Nutrient Interactions and Toxicity
Research Communication

Oral Iodine Toxicity in Chicks Can Be Reversed by Supplemental Bromine

(Manuscript received 28 March 2003. Initial review completed 22 April 2003. Revision accepted 28 April 2003.)

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ABSTRACT Four chick bioassays were conducted to quantify iodine (I) toxicity and its amelioration in young chicks. A supplemental I level from KI of 600 mg/kg depressed growth in chicks fed methionine-deficient diets but not in those fed methionine-adequate diets. An I dose level ≥ 900 mg/kg was required to cause growth depression in chicks fed a methionine-adequate corn-soybean meal diet. Iodine intoxicated chicks also displayed neurological symptoms and extreme malaise, but dose levels up to 1200 mg I/kg had no effect on blood hemoglobin or hematocrit. Supplemental I levels of 1000–1500 mg/kg caused severe growth depressions that could be totally reversed by dietary addition of 50 or 100 mg/kg bromine provided as NaBr. Nuclear accidents or terrorist actions that result in I toxicity and thyroid cancer or goiter may benefit from use of NaBr as a therapeutic agent. J. Nutr. 133: 2309–2312, 2003.

KEY WORDS: • iodine • toxicity • bromine • chicks

In a recent attempt to determine the methionine bioactivity of S-methylmethionine (SMM), a compound found in foods (1,2), we unwittingly encountered iodine (I) toxicity. Our SMM compound had been synthesized as the iodide salt, and when this compound was fed to chicks consuming a Met-deficient diet, poor growth and bizarre symptoms occurred. Chicks receiving excess I were observed to fall over and lie relatively motionless. However, after staying motionless for several minutes, they eventually resumed their normal standing position for several minutes, only to fall over once again. Upon surveying the literature on I and other mineral toxicities (3–5), we were surprised to learn that I toxicity had apparently never been quantified in young growing chickens.

Iodine toxicity is of more than mere “academic” interest in light of the occurrence of thyroid cancer following radiation exposure or nuclear explosions (6,7). Indeed, employees of nuclear power companies currently have KI tablets in their possession to be consumed should an accident or terrorist activity occur. “Cold” iodine consumption is recommended therapy when nuclear explosions give off radioactive I (primarily 131I through 129I) so that the thyroid will take up “cold” I rather than radioactive I. Thus, overconsumption of I by adults or children remains a possibility.

We endeavored herein to quantify I toxicity in young chicks. Also, because amelioration of I toxicity is not well understood (4,8–10), we evaluated several alleged means of minimizing the growth depressing effects of excess dietary I using chicks as an animal model. To our knowledge, there is no established means of ameliorating I toxicity, other than withdrawing the source of contaminating I from the food or water supply, or the air.

MATERIALS AND METHODS

General procedures. All procedures were approved by the University of Illinois Committee on Laboratory Animal Care. Experiments were carried out using color-sexed male New Hampshire × Columbian chicks. Chicks were housed in thermostatically controlled starter batteries with raised wire floors in an environmentally controlled building. Chicks were pretested on a fully fortified corn-soybean meal diet containing 23% crude protein (CP) until 1600 h of d 7 posthatching. On d 8 after being subjected to an overnight period of feed withdrawal, chicks were weighed, wing banded and randomly allotted to pens such that each pen of chicks had a similar initial weight and weight distribution. The average initial weight of chicks at trial initiation ranged from 86 to 95 g.

Four bioassays were conducted, and four replicate groups of four chicks consumed each experimental diet ad libitum from d 8 to 17 (Assay 1) or d 8 to 21 (Assays 2, 3 and 4) posthatching. Body weight of individual chicks and pen diet intakes were measured at the termination of each trial. Weight gain, food intake and food efficiency (gain:food ratio) were then calculated for each pen replicate.

Basal diets for the four assays are shown in Table 1. In Assay 1, a soybean meal (SBM) semipurified diet containing either 150 or 180 g CP/kg was used; in Assays 2, 3 and 4, a Met-fortified corn-SBM diet (230 g CP/kg) was used. Considering the I contributed by corn and SBM (11) as well as the I provided by ethylene diamine dihydroiodide in the trace-mineral premix, the SBM basal diet was estimated to contain 0.77 mg I/kg and the corn-SBM basal diet 0.78 mg I/kg. The NRC requirement estimate (12) for I is 0.35 mg/kg for young broiler chicks.

Assay 1. Because our initial encounter with I toxicity involved a low CP Met-deficient assay diet, Assay 1 employed this same basal diet (Table 1). Also, because the SMM compound (I salt) evaluated in this trial contributed ~1200 mg I/kg, we tested this level of I (from KI) as well as half this dose (600 mg I/kg), both compared with diets containing no supplemental KI. Both dietary protein level (130 vs. 180 g/kg) and Met (deficiency vs. adequacy) were evaluated in the presence of 0, 600 or 1200 mg I/kg provided as KI. The assay, therefore, had a 3 × 2 factorial arrangement of treatments, and amino acid additions (other than Met) were provided to ensure adequacy.

