Hypothyroidism and Anemia Related to Fluoride in Dairy Cattle

DONALD HILLMAN, DAVID L. BOLENBAUGH, and EDWARD M. CONVEY
Department of Dairy Science
Michigan State University
East Lansing 48824

ABSTRACT

Blood and urine were collected from 72 cows in six dairy herds with varying severity of dental and bone fluorotic lesions. Urinary fluoride averaged 5.13 ppm and ranged from 1.04 to 15.7 ppm fluoride. Thyroxine and triiodothyronine in serum decreased with increasing urinary fluoride, eosinophils increased, and cholesterol tended to decrease. Cattle afflicted with fluorosis developed hypothyroidism, anemia, and eosinophilia of leukocytes. Bone ash averaged 2400 ppm fluoride in 22 specimens from eight herds (range 850 to 6935 ppm fluoride). Mineral supplements were the main sources of excess fluoride. Fluoride lesions were on some cows of all herds suggesting that fluoride may affect the health and performance of some cows in "normal" herds. Fluoride lesions were on young cattle and calves in fluorosis herds.

INTRODUCTION

Several investigators (8, 10, 14, 17, 23, 28, 29) have documented development of dental and bone fluorotic lesions in cattle from ingestion of excessive fluoride.

Nonskeletal effects accompanying chronic fluoride toxicity (fluorosis) include inanition, anorexia, reduced milk production, and delayed estrus postcalving (2, 14, 16, 22, 25). Excessive dietary fluoride has produced anemia (18, 25), eosinophilia (9), reduced blood folic acid activity (9), inhibited synthesis of vitamin B$_{12}$ (18), and reduced rumen microbial growth (8, 18).

Fluoride inhibits intermediary carbohydrate metabolism by formation of a magnesium-fluoride-phosphate complex (31) and by interference with the glycolytic enzyme enolase (20, 31) and oxidative phosphorylation of adenosine triphosphate (1). Enlargement of the thyroids (12) decreased thyroid adenylate cyclase, reduced thyroxine and triiodothyronine concentrations in blood (11), reduced calcium absorption (16), inhibited bone calcium resorption (3, 4), reduced collagen formation (5), and curling of hoofs (2, 10), have resulted from feeding excessive fluoride.

Complaints of inanition, anorexia, reduced milk production, infertility, lameness, and high mortality of cattle in Michigan dairy herds were investigated. Classical fluorotic lesions on teeth and bones were observed. Fluoride analysis of teeth and bones of cattle from 11 herds confirmed elevated bone ash fluoride ranging from 850 to 6918 ppm fluoride (F). Values of 2000 to 3000 ppm were most common (7). Preliminary data suggested anemia, low thyroxine in blood serum, eosinophilia, hypocholesterolemia, and reduced blood calcium in cattle from such herds.

A field study was conducted to determine the relationship of fluorine in urine to thyroid hormones and other blood criteria.

METHODS AND PROCEDURES

Blood and urine were collected simultaneously from 72 Holstein cows in six herds. Each herdsman selected from his herd two cows lactating <30 days, two 31 to 100 days, four 100 to 200 days, and four lactating 201 to 300 days. Blood cell counts, hemoglobin, leukocytes, and differential counts were made on whole blood, serum metabolic profiles were by SMA$_{12}$ autoanalyzer, thyroxine and triiodothyronine in serum by radioimmunoassay $^2$, and urinary fluoride by methods described in another report (7).

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$^2$ Radioassay System Laboratory, Inc., 1511 East Del Amo Boulevard, Carson, CA 90746.

Dental fluorotic lesions scored 1 to 5 with increasing severity as described by Hobbs et al. (8) were relatively minimal, incisors white with bright luster on enamel (Fig. 1) 1 to 2 in herd W, 1 to 3 in herd B, 1 to 4 (bilateral pitting of enamel) in herd G, 3 to 4 (mottled and hypoplasia of enamel) (Fig. 2) in herds M and P, and 4 to 5 (brown to black and severely worn) (Fig. 3) in herd S1. Herds averaged above 7000 kg milk per lactation except for M and S1. Additional herds with minimal signs of dental fluorotic lesions comparable to W were not found in more than 25 herds examined during a search for herds with a low incidence of fluoride lesions to serve as controls.

