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Efficacy of Oral Administration of Sodium Iodide to Prevent Bovine Respiratory Disease Complex

B.M. Shoemake, B.L. Vander Ley, B.W. Newcomer, and M.C. Heller

Background: The prevention of bovine respiratory disease complex (BRD) in beef cattle is important to maintaining health and productivity of calves in feeding operations.

Objective: Determine whether BRD bacterial and viral pathogens are susceptible to the lactoperoxidase/hydrogen peroxide/iodide (LPO/H_2O_2/I^-) system in vitro and to determine whether the oral administration of sodium iodide (NaI) could achieve sufficient concentrations of iodine (I) in the respiratory secretions of weaned beef calves to inactivate these pathogens in vivo.

Animals: Sixteen weaned, apparently healthy, commercial beef calves from the University of Missouri, College of Veterinary Medicine teaching herd.

Methods: In vitro viral and bacterial assays were performed to determine susceptibility to the LPO/H_2O_2/I^- system at varying concentrations of NaI. Sixteen randomly selected, healthy crossbred beef weanlings were administered 70 mg/kg NaI, or water, orally in a blinded, placebo-controlled trial. Blood and nasal secretions were collected for 72 hours and analyzed for I^- concentration.

Results: Bovine herpesvirus-1, parainfluenza-3, *Mannheimia haemolytica* and *Bibersteinia trehalosi* were all inactivated or inhibited in vitro by the LPO/H_2O_2/I^- reaction. Oral administration of NaI caused a marked increase in nasal fluid I concentration with a C_{max} = 181 (1,420 μM I), T_{12}, a sufficient concentration to inactivate these pathogens in vitro.

Conclusions and Clinical Importance: In vitro, the LPO/H_2O_2/I^- system inactivates and inhibits common pathogens associated with BRD. The administration of oral NaI significantly increases the I concentration of nasal fluid indicating that this system might be useful in preventing bovine respiratory infections.

Key words: Hypoiodous acid; Lactoperoxidase; Bovine respiratory disease; cattle.

Bovine respiratory disease complex (BRD) is a multifactorial disease process that is currently thought to be initiated by a stressful event, such as transport and commingling of cattle, which results in immune

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Work locations: The viral in vitro experiment was performed at Auburn University College of Veterinary Medicine. The bacterial in vitro experiment was performed at the University of California-Davis College of Veterinary Medicine. The in vivo sodium iodide experiment was performed at the University of Missouri College of Veterinary Medicine.

Prior presentations: This research was presented as a research abstract at the 2015 Conference of Research Workers of Animal Diseases, and as a Research Report at 2016 ACVIM Forum, Denver, CO.

Portions of this research and this manuscript were included in the master's thesis submitted by Dr. Brian Shoemake to the University of Missouri.

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Abbreviations:

μg	micrograms
μM	micromolar
ANOVA	analysis of variance
ASL	airway surface liquid
B. trehalosi	*Bibersteinia trehalosi*
BHI	brain heart infusion agar
BoHV1	bovine herpesvirus-1
BPI3V	parainfluenza-3 virus
BRD	bovine respiratory disease complex
BRSV	bovine respiratory syncytial virus
BVDV	bovine viral diarrhea virus
CCID50	cell culture infective dose
CFU	colony forming units
CI	95% confidence interval
C_{max}	maximum concentration
DTT	dithiothreitol
DUOX	dual oxidase enzymes
H_2O_2	hydrogen peroxide
HOI	hypoiodous acid
I	iodine
I^-	iodide
KI	potassium iodide
LPO	lactoperoxidase
M. haemolytica	*Mannheimia haemolytica*
MALDI-TOF	matrix-assisted laser desorption/ionization-time of flight
NaI	sodium iodide
$OSCN^-$	hypothiocyanite
P. multocida	*Pastuerella multocida*
PBS	phosphate-buffered saline
SAS	Statistical Analysis System
SCN^-	thiocyanate
T. pyogenes	*Trueperella pyogenes*
T_0	baseline data point
T_{12}	12-hour study time point
T_{30}	30-minute study time point
T_{48}	48-hour study time point
T_{72}	72-hour study time point

compromise and reduced resistance to infection. Commingling of cattle also increases exposure to respiratory pathogens. Subsequent viral infections compromise respiratory defenses that normally limit the migration of pharyngeal flora into the lower respiratory tract. Bacterial bronchopneumonia of the lungs causes pulmonary damage compromising animal health and production. Methods to decrease BRD and BRD-associated losses include mitigating stress, preventing viral and bacterial infections, and metaphylactic administration of antimicrobials. While these methodologies can reduce BRD, they are often unsuccessful and require further antibiotic treatment of the bacterial bronchopneumonia.[1] Concerns regarding antibiotic use continue to increase, and alternative means of maintaining animal health and welfare will be required as antibiotic use practices evolve.

