Hypernickelemia Following Coronary Arteriography, Caused by Nickel in the Radiographic Contrast Medium*

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ABSTRACT

Meglumine diatrizoate ("Renografin-76", a radiographic contrast medium) contains sufficient nickel to cause hypernickelemia in patients after coronary arteriography. Nickel analyses by electrothermal atomic absorption spectrophotometry showed that nine lots of "Renografin-76" (760 g of meglumine diatrizoate per L) contained 144 ± 44 μg Ni per L. Serum Ni concentrations became elevated in 11 patients after coronary arteriography (Ni dose = 19 ± 4 μg per patient); peak Ni concentrations (increment = 1.8 ± 0.4 μg Ni per L) occurred 0.25 or 0.5 h post-injection. Serum Ni concentrations diminished at 2 and 4 h post-injection and returned to base-line values at 24 h. The half-time (T½) for reduction of serum Ni concentrations averaged 1.5 h.

Analysis of urine specimens from two patients showed that most of the Ni dose was excreted in urine within 24 hours. After iv administration of meglumine diatrizoate to rabbits (0.5 or 1.0 μg Ni per kg body wt), T½ values for elimination of Ni from the serum volume averaged 1.2 h, compared to T½ values of 5.7 and 7.4 h, respectively, when Ni was administered iv in NiCl₂ or albumin solutions. Since "Renografin-76" contains edetate disodium (0.4 g per L), Ni is probably present as a Ni-EDTA complex, accounting for the rapid elimination of Ni following iv administration of the contrast medium to patients and rabbits. To reduce possible hazards of allergic or cardiovascular reactions to nickel, the authors recommend that Ni concentrations in radiographic contrast media should not exceed 10 μg per L.

Introduction

Hypernickelemia develops in three-fourths of patients with acute myocardial
infarction and, to lesser degree, in approximately one-half of patients with unstable angina pectoris during three days after admission to the hospital. In the course of our studies of the pathogenesis of hypernickelemia in cardiac patients, substantial concentrations of nickel were observed in a preparation of meglumine diatrizoate that is commonly employed as the radiographic contrast agent for coronary arteriography. This study shows that patients consistently develop transient hypernickelemia following coronary arteriography with meglumine diatrizoate. Similar hypernickelemia is induced in rabbits by iv injection of the meglumine diatrizoate preparation. Therefore, meglumine diatrizoate is identified as one of the causes of iatrogenic hypernickelemia, which also include (a) extracorporeal or peritoneal dialysis, (b) implanted orthopedic prostheses, (c) iv infusion of albumin solutions, (d) intradermal injections with the “Dermo-Jet”, an instrument used to administer local anesthetics and vaccines, and (e) oral administration of disulfiram and indomethacin.

For background information on nickel metabolism and toxicology, readers are referred to recent monographs and reviews.

Materials and Methods

The research protocol was approved by the Human Experimentation Committees of New Britain General Hospital and University of Connecticut Health Center. The subjects comprised 11 patients (eight men, three women; mean age = 61 ± 10 years; range = 38 to 77 years) at New Britain General Hospital, who underwent diagnostic cardiac catheterization with angiography of the coronary arteries and left ventricle. The patients either had, or were suspected of having, coronary artery disease. Two of the patients were diabetics; none had significant renal disease. Blood samples were collected via a polyethylene iv catheter prior to angiography and at intervals of 0.25, 0.5, 2, 4, 6, and 24 hours after the last intra-arterial injection of radiographic contrast medium. The contrast medium* contained meglumine diatrizoate (760 g per L) and edetate disodium (sodium EDTA, 0.4 g per L); the contrast medium was injected as multiple small boluses into the coronary arteries and left ventricle during radiographic visualization; the total volume of contrast medium averaged 164 ± 10 mL per patient. Blood samples were collected with stringent precautions to avoid nickel contamination, as previously described. In two patients, serial urine collections were obtained via indwelling urethral catheter on the day following coronary arteriography.

The experimental animals were six male rabbits, caged individually and fed Purina laboratory rabbit chow with supplemental fresh vegetables. Each rabbit received three iv injections of (a) the meglumine diatrizoate preparation (“Renografin-76”, injected volume = 2.85 or 5.70 mL per kg body wt), (b) human albumin solution for iv infusion (250 g of albumin per L, injected volume = 5.70 mL per kg body wt), and (c) nickel chloride (1 mg Ni per L) dissolved in sterile NaCl solution (140 mmol per L), (injected volume = 2.85 mL per kg body wt). The three injections were given to the rabbits in random sequence on three successive weeks via marginal veins of the right ear; blood specimens were collected from marginal veins of the left ear before each injection and at 0.5, 2, and 4 hours post-injection.