Classical fluorotic lesions were on teeth (mottling and excessive wear) and bones (exostosis) of cows in problem herds C4, V3, and B2. Fluoride concentrations in bones and teeth confirmed by analysis were comparable to S1 (1640 to 6918 ppm F in ash) indicating previous excessive intake of fluoride.

A mineral supplement containing soft rock phosphate (6000 ppm F) and a protein supplement containing 1088 ppm F had been fed to herd S1. Estimated average intake was 1143 mg F per day for an unknown time until about 9 mo before sampling, but supplements containing fluoride equivalent to other herds (1000 to 1500 ppm F in minerals) were fed at sampling. Herd W was fed dicalcium phosphate mixed with a commercial mineral supplement (1:1) free choice. Herd P was fed a mixture of commercial mineral and monosodium phosphate (17 ppm F) (1:1) free choice at sampling, herd B was fed a commercial mineral (750 ppm F) in the grain mix, herd G was fed dicalcium phosphate in the grain mix. Cows in herd M

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**FIG. 1.** Normal incisor teeth of 8 year-old cow, white, lustrous, and intact.
were fed a pelleted concentrate containing 7.5 ppm F at sampling.

Estimates of fluoride intake for individual cows were not attempted since consumption of minerals fed ad libitum could not be determined accurately under farm conditions. Fluoride concentrations in urine reflect current fluoride intake and are highly related to length of exposure or total fluoride consumed (22).

**RESULTS AND DISCUSSION**

Fluoride concentrations in urine from 72 cows in six herds averaged 5.13 ppm (Table 1) and ranged from 1.04 to 15.7 ppm on single specimens. By extrapolation from data of others (22, 26) these F concentrations were equivalent to those of cattle with a fluoride intake within the range of 1 to 22 ppm F. None of the herds was fed supplements unusually high in fluoride at sampling.

Urine of cows in herd W averaged 2.92 ppm F, lower (P<.05) than all other herds sampled and equivalent to F intake less than 10 ppm (22, 26). Herd P was second lowest, averaging 3.48 ppm F in urine, although teeth of most cows were mottled suggesting excessive fluoride intake previously.

Variations in urinary F were greater (P=.02) in herds S1 and M when variances were pooled and tested against variances of the other herds. Previous sources of elevated fluoride intake and bone fluoride concentrations within the toxic range were confirmed for herd S1 but not for M although clinical signs were apparent in both herds.

Urinary fluoride was correlated with days in lactation (r = -.44, P<.01) as were several blood measures. When effects of days in lactation were removed by least-squares regression analysis, thyroxine (T4) in blood serum decreased (P=.03), triiodothyronine (T3) decreased (P=.02), eosinophils increased (P=.004) (Fig. 2), and cholesterol tended to decrease (P=.06) with increasing urinary fluoride.

The regression equation for predicting T4 was: \( Y \text{ (micrograms T4/dl)} = 4.53 - .006 \text{(age, mo)} + .006 \text{(days in lactation)} - .098 \text{(urinary} } \)}
FIG. 3. Black and partially eroded incisors of cow 6 years of age.

F ppm). Standard errors of coefficients were: age (.006), days (.001), and urinary F (.044).

The regression equation for T3 was: Y (nanograms T3 per ml) = 1.6937 − .00067 (age, mo) + .0007 (days in lactation) − .02958 (urinary F ppm). Standard errors were: age (.00163), days (.0004), and urinary F (.01284).

The regression equation for predicting eosinophils as percent of leukocytes was: Y = .16 + .71 (urinary F ppm) + .02 (age, mo) + .01 (days in lactation). The standard error of the coefficient for urinary F was .24. Eosinophils were not significantly correlated with age or stage of lactation.

The T3 and T4 were lower (P<.05) for cows in herd S1 than in other herds sampled at the same time, and T4 was comparable to that of cows in fluorosis herds C4, V3, and B2 which had lower serum thyroxine than herds W, B, M, and G (P<.05) (Table 1). Excessive intake of fluoride may explain decreased thyroid function of cows in these herds. Thyroid glands of calves from herds S1 and V3 were two to six times normal weight, fluorotic lesions were on teeth and bones, and bones of calves 3 to 4 mo of age contained up to 2000 ppm F (7).