A novel approach to preventing and treating BRD infections might be naturally present within the respiratory system. The upper respiratory tract utilizes innate defense mechanisms to protect the respiratory system. One component is an oxidative antimicrobial system in the airway surface liquid (ASL), composed of hydrogen peroxide (H_2O_2) produced by dual oxidase enzymes (DUOX), lactoperoxidase (LPO) from epithelial submucosal glands, and a halide/pseudohalide ion.[2] Lactoperoxidase catalyzes a reaction of H_2O_2 with thiocyanate (SCN^-), a pseudohalide secreted by the sodium iodide (NaI) symporter found on the basolateral plasma membrane, resulting in the formation of hypothiocyanite ($OSCN^-$) within the ASL.[2,3] The submucosal glands required for this reaction are not present equally in all mammals. Humans, sheep, and cattle have submucosal glands, rats have few present, and smaller mammals lack submucosal glands.[2,4] A recent discovery in sheep and humans is that the oxidative antimicrobial system not only catalyzes SCN^- to $OSCN^-$ but can also produce hypoiodous acid (HOI) from iodine (I). Hypoiodous acid is normally produced at negligible concentrations because serum SCN^- concentration is relatively greater than serum I concentration; therefore, $OSCN^-$ is preferentially formed. When I is supplemented as a single, high-dose bolus, iodide (I^-) secretion in the upper respiratory tract increases. As I^- concentration increases in the ASL, SCN^- concentration decreases, indicating that I^- and SCN^- compete for secretion into the respiratory tract.[2,3,5–7] Hypoiodous acid has potent antimicrobial activity.[2] In in vitro models, increasing I^- concentration in the $LPO/H_2O_2/I^-$ system to 500 μM results in a significant reduction in viral pathogens.[6] The administration of oral potassium iodide (KI) resulted in ASL I^- concentration of 500 μM in humans. Thus, the oral administration of KI was capable of providing I^- in the ASL at concentrations high enough to achieve effective in vivo antimicrobial activity.[6] The objectives of the presented study were to determine whether the selected BRD pathogens were susceptible to the oxidative antimicrobial system composed of $LPO/H_2O_2/I^-$ in vitro and determine whether the oral administration of NaI could achieve concentrations of I in the respiratory secretions of weaned beef calves equivalent to those required to inactivate these pathogens in vivo.

Materials and Methods

Viral In Vitro *Susceptibility*

The in vitro susceptibilities of BPI3V, BoHV1, and BVDV to the $LPO/H_2O_2/I^-$ reaction were tested using the following procedure. All assays were performed in triplicate. The viral strains used were TVMD60, Colorado, and 125C, respectively. The titer of the stock virus for BPI3V and BoHV1 was 3.5×10^8 50% cell culture infective dose (CCID50), and the beginning titer for the BVDV stock concentration was 5.2×10^7 CCID50. In a 24-well plate, minimum essential media were added (720–860 μL) to each reaction well in the amount needed for a total reaction volume of 1,000 μL. Test assays were performed as previously described in the following manner.[6] NaI was added to each well to achieve a final concentration of 0, 10, 100, or 250 μM NaI. Subsequently, 20 μg of LPO diluted to a concentration of 1 μg/μL in distilled water was added to each well followed by the addition of 100 μL of the appropriate stock virus solution. Finally, H_2O_2 was added to achieve a final concentration of 100 μM. Each viral assay was performed on a separate 24-well plate. Control reactions for LPO, H_2O_2, and NaI individually, as well as negative and positive control wells, were included on each plate. Plates were incubated at 37°C for 5, 15, or 60 minutes and then frozen at −80°C for a minimum of 48 hours. Following a thaw cycle, virus titration of each well was performed by direct observation of cytopathic effect in cultured cells as previously described.[8]

Bacterial In Vitro *Susceptibility*

Bacterial isolates of *Mannheimia haemolytica* and *Bibersteinia trehalosi* were obtained from clinical bovine pneumonia cases submitted to the California Animal Health and Food Safety Laboratory for necropsy. *M. haemolytica and B. trehalosi* were isolated from submitted necropsy samples and replicated in vitro. Attempts were made to assess *P. multocida* but it was not amenable to replication or consistent growth and thus was not utilized in this study. Isolates were identified via traditional biochemical tests and confirmed via matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry. Identified isolates were stored at −80°C in glycerol broth. For each experiment, an aliquot of each isolate was subcultured to brain heart infusion agar (BHI) and incubated overnight at 37°C. Isolated colonies from the BHI agar plates were inoculated into 5 mL of BHI media and incubated at 37°C and 250 rpm until log-phase growth was achieved. Colony forming units (CFU) per mL of culture media were estimated by optical density reading at 600 nm wave length, and media were diluted to the desired concentration of 10^5 CFU/mL for experimental treatments.