* “Renografin-76”, E. R. Squibb Co., New Brunswick, NJ.
† Albino, New Zealand strain, body weight = 3.5 ± 0.2 kg; Charles River Breeding Laboratories, Inc., North Wilmington, MA.
‡ New York Blood Center, New York City, NY.
Nickel concentrations in serum, urine, albumin solutions, and radiographic contrast media were measured by electrothermal atomic absorption spectrophotometry (EAAS) with Zeeman background correction, using a Model 5000-Z EAAS spectrometer,$ as previously described.24,25,26 The radiographic contrast media that were analyzed for nickel included nine lots of meglumine diatrizoate ("Renografin-76", 760 g per L)*, one lot of iopramide ("Ultravist-300", 623 g per L),§ and one lot of metrizamide ("Amipaque", 134 g per L).‖ Body surface areas of patients were estimated by means of a nomogram, based on measurements of height and weight.8 Percentages of administered nickel within the serum compartment of rabbits were calculated, assuming an average serum volume of 38.8 mL per kg body wt.1 Statistical and pharmacokinetic computations (mean, standard deviation, linear regression, correlation coefficient, renal clearance, serum elimination half-time) were performed according to Bolton2 and Gibaldi and Perrier.5

### RESULTS

Measurements of nickel concentrations in samples of iodinated radiographic contrast media are summarized in table I. Nine lots of meglumine diatrizoate ("Renografin-76") contained an average of 144 ± 44 µg Ni per L (range = 96 to 233 µg Ni per L). For comparison, single lots of iopramide ("Ultravist-300") and metrizamide ("Amipaque") contained, respectively, 35 and 3.6 µg Ni per L. The solution of human serum albumin contained 96 µg Ni per L.

Concentrations of nickel in serum specimens from patients, before and after coronary arteriography with meglumine diatrizoate, are listed in table II. For comparison, nickel concentrations in serum specimens from 30 healthy adults averaged 0.28 ± 0.24 µg per L (range = <0.05 to 1.1 µg per L), as previously reported.11 Serum nickel concentrations exceeded the upper limit of the reference range in pre-injection specimens from four of 11 patients. These patients with pre-injection hypernickelemia included (a) case #8, with congestive heart failure, (b) case #9, with a recent myocardial infarction, unstable angina pectoris, and congestive heart failure, (c) case #10, with coronary arterial spasm,

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**TABLE I**

<table>
<thead>
<tr>
<th>Radiographic Contrast Media</th>
<th>Concentration of Contrast Agent (g/L)*</th>
<th>Concentration of Iodine (g/L)*</th>
<th>Number of Lots Tested</th>
<th>Nickel Concentration in Contrast Media (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diatrizoate (&quot;Renografin-76&quot;)†</td>
<td>760</td>
<td>370</td>
<td>9</td>
<td>144 ± 44‡</td>
</tr>
<tr>
<td>Iopramide (&quot;Ultravist-300&quot;)§</td>
<td>623</td>
<td>300</td>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td>Metrizamide (&quot;Amipaque&quot;)‖</td>
<td>134</td>
<td>65</td>
<td>1</td>
<td>3.6</td>
</tr>
</tbody>
</table>

*Manufacturer's data
†E.R. Squibb Co.
‡Mean ± SD; range = 96 to 233 µg/L
§Schering Corp.
‖Sterling-Winthrop, Inc.
TABLE II