Thyroid involvement was implicated further when a fluorosis herd (B2) was fed thyroprotein (iodinated casein) for 3 wk. Milk production increased 100%, hemapoiesis was stimulated, eosinophils were reduced from 12% to 5.6% of leukocytes, serum calcium increased and phosphorus decreased while serum thyroxine increased from 3.4 to 14.1 µg/dl (7).

Reproductive efficiency was higher (P<.05) in herd W having the lowest urinary fluoride and least visual evidence of excessive fluoride intake than herd S1, as measured by services per conception (S/C) (W-1.4 vs. S-2.9) and days open postcalving (W-79 vs. S1-137 days) (P<.05), while other herds were 1.5 to 2.1 S/C and 85 to 96 days open. The data support farmer complaints that cattle afflicted with
TABLE 1. Urinary fluoride, thyroxine ($T_4$), triiodothyronine ($T_3$), calcium, phosphorus, and cholesterol in blood serum of dairy cows with varying severity of fluorosis.

<table>
<thead>
<tr>
<th>Herd</th>
<th>No. obs.</th>
<th>Urine F (ppm)</th>
<th>$T_4$ (µg/dl)</th>
<th>$T_3$ (ng/ml)</th>
<th>Calcium (mg/dl)</th>
<th>Phosphorus (mg/dl)</th>
<th>Cholesterol (mg/dl)</th>
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<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
<td>SE</td>
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<tr>
<td>W</td>
<td>12</td>
<td>2.92</td>
<td>.52</td>
<td>4.60</td>
<td>.34</td>
<td>1.75</td>
<td>.072</td>
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<td>B</td>
<td>12</td>
<td>5.37</td>
<td>.43</td>
<td>4.83</td>
<td>.19</td>
<td>1.68</td>
<td>.058</td>
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<tr>
<td>M</td>
<td>12</td>
<td>6.39</td>
<td>.92</td>
<td>5.30</td>
<td>.38</td>
<td>1.77</td>
<td>.084</td>
</tr>
<tr>
<td>G</td>
<td>12</td>
<td>6.33</td>
<td>.74</td>
<td>4.82</td>
<td>.28</td>
<td>1.59</td>
<td>.077</td>
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<tr>
<td>P</td>
<td>12</td>
<td>3.47</td>
<td>.47</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>12</td>
<td>6.29</td>
<td>1.08</td>
<td>3.59</td>
<td>.26</td>
<td>1.26</td>
<td>.084</td>
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<tr>
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<td></td>
<td></td>
<td>2.21</td>
<td>.54</td>
<td></td>
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</tr>
<tr>
<td>V3</td>
<td>10</td>
<td></td>
<td></td>
<td>3.35</td>
<td>.47</td>
<td></td>
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<td>13</td>
<td></td>
<td></td>
<td>3.39</td>
<td>.42</td>
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<td></td>
</tr>
</tbody>
</table>

Means (x) different (P<.05)

- W<all
- C4<all
- S1<all
- S1, V3, B2<
- W, B, M, G

Dental fluorosis confirmed by elevated bone fluoride in herds S1, C4, V3, and B2. Cows were uniformly distributed throughout lactation in all herds.
TABLE 2. Hematology values for lactating Holstein cows with varying severity of fluorosis sampled uniformly throughout lactation.