Experiments were carried out in deep well, 96-well plates. Reagents were filter sterilized with 0.22-μm filter. Experimental conditions were different than those of the viral assays and included: NaI at concentration of 50, 100, 250, and 500 μM, LPO (200 μg/mL), bacteria (10^5 CFU/mL), and H_20_2 (100 μM). Control conditions included: NaI at concentrations stated above (50, 100, 250, and 500 μM) with bacteria alone; LPO with bacteria alone; H_20_2 with bacteria alone; phosphate-buffered saline (PBS) with bacteria alone; and a negative control with all reagents but without bacteria. A prereaction aliquot was taken for colony count determination before adding H_2O_2 (starting titer); additional aliquots were collected 5 minutes (T_5), and 30 minutes (T_{30}) after adding H_2O_2. Colony counts were determined using 10-fold serial dilutions of each aliquot in sterile PBS, which were plated on BHI

agar, incubated overnight at 37°C, and quantified to calculate CFU/mL. Experiments were carried out on each isolate in duplicate and on 2 separate days.

Oral Sodium Iodide

Animals

Sixteen weaned commercial beef calves (average weight 270.5 kg ± 18.2 kg) were selected from the University of Missouri, College of Veterinary Medicine teaching herd to be included in the randomized, blinded, placebo-controlled study. The group consisted of 4 steers and 12 heifers. The cattle were housed at the College of Veterinary Medicine Middlebush Teaching Farm and sample collection occurred through standard cattle processing facilities on site. The calves were fed, watered, and cared for in accordance with standard farm protocols. Animal use and methods were approved by the University of Missouri Animal Care and Use Committee, protocol number 8207.

Calves were divided into 2 groups of 8 animals each, control and treatment, by random number generator.[a] The 2 groups were maintained in the same herd and pasture. Both primary investigators were blinded to treatment and control groups throughout the study period. The treatment group was administered a single dose of 70 mg/kg, 200 mg/mL (20%) NaI[b] by ororumen intubation. The control group was administered an equivalent volume of water by ororumen intubation.

Samples were collected immediately before administration of treatments, T_0, then every 12 hours for 72 hours. Samples collected included blood and nasal secretions. Basic physical examination consisting of temperature, heart rate, respiratory rate, rumen auscultation, and general visual inspection of the cattle was performed at each sample collection. The calves were observed for indications of iodine intoxication which included but are not limited to: salivation, diarrhea, excessive coughing, nasal discharge, lacrimation, epiphora, alopecia, dermatitis, scaly hair coats, and hyperthermia.[9–11] Nasal fluid was collected from all calves by use of a modified 1 mL serologic pipette[c] attached to a sample collection tube[d] and vacuum pump, as illustrated in Figure 1. Samples were stored at −20°C until final processing on all samples could be performed. Dithiothreitol (DTT)[e] was used to lyse the mucous component of the ASL. This allowed for optimal iodine recovery and successful sample analysis, similar to the method described by Popov et al[12] Blood samples were collected by jugular venipuncture into 10 mL serum separator vacutainer blood tubes.[d] Blood samples were centrifuged at 1,500 × *g* for 30 minutes at 4°C. The serum was removed and stored at −20°C until analysis. The nasal fluid and serum were submitted to the Michigan State University Diagnostic Center for Population and Animal Health and analyzed by inductively coupled plasma mass spectroscopy.

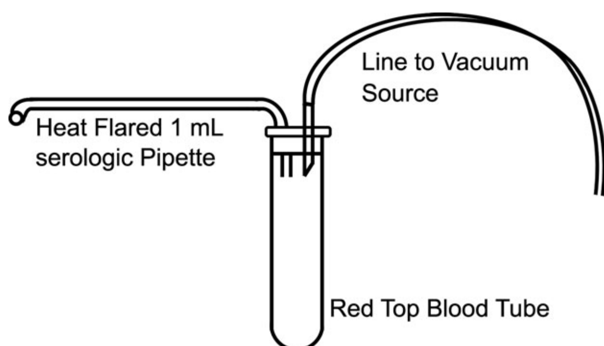

Fig 1. Nasal suction device. A 1 mL serologic pipette that was heat flared at the proximal aspect to create a smooth suction surface. Two, 90° bends were placed in the length of the pipette to allow for ease of handling of the device. The distal aspect of the pipette was placed through the rubber tube stopper of a red top serologic tube. A 16-gauge needle attached to a vacuum line and vacuum source was then inserted into the same rubber tube stopper.

Data Analysis

In vitro viral[f] and bacterial[g] growth data were analyzed by 2-way nonparametric ANOVA for time and treatment, with post hoc testing. The concentration of iodine[h] measured in blood and nasal secretions was analyzed by repeated measures ANOVA in which the dependent variable was iodine concentration, and the independent variable was the treatment group. Tukey's post hoc analysis was applied between groups and treatment time points.