Serum Nickel Concentrations Before and After Coronary Arteriography

<table>
<thead>
<tr>
<th>Patient, Sex, Age</th>
<th>0 hr</th>
<th>0.25 hr</th>
<th>0.5 hr</th>
<th>2 hrs Pre- and Post-Injection*</th>
<th>4 hrs</th>
<th>6 hrs</th>
<th>24 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1, f, 38</td>
<td>0.11</td>
<td>1.85</td>
<td>1.48</td>
<td>0.32</td>
<td>0.32</td>
<td>0.27</td>
<td>0.16</td>
</tr>
<tr>
<td>#2, m, 51</td>
<td>0.25</td>
<td>2.24</td>
<td>1.79</td>
<td>0.65</td>
<td>0.45</td>
<td>0.25</td>
<td>0.20</td>
</tr>
<tr>
<td>#3, m, 77</td>
<td>0.32</td>
<td>1.80</td>
<td>3.06</td>
<td>0.33</td>
<td>0.26</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>#4, m, 67</td>
<td>0.36</td>
<td>1.50</td>
<td>1.81</td>
<td>1.03</td>
<td>0.67</td>
<td>0.31</td>
<td>0.05</td>
</tr>
<tr>
<td>#5, m, 67</td>
<td>0.37</td>
<td>1.80</td>
<td>1.90</td>
<td>1.48</td>
<td>0.62</td>
<td>0.63</td>
<td>0.05</td>
</tr>
<tr>
<td>#6, m, 57</td>
<td>0.45</td>
<td>2.09</td>
<td>1.94</td>
<td>1.04</td>
<td>0.70</td>
<td>0.60</td>
<td>0.30</td>
</tr>
<tr>
<td>#7, f, 55</td>
<td>1.12</td>
<td>3.32</td>
<td>2.35</td>
<td>1.63</td>
<td>1.58</td>
<td>1.43</td>
<td>1.09</td>
</tr>
<tr>
<td>#8, m, 57</td>
<td>1.71</td>
<td>3.13</td>
<td>2.28</td>
<td></td>
<td>2.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#9, m, 68</td>
<td>2.15</td>
<td>4.13</td>
<td>3.51</td>
<td>3.23</td>
<td>2.49</td>
<td>2.27</td>
<td>1.93</td>
</tr>
<tr>
<td>#10, f, 65</td>
<td>2.34</td>
<td>3.34</td>
<td>3.93</td>
<td>3.28</td>
<td>2.83</td>
<td>2.98</td>
<td>2.49</td>
</tr>
<tr>
<td>#11, m, 63</td>
<td>5.53</td>
<td>7.19</td>
<td>6.21</td>
<td>6.02</td>
<td>6.08</td>
<td>5.57</td>
<td></td>
</tr>
</tbody>
</table>

*Blood samples obtained via venous catheter before and after intraarterial injection of diatrizoate meglumine.
hr = hour

and (d) case #11, with hypotension, severe aortic stenosis, unstable angina pectoris, and congestive heart failure.

The intra-arterial injections of meglumine diatrizoate contained 19.1 ± 4.0 \( \mu g \) Ni per patient (range = 14 to 24 \( \mu g \) Ni per patient), equivalent to 0.23 ± 0.07 \( \mu g \) Ni per kg body wt (range = 0.15 to 0.35 \( \mu g \) Ni per kg). Serum nickel concentrations increased in all of the patients following coronary arteriography; the peak concentrations of nickel in venous serum occurred 0.25 or 0.5 hours after the last bolus of radiocontrast medium had been injected; the increments of serum nickel concentrations averaged 1.81 ± 0.39 \( \mu g \) per L (range = 1.42 to 2.74 \( \mu g \) per L). Serum nickel concentrations diminished progressively at two and four hours post-injection, and returned to near-baseline values by 24 hours. As illustrated in figure 1, the halftime (T\( \frac{1}{2} \)) for elimination of the injected nickel from serum averaged 1.5 hours in the 11 patients.

Renal excretion of nickel during the day after coronary arteriography was measured in two patients (table III). In patient #6, approximately 97 percent of the nickel that was administered in the contrast medium was recovered in urine during 23 hours post-injection; in patient #8, approximately 75 percent of the administered nickel was recovered in urine during 20 hours post-injection. Lower elimination of nickel in the latter patient may reflect his congestive heart failure.

Nickel was administered iv to rabbits in three forms: (a) as a nickel chloride solution (2.85 \( \mu g \) Ni per kg body wt), (b) as a constituent of a pharmaceutical solution of human albumin, (0.55 \( \mu g \) Ni per kg body wt), and (c) as a constituent of the pharmaceutical preparation of meglumine diatrizoate ("Renografin-76", 0.5 or 1.0 \( \mu g \) Ni per kg body wt). Baseline concentrations of serum nickel in the 6 rabbits averaged 1.9 ± 0.6 \( \mu g \) per L (range = 1.0 to 2.8 \( \mu g \) per L). At 30
HYPERNICKELEMIA FOLLOWING CORONARY ARTERIOGRAPHY