1 To whom correspondence should be addressed. E-mail: dhbaker@uiuc.edu.
2 Abbreviations used: CP, crude protein; SMM, S-methylmethionine; SBM, soybean meal.

0022-3166/03 $3.00 © 2003 American Society for Nutritional Sciences.
Supplemental I was considerably less growth depressing when added to the corn-SBM diet, adequate in both CP and Met, than when added to the Met-deficient SBM semipurified diet used in Assay 1 (Table 3). Levels of supplemental I < 600 mg/kg did not depress (P > 0.10) weight gain, but I levels ≥ 600 mg/kg reduced (P < 0.01) food intake. Remarkably, the gain:food ratio was not depressed by any level of supplemental I, and the same was true for both hemoglobin and hematocrit.

Assay 3. Supplemental I at 1000 mg/kg depressed both weight gain and food intake, but food efficiency was actually better (P < 0.05) in chicks fed excess dietary I (Table 4). Dietary addition of Mn, Co and As (as Roxarsone) to diets containing 1000 mg I/kg neither increased nor decreased chick performance compared with that of the negative-control diet.
Supplemental Br at either 50 or 100 mg/kg, however, restored both weight gain and food intake to a level that was similar to that of the positive-control diet.

Assay 4. The final assay involved an even higher dose of supplemental I (1500 mg/kg), and because 100 mg Br/kg was ameliorative in Assay 3, this level of Br was tested in both the absence and presence of 1500 mg I/kg (Table 5). The higher dose level of I accomplished the experimental objective of markedly depressing weight gain, food intake and gain:food ratio. Adding 100 mg Br/kg was without effect when added to the positive-control diet (no supplemental I), but it totally reversed the I-induced growth depression when it was added to the negative-control diet containing 1500 mg I/kg. Thus, the I × Br interaction was significant (P < 0.01).

TABLE 4
Evaluation of means of ameliorating iodine toxicity in chicks fed a Met-fortified corn-soybean meal basal diet (Assay 3)1

<table>
<thead>
<tr>
<th>Dietary addition</th>
<th>Weight gain</th>
<th>Food intake</th>
<th>Gain:food</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g/kg</td>
<td>g/kg</td>
<td>g/L/g/100 g</td>
</tr>
<tr>
<td>1. None2</td>
<td>323a</td>
<td>483a</td>
<td>669a</td>
</tr>
<tr>
<td>2. 1000 mg I/kg (KI)</td>
<td>287b</td>
<td>402b</td>
<td>713a</td>
</tr>
<tr>
<td>3. As 2 + 50 mg Br/kg (NaBr)</td>
<td>314a</td>
<td>469a</td>
<td>670b</td>
</tr>
<tr>
<td>4. As 2 + 100 mg Br/kg (NaBr)</td>
<td>315a</td>
<td>466a</td>
<td>676a,b</td>
</tr>
<tr>
<td>5. As 2 + 1000 mg Mn/kg (MnSO4 · H2O)</td>
<td>270b</td>
<td>392b</td>
<td>688a,b</td>
</tr>
<tr>
<td>6. As 2 + 100 mg Co/kg (CoCl2 · 6H2O)</td>
<td>275b</td>
<td>405b</td>
<td>678a,b</td>
</tr>
<tr>
<td>7. As 2 + 100 mg Roxarsone9/kg</td>
<td>283b</td>
<td>412b</td>
<td>686a,b</td>
</tr>
<tr>
<td>Pooled SEM4</td>
<td>8</td>
<td>9</td>
<td>11</td>
</tr>
</tbody>
</table>

1 Data are mean values per chick of four pens of four chicks during a 13-d feeding period (d 8–21 posthatching); average initial weight was 86 g.
2 The basal corn-soybean meal diet (Table 1) contained 230 g crude protein (CP)/kg and 0.78 mg I/kg.
3 Roxarsone is 3-nitro-4-hydroxyphenylarsonic acid; 100 mg/kg furnished 28.5 mg As/kg.
4 Means within columns that have different superscript letters are different, P < 0.05.

DISCUSSION
The most important finding in these experiments was that Br administered orally as NaBr was able to completely overcome the malaise, debilitation and severe growth depression caused by a large excess of dietary I. Reviews that have been written on I toxicity (4,5,8–10) mention (in passing) that salts of Mn, As, F, Co, NO3 and Br may have ameliorative effects on I toxicity. Among these, our chick studies revealed that only Br had efficacy in reversing the growth depression caused by excess dietary I.