Results

Viral In Vitro *Susceptibility*

Viral titers for BPI3V were significantly decreased ($P = 0.001$) in all reactions containing even the lowest concentration of NaI, Figure 2. The reaction containing 10 μM NaI decreased the average viral titer by 2 logs compared to the positive control wells; the 100 μM reaction further reduced the mean titer by an additional 2 logs. The virus was completely inhibited in all wells containing a NaI concentration of 250 μM regardless of the presence of LPO or H_2O_2. However, the differences in inhibition between the various NaI concentrations were not statistically different. For BoHV1, significant reduction in viral titer was seen at reactions containing >10 μM NaI ($P < 0.001$). At the 100 μM NaI concentration, the mean viral titer decreased 4 logs compared to the positive control wells, Figure 3. As with BPI3V, a NaI concentration of 250 μM completely inactivated the virus, regardless of the presence of LPO or H_2O_2. Of the 3 viruses, BVDV showed the least susceptibility to the system with no observed differences ($P = 0.33$) in titer at even the highest concentrations of NaI, Figure 4. Titers of BPI3V ($P = 0.44$), BoHV1 ($P = 0.14$), and BVDV ($P = 0.65$) were not affected by incubation time.

Bacterial In Vitro *Susceptibility*

At all concentrations of NaI in combination with LPO and H_20_2, growth of both *M. haemolytica* and *B. trehalosi* was inhibited by the complete reaction by 5 minutes after the reaction was started (T_5), Figures 5 and 6. There was no significant difference between bacterial numbers at T_0 for any of the treatment conditions, aside from the negative control. A 2-way ANOVA of results for *M. haemolytica* was significant for time ($P < 0.0001$), treatment ($P < 0.0001$), and interaction of time and treatment ($P = 0.0008$). Post hoc pairwise comparisons revealed significantly decreased bacterial counts at T_5 in all 3 NaI concentrations (50, 100, and 500 μM) that included H_2O_2 and LPO compared to the positive control. Results for

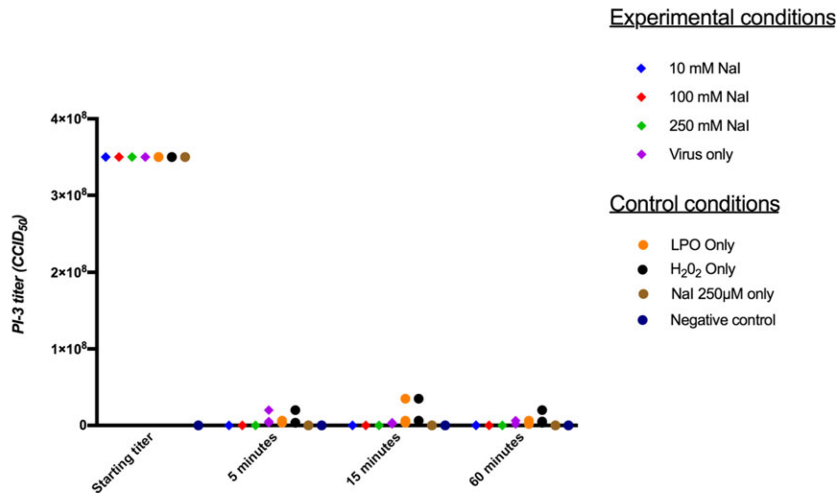

Fig 2. Bovine parainfluenza-3 virus. Presented are the experimental conditions of Bovine PI-3 virus: LPO, H_2O_2, and a concentration of NaI (10, 100, or 250 μM NaI), as depicted by the solid bars. The control conditions, represented by the checked and dashed bars, include virus only, LPO only, H_2O_2 only, NaI (250 μM) only, and media only. Standard error bars presented. BPI3V was significantly inhibited at all concentrations of NaI but no effect of time was detected.

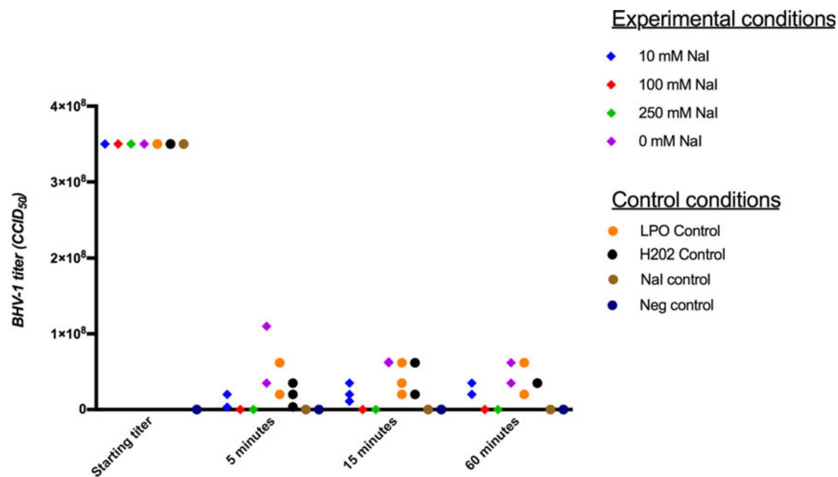

Fig 3. Bovine herpesvirus-1. Presented are the experimental conditions of BHV-1 virus: LPO, H_2O_2, and a concentration of NaI (10, 100, or 250 μM NaI), as depicted by the solid bars. The control conditions, represented by the checked and dashed bars, include virus only, LPO only, H_2O_2 only, NaI (250 μM) only, and media only. Standard error bars presented. BoHV1 was significantly inhibited at concentrations of NaI >10 μM but no effect of time was detected.

