An Experimentally Induced Case of Acute Nitrate Toxicity
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Nitrate toxicity in ruminants has caused a great deal of interest in the past few years, and many articles have appeared in various journals dealing with this problem. However, various investigators have arrived at so many different conclusions that it is difficult to know just when nitrate poisoning is or is not a problem. It has been recognized for many years that high levels of nitrate in the feed of ruminants can result in symptoms of nitrate poisoning. Nitrate itself is believed to be only slightly toxic, with poisoning being associated with reduction of nitrate in the rumen to nitrite and other nitrogenous substances. A general review of the problem indicates that two types of toxicity occur, acute and chronic. This experiment was undertaken to gain information about the acute syndrome in cattle fed a high level of nitrate.

**MATERIALS AND METHODS**

An eight month old Holstein-Angus heifer weighing approximately 455 pounds was used as the experimental subject. Prior to confinement, the animal was given a complete physical examination with special reference given to any abnormalities that might have interfered with the experimental results. No abnormalities were noted. The animal was confined to a clean pen on December 13, 1965, and all feed withheld for twelve hours.

The following morning the animal was given a known quantity of Sudax hay, the nitrate content of which varied from one to seven percent, depending on where the sample for analysis was taken. The consumption of hay was measured and the amount of nitrate per pound of body weight determined. Blood samples were taken prior to feeding and throughout the duration of the experiment to determine the blood methemoglobin and serum nitrate and nitrite levels. One sample was to be taken six hours after feeding with additional samples to be taken at twelve hour intervals until signs appeared, at which time samples were to be taken as often as seemed appropriate. Samples for methemoglobin determination were to be tested within one hour of being obtained. On post mortem examination samples of ingesta were to be collected for nitrate determination. However, during the course of the experiment, for economic reasons, it was decided to attempt to save the animal's life using the recommended antidote, methylene blue, given at the rate of 10 mg/kg body weight. Sudax was to be fed for forty-eight hours, and if no symptoms were noted the animal would be drenched with potassium nitrate at the rate of 725 mg/kg body weight. At the end of forty-eight hours no symptoms were evident and the calculated lethal dose of potassium nitrate was administered via a stomach tube. At this time thirty pounds of Sudax had been consumed.

**RESULTS**

After feeding the high nitrate Sudax hay for forty-eight hours, no symptoms were visible. Five hours and fifteen minutes post drenching with the potassium nitrate, an increase in respiratory rate and degree of salivation were noted. Respiratory difficulty rapidly developed into a dyspnea, accompanied by a muscular weakening beginning in the rear quarters and progressing forward until complete collapse occurred. A blood sample at this time revealed a very chocolate-brown

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*Iowa State University Veterinarian*
Table I

<table>
<thead>
<tr>
<th>Sample</th>
<th>Date</th>
<th>Time</th>
<th>Methb as % of Total Hb</th>
<th>Serum NO3 ug/ml</th>
<th>Serum NO2 ug/ml</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12/13</td>
<td>11:30 AM</td>
<td>0.5%</td>
<td>0.2</td>
<td>—</td>
<td>Control</td>
</tr>
<tr>
<td>2</td>
<td>12/14</td>
<td>8:30 AM</td>
<td>0.7%</td>
<td>0.3</td>
<td>—</td>
<td>Control</td>
</tr>
<tr>
<td>3</td>
<td>12/15</td>
<td>12:30 PM</td>
<td>4.6%</td>
<td>2.8</td>
<td>—</td>
<td>Sudax-24 hrs.</td>
</tr>
<tr>
<td>4</td>
<td>12/15</td>
<td>8:30 AM</td>
<td>8.1%</td>
<td>3.1</td>
<td>—</td>
<td>Sudax-48 hrs.</td>
</tr>
<tr>
<td>5</td>
<td>12/16</td>
<td>9:30 AM</td>
<td>3.3%</td>
<td>43.3</td>
<td>—</td>
<td>KNO3-1 hr.</td>
</tr>
<tr>
<td>6</td>
<td>12/16</td>
<td>10:15 AM</td>
<td>3.0%</td>
<td>52.0</td>
<td>—</td>
<td>KNO3-2 hrs.</td>
</tr>
<tr>
<td>7</td>
<td>12/16</td>
<td>10:30 AM</td>
<td>1.4%</td>
<td>60.0</td>
<td>trace</td>
<td>KNO3-2 hrs.</td>
</tr>
<tr>
<td>8</td>
<td>12/16</td>
<td>1:30 PM</td>
<td>—</td>
<td>59.0</td>
<td>—</td>
<td>KNO3-3 hrs.</td>
</tr>
<tr>
<td>9</td>
<td>12/16</td>
<td>1:30 PM</td>
<td>1.0%</td>
<td>59.3</td>
<td>0.1</td>
<td>(Plasma) KNO3-5 hrs.</td>
</tr>
<tr>
<td>None</td>
<td>12/16</td>
<td>1:45 PM</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Signs appear</td>
</tr>
</tbody>
</table>

colored blood. The mucous membranes revealed extreme cyanosis. At this point the animal was given 200 cc of a 0.4% methylene blue solution intravenously (800 mg total or 4 mg/kg body weight)\(^*\). Remission of clinical signs was rapid, and recovery appeared to be complete within two hours of administration of the antidote.