A fascinating mouse study by Huff and co-workers at Merck (17) involved attempts to overcome growth depressions caused by iodinated casein. They observed efficacy in overcoming the growth depression from adding a dried sea salt preparation to the diet. Upon analysis, they postulated that the active element in this preparation was either aluminum, boron, fluorine, rubidium or Br. Subsequent mouse studies revealed that only Br would reverse the growth depression, which was modest in their case. Unfortunately, Huff et al. (17) did not indicate the dietary level of I that was provided when

TABLE 5
Bromine ameliorates iodine toxicity in chicks fed a Met-fortified corn-soybean meal basal diet (Assay 4)1

<table>
<thead>
<tr>
<th>Dietary addition</th>
<th>Weight gain</th>
<th>Food intake</th>
<th>Gain:food</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g/kg</td>
<td>g/kg</td>
<td>g/L/g/100 g</td>
</tr>
<tr>
<td>1. None3</td>
<td>346</td>
<td>494</td>
<td>701</td>
</tr>
<tr>
<td>2. 1500 mg I/kg (KI)</td>
<td>224</td>
<td>349</td>
<td>642</td>
</tr>
<tr>
<td>3. As 1 + 100 mg Br/kg (NaBr)</td>
<td>345</td>
<td>489</td>
<td>705</td>
</tr>
<tr>
<td>4. As 2 + 100 mg Br/kg (NaBr)</td>
<td>337</td>
<td>487</td>
<td>693</td>
</tr>
<tr>
<td>Pooled SEM5</td>
<td>8</td>
<td>9</td>
<td>8</td>
</tr>
</tbody>
</table>

1 Data are mean values per chick of four pens of four chicks during a 13-d feeding period (d 8–21 posthatching); average initial weight was 92 g.
2 I × Br interaction, P < 0.01.
3 The basal corn-soybean meal diet (Table 1) contained 230 g crude protein (CP)/kg and 0.78 mg I/kg.
20 or 40 g/100 g iodinated casein was fed. Moreover, their basal diet was deficient in essential fatty acids, which made the I × Br interaction difficult to interpret.

The obvious next step in studying the I × Br interaction is to identify the mechanism by which Br reverses I toxicity. Three likely possibilities are that Br 1) reduces gut absorption of I, 2) enhances urinary excretion of I or 3) reduces I uptake by the thyroid gland. It is possible that all three of these are involved in the amelioration of I toxicity. Vobecky and co-workers (24,25) showed that oral Br decreases I uptake by the thyroid gland in rats fed normal (i.e., low) levels of I. If the I × Br interaction occurs primarily at the level of the thyroid gland, this would suggest that oral Br might effectively ameliorate either “cold” or radioactive I toxicity, and so do regardless of whether the I ingestion occurred as inspired gaseous radioactive I or as oral I, either “cold” or radioactive. Presumably, Br is displacing some of the I on the thyronine molecules (24). Currently, oral ingestion of KI tablets is the preferred method of minimizing thyroid cancer resulting from nuclear accidents that release gaseous radioactive I into the atmosphere as well as the vegetation. Supplemental NaBr may be a better solution than KI in situations of this nature. Clearly, however, the long-term implications of Br uptake by the thyroid gland on overall thyroid health have to be assessed.

Compared with several other mineral toxicities, the dietary I level (above its minimal dietary requirement) necessary to cause toxicity is large, ~1000 times the minimal requirement of both growing chickens (12) and pigs (13,26). Our results in Assay 1 (Table 2) suggested that excess I was considerably more growth depressing when Met-deficient diets were fed than when Met-adequate diets were fed. We do not believe this is necessarily unique to Met deficiency. A diet severely deficient in an indispensable amino acid, as was the case in Assay 1, is made more deficient in that amino acid when another dietary addition (e.g., excess I) causes a marked depression in voluntary food intake. Clearly, with the exception of the large dose of excess I in Assay 4, (1500 mg I/kg), the growth depression resulting when excess I was added to Met-adequate corn-SBM diets was caused almost entirely by reduced food intake and not by reduced food utilization.

Although release of at least 15 different radioactive isotopes of I occurs as gases when the uranium or plutonium atom is split, oral I toxicity also has occurred in certain population groups in China and Japan that have been exposed to chronic and high (50 to 80 mCi/kg) intakes of I (9,27). Moreover, the 1986 Chernobyl accident in the Soviet Union caused I contamination of pasture land, with dairy cows therefore consuming excess I that ultimately was present in the milk, causing I toxicity in young children (28–30). It seems possible that NaBr might have been helpful in reversing the oral I toxicity problems that occurred in these situations. Indeed, Pavelka et al. (31) showed in rats that high Br intakes by lactating dams would decrease I and increase Br in dam’s milk. It also increased urinary I excretion.

The nutrition literature on Br is sparse. The Merck group (17,18) evaluated a dietary Br level of 15 mg/kg, whereas the Czech group (24,25,31) used Br levels (in drinking water) as high as 100 mg/L for rats consuming normal (0.8 mg/kg) levels of I, Our ameliorative dose level was 50 or 100 mg Br/kg diet, and we cannot conclude that a lower dose level of Br might also have been efficacious in reversing I toxicity. Nonetheless, that 100 mg Br/kg could totally reverse the severe growth depression and malaise caused by 1500 mg I/kg (Table 5) is remarkable.

LITERATURE CITED