B. trehalosi were similar; a 2-way ANOVA showed significant effect of time ($P < 0.0001$) and treatment ($P < 0.0001$); however, effect of interaction of time and treatment was not significant ($P = 0.69$). NaI alone at higher concentrations (100 and 500 μM) inactivated both bacterial pathogens in vitro, in the absence of LPO and H_2O_2; however, this trend was not statistically significant. Failure to show significance is likely due to variability in bacterial counts of control conditions.

In Vitro *Sodium Iodide Animal Model*

Serum Iodine Concentration

Both groups had no significant difference in serum I concentrations at T_0 with an average of 0.04 mg/L (0.3 μM) and 95% confidence interval (CI) of 0.03–0.05 mg/L. After NaI administration, the serum I concentrations were significantly increased ($P < 0.05$) at each collection time point beginning with T_{12} through the final collection time point of T_{72} post-NaI administration, as depicted in Figure 7. The highest measured average serum I concentration at T_{12} was 106 mg/L (834 μM) and CI of 92–120 mg/L; subsequently, serum I concentration steadily declined during the remainder of the study period. During the 72-hour study period, at each collection time point, the control group did not have a significant change in serum I concentration.

Nasal Secretion Iodine Concentration

Both groups had similar average I concentrations at T_0 in nasal secretions: control 0.915 mg/L (7.21 μM), CI of

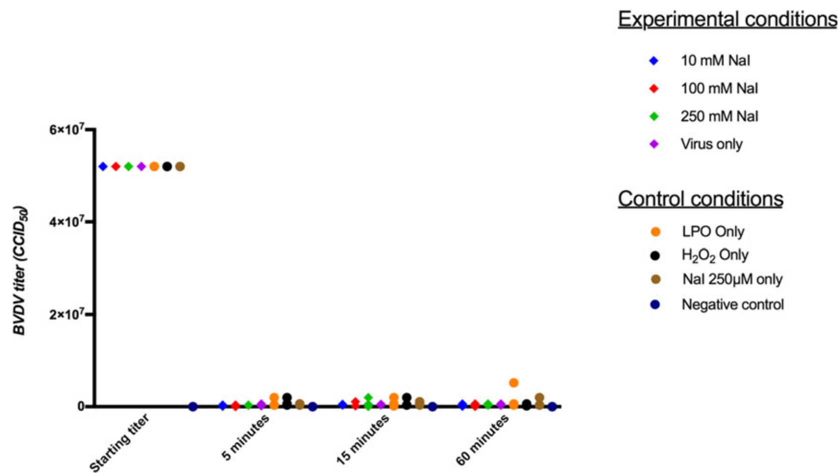

Fig 4. Bovine Viral Diarrhea Virus. Presented are the experimental conditions of BVDV: LPO, H_2O_2, and a concentration of NaI (10, 100, or 250 μM NaI), as depicted by the solid bars. The control conditions, represented by the checked and dashed bars, include virus only, LPO only, H_2O_2 only, NaI (250 μM) only, and media only. Standard error bars presented. No significant effect of treatment on BVDV titers was detected.