Laboratory reports indicated that blood samples taken during the course of the experiment became progressively more brown as determined by visual examination. Chemical results (table I) revealed an inconsistent methemoglobin level, a constantly rising serum nitrate level, and a trace of nitrite in the plasma.

As is evident from table I, a definite increase in the serum nitrate level occurred while the animal was being fed Sudax hay (sample 3, 4), although no clinical signs were evident. Following oral administration of potassium nitrate, serum nitrate levels rose rapidly (samples 5–9) with the appearance of signs coinciding with a serum nitrate level above 60 ug/ml. The erratic methemoglobin levels could not be correlated with the appearance of clinical signs. Nitrite levels show a slight rise with the appearance of symptoms (samples 7, 9).

**DISCUSSION**

Chemical results revealed that poisoning from feeding Sudax hay alone may have occurred had the hay been fed a longer period. With the serum nitrate level rising from a base of 0.57% to 8.1% in the forty-eight hours on hay alone, another forty-eight to seventy-two hours may have raised the nitrate level to the point of acute toxicity. This would be an interesting point to pursue in further experiments. The lack of detectable serum nitrite until symptoms were about to appear is explained by an understanding of the pathogenesis of nitrate toxicity.

When nitrate is consumed by the ruminant, the majority of the anion is oxidized to nitrite in the rumen by the rumen microorganisms. The unchanged nitrate and nitrite ion are absorbed into the blood stream where the nitrate ion accumulates while the nitrite ion combines with hemoglobin oxidizing it to methemoglobin. That is, the ferrous portion of the hemoglobin is oxidized to the ferric state while the nitrite ion is reduced.\(^1\) Symptoms appear because methemoglobin is not able to carry oxygen and the animal dies of suffocation. The delay of approximately five hours is due to the time necessary for conversion of nitrate to nitrite, absorption of the nitrite, and subsequent conversion of hemoglobin to methemoglobin. In addition, signs are not exhibited until 30–40% of the hemoglobin is oxidized to methemoglobin.\(^7\) In this experiment, however, the methemoglobin level was low (1.0%) near the time signs appeared. Because the determination of methemoglobin was not conducted within the recommended one hour interval of being obtained, little significance can be placed on this variable in table I.

\(^*\) Radeleff suggests methylene blue be given at the rate of 10 mg/Kg body weight.\(^*\) Blood and Henderson suggest a dosage of .5–1 mg/lb of body weight for this condition.\(^*\)

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With regard to the antidote, methylene blue is the chemical of choice. Although it acts as both an oxidizing and a reducing agent in an isolated chemical reaction, it always acts to reduce ferric (methemoglobin) to ferrous (hemoglobin) iron when used as an antidote for nitrate toxicity, providing the dosage is not too high. (Three different dosage levels were mentioned in this report.)

Prevention of nitrate toxicity when high nitrate feeds are being fed can be enhanced by feeding a high energy feed along with the nitrate feed, and by reducing the amount of nitrate forage fed. Perhaps the best method of preventing acute nitrate toxicity is to feed a forage with less than 1.5% nitrate on a dry weight basis, and not over 0.5% nitrate in the total ration.5

Nitrate toxicity may be suspected on the basis of clinical signs. It may be confirmed by laboratory analysis of nitrate levels in the feed, water, ingesta, serum and the methemoglobin level in the blood. It must be differentiated from cyanide poisoning, anaphylaxis, chlorate poisoning, and pulmonary edema and emphysema. Color of the blood can be used to differentiate cyanide; anaphylaxis may have a history of some kind of foreign substance administration; chemical analysis will determine chlorate levels; and post mortem lesions will reveal pulmonary edema and/or emphysema. Chronic nitrate toxicity is very hard to diagnose, and can only be accomplished by elimination of other possible causes.1

**SUMMARY**

This experiment was conducted to gain information about the acute syndrome of nitrate toxicity. An eight month old, 455-pound Holstein-Angus heifer was fed a high nitrate hay (Sudax, 1–7% nitrate) for forty-eight hours, and then given 150 grams of potassium nitrate orally. Acute symptoms appeared five hours later and progressed rapidly toward a fatal termination. However, methylene blue (800 mg) was administered intravenously with rapid recovery resulting.

Laboratory results revealed a progressive brown coloration of the blood, an elevated serum nitrate level, a trace of serum nitrite, and an inconsistent methemoglobin level.

The pathogenesis of the disease and action of the antidote, as well as prevention of nitrate toxicity and differential diagnosis were discussed.

**REFERENCES**