<table>
<thead>
<tr>
<th>Herd</th>
<th>No. obs</th>
<th>Red blood cells (per mm$^3 \times 10^6$)</th>
<th>Hemoglobin (g/dl)</th>
<th>Hematocrit (%)</th>
<th>Mean corpuscular volume (μm$^3$)</th>
<th>Total leukocytes (per mm$^3 \times 10^3$)</th>
<th>Eosinophils (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
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<td>6.46</td>
<td>.16</td>
<td>12.09</td>
<td>.27</td>
<td>33.4</td>
<td>.70</td>
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<tr>
<td>B</td>
<td>12</td>
<td>6.46</td>
<td>.20</td>
<td>11.57</td>
<td>.32</td>
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<td>.78</td>
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<tr>
<td>M</td>
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<td>.17</td>
<td>11.54</td>
<td>.25</td>
<td>31.3</td>
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<tr>
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<td>12</td>
<td>6.22</td>
<td>.16</td>
<td>11.40</td>
<td>.24</td>
<td>31.4</td>
<td>.58</td>
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<tr>
<td>P</td>
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<td>5.96</td>
<td>.12</td>
<td>10.91</td>
<td>.23</td>
<td>30.6</td>
<td>.61</td>
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<tr>
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<td>12</td>
<td>5.69</td>
<td>.18</td>
<td>9.93</td>
<td>.27</td>
<td>27.8</td>
<td>.69</td>
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<tr>
<td>C4</td>
<td>9</td>
<td>5.58</td>
<td>.19</td>
<td>9.79</td>
<td>.35</td>
<td>26.2</td>
<td>1.00</td>
</tr>
<tr>
<td>V3</td>
<td>10</td>
<td>5.65</td>
<td>.18</td>
<td>9.92</td>
<td>.34</td>
<td>25.8</td>
<td>1.10</td>
</tr>
<tr>
<td>B2</td>
<td>13</td>
<td>5.39</td>
<td>.12</td>
<td>9.94</td>
<td>.24</td>
<td>27.6</td>
<td>.60</td>
</tr>
</tbody>
</table>

Means different (P<.05)

B2<G, W, B, S1, C4, V3 <WB  
S1, C4, V3, B2  
V3, C4 <P  
B2, S1 <W, B, M, C  
V3 <B2, B, S1  
C4 <W, M, G, P  
NS  
NS

Herds S1, C4, V3, B2 visual fluoride lesions confirmed by elevated bone fluoride. Visual F lesions were on some cows in M, G, P, minor in B, minimal in W. Eosinophils increased with urinary F (P=.004).
Osteofluorotic lesions may result from resorption of bone calcium and eventual depletion of available bone calcium through increased activity of the parathyroids as proposed by Faccini (3, 4), particularly in the presence of excess dietary phosphorus which also inhibits bone calcification (30).

Serum phosphorus was high in some of the fluorosis herds (Table 1). The postcalving inanition in cattle fed excessive fluoride (14, 26) is similar to the displaced abomasum syndrome. Cows with previous displaced abomasum had black and eroded teeth suggesting a possible relationship to fluoride.

High eosinophils may be an early manifestation of fluoride toxicity and reduced resistance to infectious diseases as suggested by Utah workers (9) since three of eight cows in their high fluoride group died early.

The number of red blood cells per unit volume, blood hemoglobin, hematocrit, and mean corpuscular volume (MCV) were lower (P<.05) in fluorosis herds (Table 2). These data indicate development of anemia in cattle afflicted with fluorosis which agrees with other reports (18, 25). Anemia may result from lower blood folic acid (9), reduced synthesis of vitamin B₁₂ (18), reduced dry matter intake, apparent protein absorption (6), and reduced rumen microbial growth (8, 18) when excessive fluoride is fed to cattle and sheep.

Calcium in blood serum was highest in herd W (lowest fluoride; Table 1) and highly correlated (r = .52; P<.01) with serum T₃ and T₄ (r = .30; P<.05). Fluoride reduced calcium absorption at high concentrations of F in the diet of calves (16). Osteofluorotic lesions may result from resorption of bone calcium and eventual depletion of available bone calcium through increased activity of the parathyroids as proposed by Faccini (3, 4), particularly in the presence of excess dietary phosphorus which also inhibits bone calcification (30).

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CONCLUSIONS

This report demonstrates that intakes of fluoride currently judged to be acceptable adversely affect thyroid and blood of cows and should serve as a warning that this might be a widespread problem.

Increased bone fluoride may provide historical evidence of excessive intake of fluoride, but must be interpreted with caution since fluorotic lesions and blood changes associated with fluoride occur over a wide range of bone fluoride concentrations. Under field conditions fluorosis may not be recognized until some time after the period of high fluoride intake. Bone fluoride is reduced 30 to 60% over 6 mo to 2 yr (15, 21) and may result in misinterpretation of the findings. Blood fluoride tends to remain high during this excretion period although urinary fluoride returns to near normal concentrations (15).

The finding of dental and bone fluorotic lesions in some cows of all herds and adverse relationships between blood criteria and urinary fluoride in "normal" herds suggests that fluoride must be considered among factors that affect the health and performance of cattle.

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