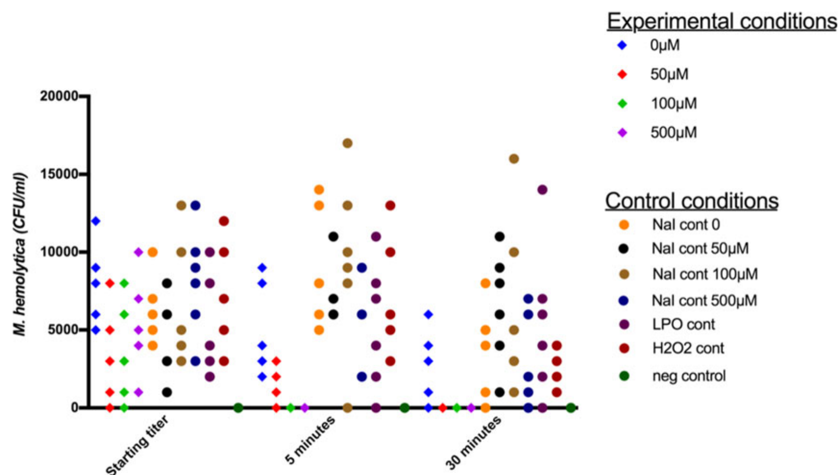

Fig 5. *Mannheimia haemolytica*. Presented are the experimental conditions of *M. haemolytica*, LPO, H_2O_2, and a concentration of NaI (0, 50, 100, or 500 μM NaI), depicted by the solid bars. The control conditions, represented by the checked and dashed bars, include PBS and *M. haemolytica*; NaI alone at 50, 100, or 500 μM concentrations and *M. haemolytica*; LPO and *M. haemolytica*; H_2O_2 and *M. haemolytica*; and LPO, H_2O_2, 100 μL NaI, and no *M. haemolytica*. Standard error bars presented. All treatments except for 0 μM NaI achieved statistically significant differences at T_5. Statistical significance could not be achieved at T_{30} despite lack of bacterial growth in culture in all experimental reactions except for 0 μM NaI.

0.067–1.76 mg/L, and treatment 0.529 mg/L (4.17 μM), CI of 0.185–0.873 mg/L. The concentration of I in the nasal secretions was significantly increased ($P < 0.05$) after the administration of a NaI oral bolus as demonstrated in Figure 8. At the T_{12} sample collection time point, the treatment group had a significantly higher average I concentration of 181 mg/L (1,420 μM) and CI of 155–206 mg/L in the nasal secretions that remained significantly different throughout the 72-hour study period of the treatment group. The I concentration of nasal secretions steadily declined during the study period. The control group nasal secretion I concentration did not change throughout the study period.

Physical Examination

Physical examination findings for temperature and respiratory rates between the 2 study groups were not statistically different. At the T_0 and T_{48}, the heart rates of the control group were significantly greater than the treatment group, 166 beats per minute and 145 beats per minute, respectively. Throughout the study period, evidence of I toxicity was not observed during routine physical examinations and sample collection. Herd caretakers

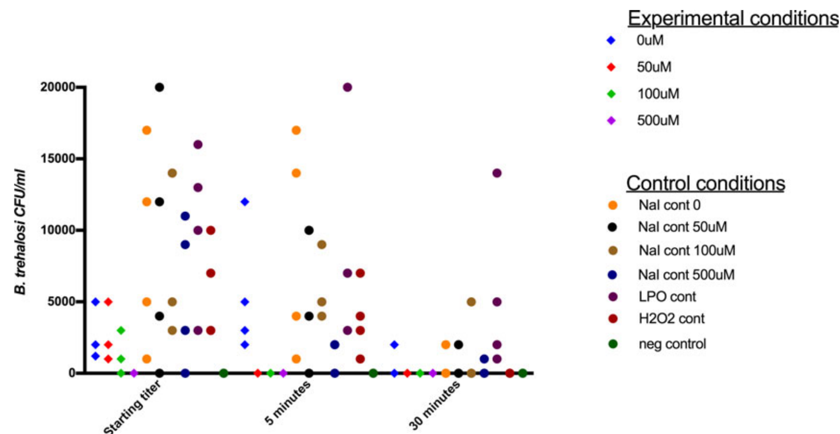

Fig 6. *Bibersteinia trehalosi*. Presented are the experimental conditions of *B. trehalosi*, LPO, H_2O_2, and a concentration of NaI (0, 50, 100, or 500 μM NaI), depicted by the solid bars. The control conditions, represented by the checked and dashed bars, include PBS and *B. trehalosi*; NaI alone at 50, 100, or 500 μM concentrations and *B. trehalosi*; LPO and *B. trehalosi*; H_2O_2 and *B. trehalosi*; and LPO, H_2O_2, 100 μL NaI, and no *B. trehalosi*. Standard error bars presented. Statistical significance of time and treatment was achieved in all reactions except 0 μM NaI. Bacterial growth did not occur in all experimental reactions expect for 0 μM NaI test conditions.

did not indicate concerns of any health abnormalities during or immediately after the study period.

Discussion

The results of the experiments presented in this report demonstrate that the LPO/H_2O_2/I^- system inactivates BoHV1, BPI3V, *M. haemolytica,* and *B. trehalosi* in vitro. This study also demonstrated that weanling beef calves are capable of secreting I in the upper respiratory tract after a single bolus of oral NaI. While more investigation into the application of these findings is required, the use of a single oral bolus of NaI might be a new methodology in the prevention or mitigation of BRD.

The one pathogen that was not found to be susceptible to inactivation by the LPO/H_2O_2/I^- system was BVDV, which is a member of the Flaviviridae family and of the genus *Pestivirus*. It is a single-stranded RNA, nonsegmented, enveloped virus with 2 biotypes that can cause immunosuppression.[13,14] The reason for this difference in susceptibility to the LPO/H_2O_2/I^- is unknown. One consideration might be that BVDV is fairly hardy in the environment and is resistant to most disinfectants and environmental conditions.[13] If this is the case, a higher concentration of NaI might be required to inactivate BVDV. The importance of BVDV's lack of inactivation by the LPO/H_2O_2/I^- system will require further investigation.

