar signs in the calves of the pharmacokinetic trial, and the lack of such clinical signs in calves of another study[14] that received higher doses of NaI.

In the on-farm trial, the magnitude of the ΔTUS from day 1 to day 7 for the NaI-treated calves was significantly greater than that for the control calves. The TUS should not have been affected by an increase in iodine concentration. To our knowledge, the effect of iodism on the ultrasonographic appearance of lung tissue has not been investigated. Iodine might directly damage the lungs or epithelial cells of the airways. Investigators of another study[14] report that iodine concentrations up to 500µM were not toxic to Madin-Darby bovine kidney cells in vitro. However, iodine was administered to live calves in the present study, and the effects of iodine on in vivo cells may differ from cells maintained in vitro, and epithelial cells of the respiratory tract may react differently to iodine than cultured Madin-Darby bovine kidney cells. Evaluation of the respiratory mucosal integrity was beyond the scope of the present study.

The microbiome is an important defense mechanism of any mucosal surface. Probiotics can inhibit *M haemolytica* through competition and displacement on bovine respiratory epithelial cells in vitro.[18] Oral administration of iodine may alter the microbiome of the respiratory tract and allow pathogens in the pharynx to migrate into the trachea, bronchi, and lower airways. In beef cattle, the microbiome of the nasopharynx undergoes substantial changes during periods of stress such as transport to a feedlot, and feedlot cattle are at greatest risk for BRD during the first few weeks after feedlot arrival.[19] Iodine-induced alterations in the microbiome of the respiratory tract may have contributed to some of the differences observed between the NaI-treated and control calves of the on-farm trial and warrant further investigation.

It is possible that oral administration of NaI to calves and the subsequent increase of iodine in nasal secretions selected for pathogens not susceptible to the lactoperoxidase-hydrogen peroxide-iodide reaction, such as bovine viral diarrhea virus.[14] Evaluation of respiratory tract secretions of cattle for bacterial and viral pathogens before and after NaI administration would facilitate identification of pathogens resistant to the lactoperoxidase-hydrogen peroxide-iodide reaction and may help elucidate the effects of iodine on the respiratory tract microbiome.

Although NaI is labeled for cattle (70 mg/kg, IV) for the treatment of *A lignieresii* and *A bovis* infections, there is no published withdrawal time. Currently, there is no recommended withdrawal interval for meat or milk from cattle that are orally administered NaI at a dose of 20 mg/kg.

A limitation of the pharmacokinetic trial was the short sampling period (72 hours), which prohibited estimation of parameters associated with iodine elimination in nasal secretions. The short sampling period necessitated extensive extrapolation of the terminal portion of the concentration-time curve, which affected the estimates for the AUC, terminal rate constant, and $t_{1/2\lambda}$. For the calves of the pharmacokinetic trial, the mean serum and nasal fluid iodine concentrations remained significantly increased from baseline concentrations and exceeded the presumed therapeutic concentration at the end of the sampling period. Therefore, it is unknown whether administration of the second dose of NaI on day 4 to the calves of the on-farm trial was necessary to maintain the nasal secretion iodine concentration above the presumed therapeutic concentration for the duration of the 7-day observation period. That information could have been gleaned by extending the sampling period during the pharmacokinetic trial. Administration of NaI at a smaller dose more frequently (eg, daily) might alter the compound's pharmacokinetics and might have affected the results of the on-farm trial. Also, given the rapid increase in iodine concentration in both serum and nasal fluid following NaI administration, collection of samples < 1 hour after ingestion of the compound would have allowed for more precise calculation of parameters associated with peak concentrations. The iodine concentrations in serum and nasal fluid samples were not determined for the calves of the on-farm trial. The calves of the on-farm trial received 2 doses of NaI (20 mg/kg) on days 1 and 4, which was extrapolated on the basis of information obtained during the pharmacokinetic trial. Further research is necessary to refine and determine the optimal dosing interval for NaI in calves.

Sodium iodide is a fairly inexpensive and easy-to-administer compound that is generally considered safe for use in adult cattle and was associated with no adverse effects in calves of another study[14] and the present study. Results of the present study indicated that

oral administration of NaI (20 mg/kg) increased the iodine concentration in nasal secretions of preweaned dairy calves to greater than the presumed therapeutic concentration for augmentation of the defense mechanisms of the upper respiratory tract. However, in the on-farm trial, oral administration of 2 doses of NaI (20 mg/kg) 72 hours apart to clinically normal preweaned dairy calves was not protective against BRD and, in fact, appeared to be associated with clinical signs of BRD and ultrasonographically evident changes in lung tissue. Therefore, oral administration of NaI to preweaned calves for the prevention of BRD is not recommended at this time. Further research regarding the effects of NaI on the respiratory tract microbiome and epithelium of calves is warranted, as are additional pharmacokinetic studies in which multiple doses of the compound are administered, to better understand how cattle respond to NaI and whether that compound can be used to augment the innate immune response of cattle at high risk for BRD.

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Footnotes

a. Optimum Calf Milk Replacer, Calva Products, Acampo, Calif.
b. VetOne, MWI Animal Health, Boise, Idaho.
c. Covidien Monoject, Tyco Health Care Group, Mansfield, Mass.
d. Bioseal, Covidien Inc, Mansfield, Mass.
e. BD Falcon Conical tubes, BD Biosciences, San Jose, Calif.
f. Mediatech Inc, Manassas, Va.
g. Inorganic Ventures, Christiansburg, Va.
h. Inforce 3, Zoetis Animal Health, Parsippany, NJ.
i. Entervene D, Boehringer Ingelheim Vetmedica Inc, St Joseph, Mo.
j. Once PMH, Merck Animal Health Intervet Inc, Madison, NJ.
k. IBEX, EI Medical Imaging, Loveland, Colo.
l. Healthsum, The Healthsum Syndicate LLC, Sunnyside, Wash.
m. Phoenix WinNonlin, version 6.2, Certara, Princeton, NJ.
n. SAS, version 14.3, SAS Institute Inc, Cary, NC.

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