1. Increment of serum Ni (μg/L)

[log y = 0.24 - 0.94x]
Corr. Coef. = 0.71

$T^{1/2} = 1.5$ hours

2. % of Ni dose in serum volume

Albumin
$T^{1/2} = 7.4$ hours

Diatrizoate
$T^{1/2} = 1.2$ hours

NiCl$_2$
$T^{1/2} = 5.6$ hours

Mean ± SE
TABLE III
Renal Excretion of Nickel After Coronary Arteriography

<table>
<thead>
<tr>
<th>Patient, Sex, Age (y)</th>
<th>Collection Period (hr)</th>
<th>Urine Flow Volume (mL)</th>
<th>Urine Flow Rate (mL/min)</th>
<th>Urine Ni Conc. (µg/L)</th>
<th>Renal Clearance of Ni (mL/min)*</th>
<th>Excretion of Ni in Urine (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#6, m, 57†</td>
<td>(A) -1 to 0 hr</td>
<td>94</td>
<td>1.57</td>
<td>2.1</td>
<td>5.9</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>(B) 0 to 4 hrs</td>
<td>937</td>
<td>3.86</td>
<td>14.1</td>
<td>35.2</td>
<td>13.2</td>
</tr>
<tr>
<td></td>
<td>(C) 4 to 23 hrs</td>
<td>864</td>
<td>0.76</td>
<td>9.6</td>
<td>12.4</td>
<td>7.3</td>
</tr>
<tr>
<td></td>
<td>1 to 23 hrs</td>
<td>1,895</td>
<td>11.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#8, m, 57‡</td>
<td>(A) 0 to 2 hrs</td>
<td>250</td>
<td>2.08</td>
<td>13.0</td>
<td>10.1</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>(B) 2 to 4 hrs</td>
<td>494</td>
<td>4.12</td>
<td>13.6</td>
<td>24.9</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>(C) 4 to 20 hrs</td>
<td>1,395</td>
<td>1.46</td>
<td>4.2</td>
<td>2.7</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>0 to 20 hrs</td>
<td>2,139</td>
<td>6.4</td>
<td></td>
<td></td>
<td>15.9</td>
</tr>
</tbody>
</table>

*Normalized to body surface area = 1.73 m²
† Patient #6 (98 kg, 2.15 m² body surface area) received 163 mL of Renografin-76, (Ni conc. = 120 µg/L); the total dose of Ni was 19.6 µg. If the average urinary excretion of Ni (2.6 µg/day) is subtracted, approximately 97% of administered Ni was recovered in the urine.
‡ Patient #8 (75 kg, 2.06 m² body surface area) received 176 mL of Renografin-76, (Ni conc. = 136 µg/L); the total dose of Ni was 23.9 µg. If the average urinary excretion of Ni (2.6 µg/day) is subtracted, approximately 75% of administered Ni was recovered in the urine.
hr = hour

Discussion

This study demonstrates that a pharmaceutical preparation of meglumine diatrizoate ("Renografin-76"), which is commonly used as a radiographic contrast medium, contains sufficient nickel to cause hypernickelemia in patients following coronary arteriography. The nickel content of the contrast medium fluctuates substantially from lot to lot, probably reflecting variable concentrations of nickel in diatrizoic acid and/or variable release of nickel from vessels and fittings made of stainless-steel and other nickel alloys during manufacture and bottling. Since "Renografin-76" contains ethylenediamine tetraacetic acid (EDTA) as a metal scavenger to inhibit catalytic deiodination, the nickel is probably present as a Ni-EDTA complex, accounting for the rapid elimination T½ values for nickel that were observed in patients and rabbits after injection of the radiocontrast medium.

Allergic and cardiovascular reactions to meglumine diatrizoate are discussed in recent articles. The present authors speculate that nickel, possibly in the form of Ni-EDTA, may contribute to such adverse effects. Nickel hypersensitivity has been reported to cause asthma, eosinophilic pneumonitis, conjunctivitis, dermatitis, and generalized allergic reactions after parenteral administration of nickel-containing medications, as reviewed by Sunderman et al. Electrophysiological disturbances of the myocardiun and acute coronary vasoconstriction have been observed in
Ni\(^{2+}\)-treated animals, as summarized by Leach et al. \(^{11}\) Little information is available regarding acute toxicity of Ni-EDTA in humans, but an animal experiment suggests that administration of edathamil is deleterious in acute nickel carbonyl poisoning.\(^{30}\) Sunderman\(^{20}\) recommended that the maximum permissible concentration of nickel be 5 \(\mu\)g per L for common iv solutions and 10 \(\mu\)g per L for iv solutions that contain albumin or amino acids that avidly bind nickel. The latter recommended limit should be applicable to preparations of iodinated radiographic contrast media for iv use, such as meglumine diatrizoate.

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