Bovine respiratory syncytial virus (BRSV) is another important viral pathogen of BRD. Because of its similarity to human respiratory syncytial virus (hRSV), BRSV was not examined in this study. BRSV was not examined in vitro in this study because of the previous reports of inactivation of hRSV in both in vitro studies and an in vivo challenge model in sheep of the LPO/H_2O_2/I^-.[2,6] In the in vivo challenge model, lambs administered KI had decreased gross pulmonary lesions, viral antigen concentration, and clinical signs of respiratory disease compared to controls.[2] Human respiratory syncytial virus and BRSV are remarkably similar, to the extent that BRSV has been used as an animal model for hRSV studies.[15–17] Another limitation of this study was that the calves utilized were not stressed or commingled immediately before the onset of the study period. Commingling and stress are known factors of BRD's pathogenesis. Extrapolating these results to stressed and/or commingled calves might be premature.

This study determined that beef weanlings are capable of secreting I in the upper respiratory tract after a single bolus of oral NaI. The highest measured nasal I concentration was 181 mg/L (1,420 μM). Based on the in vitro data, this concentration of iodine could inactivate BoHV1 and BPI3V and inhibit *M. haemolytica* and *B. trehalosi* in vivo. These results are similar to those previously reported in both humans and sheep.[2,6]

In previous studies, HOI was measured directly. In the present study, the presence of I was measured as inorganic I^- as a proxy measurement of HOI in the nasal secretions of calves, as previously reported.[6] Hypoiodous acid is formed by the reaction of H_2O_2 and I^- (catalyzed by LPO oxidation) identically to $OSCN^-$ formation. Compared to $OSCN^-$, HOI is considerably virucidal as well as antibacterial. In ovine models, both respiratory syncytial virus and adenovirus were rapidly inactivated by HOI.[2] The proposed mechanism of action of HOI is that it modifies the surface proteins of the virus.[6] These changes can inhibit binding and/or entry of the virus into the host cells. This is achieved through the oxidation of sulfhydryl groups, unsaturated double bonds, and iron-sulfur centers.[18,19] A concern of any modified cellular process is whether the new output or reaction will result in cytotoxicity. By measuring lactate dehydrogenase, it has been determined that HOI is not cytotoxic. This was demonstrated by the application of LPO, H_2O_2, and NaI to well-differentiated epithelial cells in vitro. Based on these findings, HOI is a potent antimicrobial but does not damage the respiratory epithelium.[2,6]

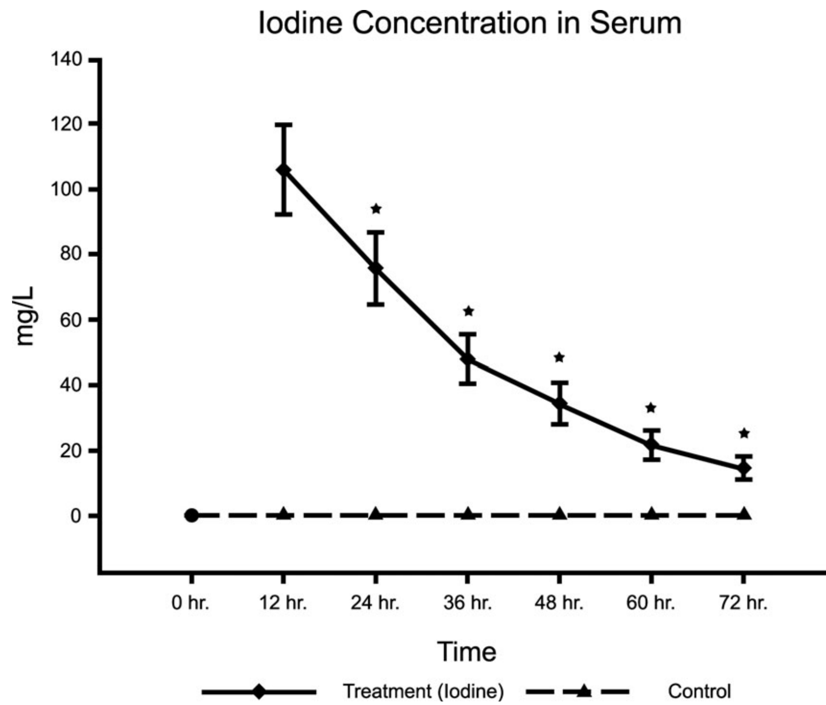

Fig 7. The serum iodine concentration of treatment (NaI, n = 8) and control (water, n = 8) groups. At T_0, grouping markers (darkened circle and triangle) overlapping. The highest measured concentration of iodine was 106 mg/L. Standard error of the mean bars graphed. * indicates statistically significant difference at $P < 0.05$.

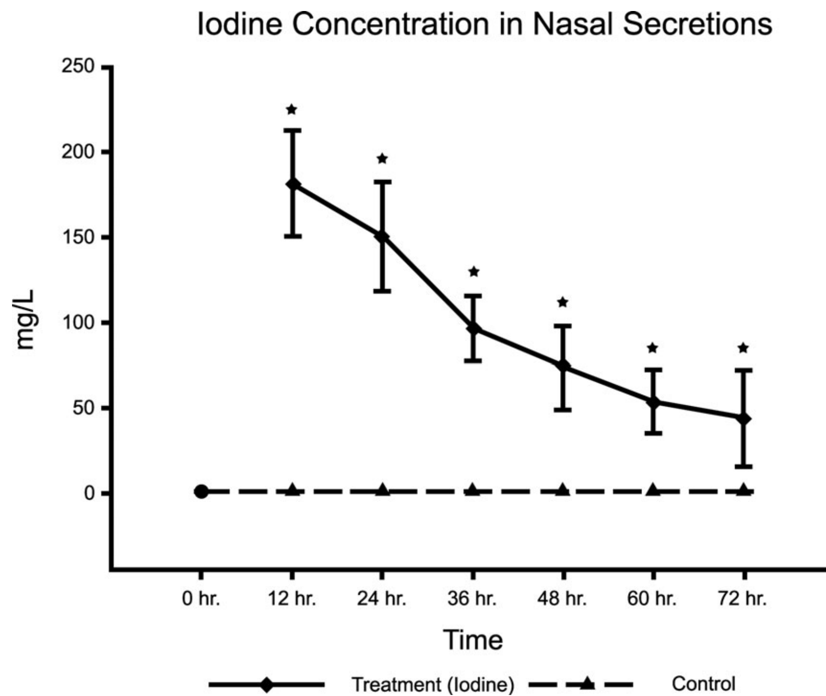

Fig 8. The concentration iodine in nasal secretions treatment (NaI, n = 8) and control (water, n = 8) groups. At T_0, grouping markers (darkened circle and triangle) overlapping. The highest measured concentration of iodine was 181 mg/L. Standard error of the mean bars graphed. * indicates statistically significant difference at $P < 0.05$.

NaI has been used for the treatment of various infectious diseases in cattle since the beginning of the last century. Traditionally, NaI is administered as an intravenous bolus at a dose of 70 mg/kg. Signs of I intoxication can be observed at this dose, especially when multiple doses are administered for treatment.

These signs include any degree or combination of the following: anorexia, salivation, diarrhea, excessive coughing, nasal discharge, pneumonia, lacrimation, epiphora, alopecia, dermatitis, scaly hair coats, and hyperthermia. Iodine toxicity usually resolves when the I^- source is removed, and clinical signs diminish over a period of 2–3 days without long-term affects.[9–11]

When considering an antimicrobial for administration in food animals, the effect on the animal and consumable product must be acknowledged. First and foremost is the effect the treatment has on the animal's health. In this study, there were no clinical signs or measurable abnormalities as a result of the administration of oral NaI at the dose administered. The only significant change between the 2 treatment groups was the heart rates at T_0 and T_{48} when the treatment group heart rates were statistically significantly lower than the control, 166 beats per minute and 145 beats per minute, respectively. Both of these values are greater than the standard heart rates of cattle. However, these heart rates were taken immediately upon entry to the processing chute and are likely attributable to physiological responses associated with handling. Secondly, there is concern as to the effect on the consumable tissues and potential harmful residues. Iodine toxicity of humans through food animal sources could present a potential risk to human health. Most of the soil throughout the world is considered I deficient.[9] Currently, table salt is iodized to help prevent the occurrence of I deficiency in people.[20] Recent investigations into the I content of food products determined that beef is not a pertinent source of I to humans (<2% of requirements), even when the animal is fed chronic doses above natural homeostatic requirements.[21]

In conclusion, $LPO/H_2O_2/I^-$ is capable of inactivating BoHV1 and BPI3V and inhibiting the growth of *M. haemolytica* and *B. trehalosi* based on the in vitro analyses performed. By reducing these viral and bacterial pathogens, the morbidity and mortality of BRD might effectively be reduced. Weanling beef calves are capable of secreting I in their upper respiratory tract after administration of a one-time oral bolus of NaI at 70 mg/kg. Further investigation of the application of oral NaI treatment as a prevention of BRD is warranted.

Footnotes

[a] Excel, Microsoft Corp., Redmond, WA
[b] Nova Tech, Inc, Grand Island, NE
[c] Celltreat Scientific Products, Shirley, MA
[d] Becton, Dickinson and Company, Franklin Lakes, NJ
[e] EMD Millipore Corp., Billerica, MA
[f] JMP Pro 13.0, SAS institute, Inc, Cary, NC
[g] GraphPad Prism 6, GraphPad Software, Inc, La Jolla, CA
[h] StataCorp LP, College Station, TX

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Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: The use of NaI (20%) in the manner described above is considered extralabel drug use.

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