Potential Toxicity from Nickel Contamination of Intravenous Fluids*

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Nickel contamination of intravenous fluids warrants concern, owing to three specific toxic effects of Ni\textsuperscript{2+:} (a) cardiac toxicity, especially increased coronary artery resistance, (b) oxytocic action on the uterus, and (c) allergic reactions, since nickel is a common allergen. In addition, high concentrations of nickel in intravenous fluids could evoke nonspecific toxic responses, such as nausea, vomiting, headache, and palpitations. Physicians should be especially cognizant of potential cardiac toxicity from nickel in intravenous fluids that are administered to patients with acute myocardial infarction.

Most experimental studies of toxic effects of nickel on the heart have been conducted at high concentrations of Ni\textsuperscript{2+:} that would be unlikely to occur in clinical situations. However, recent experiments by Rubanyi and coworkers\textsuperscript{1,10,18–23} have demonstrated adverse cardiac effects of Ni\textsuperscript{2+:} at dosages and concentrations that seem relevant to medical practice. In isolated, perfused rat hearts, addition of Ni\textsuperscript{2+:} (60 \(\mu\)g per L) to the perfusion medium significantly increased coronary artery resistance, reduced myocardial contractility, and caused ultrastructural myocardial damage\textsuperscript{1,16,18–20,22}. In excised, perfused cat coronary arteries, Ni\textsuperscript{2+:} (60 \(\mu\)g per L) significantly increased coronary resistance and decreased coronary flow.\textsuperscript{23} In their most recent experiments,\textsuperscript{21} addition of Ni\textsuperscript{2+:} (6 \(\mu\)g per L) to the perfusion medium caused significant increase of total coronary resistance in isolated rat hearts. Moreover, i.v. injection of Ni\textsuperscript{2+:} (4.7 \(\mu\)g per kg of body wt) caused 46 percent (SD ± 6 percent) increase of total coronary artery resistance \textit{in vivo} in anesthetized dogs.\textsuperscript{21} Such an increase in total coronary artery resistance might be hazardous in patients with acute myocardial infarction.

The oxytocic effect of Ni\textsuperscript{2+:} has been studied by Rubanyi and Balogh\textsuperscript{17} on rat uterine muscle strips \textit{in vitro}. Addition of Ni\textsuperscript{2+:} (6 \(\mu\)g per L) to the incubation medium increased the resting tension but did not affect the frequency of contraction. At a higher concentration (60 \(\mu\)g per L), Ni\textsuperscript{2+:} induced ultrastructural damage of mitochondria in rat uterine myocytes. Studies of Ni\textsuperscript{2+:} effects on uterine contraction \textit{in vivo} are necessary before any definite conclusions can be reached. Yet, the observations of Rubanyi and Balogh\textsuperscript{17}
stimulate concern regarding possible uterine effects of Ni\textsuperscript{2+} that may inadvertently be administered in i.v. solutions to pregnant women during late gestation.

Numerous case reports have documented nickel sensitivity (dermatitis or asthma) in patients following implantation of nickel-containing prostheses (e.g., cardiac valve replacements, intramedullary rods, joint prostheses, surgical clips, and stainless steel sutures).\textsuperscript{2,8,11,14,15,26,29} Such prostheses cause slow parenteral release of Ni\textsuperscript{2+} at rates (260 to 300 pg per cm\textsuperscript{2} per day)\textsuperscript{13} that are comparable to potential dosages of Ni\textsuperscript{2+} from i.v. solutions. For example, in a prosthesis with a surface area of 100 cm\textsuperscript{2}, the rate of parenteral release of nickel might be approximately 30 µg per day.\textsuperscript{13} To date, there have been nine reported cases of nickel dermatitis following i.v. infusions, including one patient with an anaphylactoid reaction.\textsuperscript{27,28} These allergic reactions were attributed to contact with nickel in the indwelling i.v. needles; it is possible that Ni\textsuperscript{2+} in the i.v. fluids may have contributed to the allergic responses. When Smeenk and Teunissen\textsuperscript{27} circulated 0.5 L of physiological saline solution through a stainless steel needle four times in 24 hours, they found a nickel concentration of 7 µg per L. The potential for exacerbating nickel allergy exists in a significant proportion of hospitalized patients, since nickel sensitization is surprisingly common. For example, positive patch-test reactions for nickel were observed in 5 percent (10 per 212) of patients who were tested prior to hip replacement.\textsuperscript{5}

Webster et al\textsuperscript{30} reported nickel intoxication in a group of 23 dialyzed patients, when leaching of nickel from nickel-plated stainless steel in a water heater tank contaminated the dialysate (Nickel concentration = approximately 250 µg per L). The patients' symptoms included nausea, weakness, vomiting, headache, and palpitations; remission of symptoms occurred spontaneously, generally three to 13 hours after cessation of dialysis. The study by Webster et al\textsuperscript{30} provides valuable information concerning the nonspecific symptoms that can occur in humans after inadvertent i.v. administration of Ni\textsuperscript{2+}.

Salvadeo et al\textsuperscript{24} reported that nickel concentrations in extracorporeal hemodialysis concentrate mixtures from five different manufacturers averaged 3.6 µg per L (range: 2.5 to 4.5 µg per L). Nickel concentrations in dialysis fluid samples taken from the inlet and outlet of the hemodialysis apparatus in 12 patients at two hours after the beginning of dialysis averaged 2.8 ± 0.5 µg per L (inlet) and 2.1 ± 0.2 µg per L (outlet). The reduction of nickel concentrations (inlet minus outlet) was statistically significant. No change of plasma nickel concentrations was observed (2.8 ± 0.5 µg per L, predialysis; 2.8 ± 0.5 µg per L, postdialysis).\textsuperscript{24} Based upon the following assumptions: (a) dialysis fluid flow = 0.5 L per min; (b) Ni\textsuperscript{2+} extraction = 0.7 µg per L of dialysate, and (c) dialysis treatment period = 300 min, the patients' i.v. uptake of Ni\textsuperscript{2+} averaged 105 µg per dialysis. If the patients received dialysis treatments 10 times per month, the average i.v. uptake of nickel would be approximately 1 mg per month.

The following nickel analyses were performed in the author's laboratory during care of a woman who was hospitalized owing to multiple injuries from an automobile accident. During the six weeks between admission and death from adult respiratory distress syndrome ("shock lung"), the patient received a total of 127 i.v. doses of human serum albumin (100 ml per dose). The serum nickel concentration on the day before death was 14.1 µg per L (normal range: 0.8 to 4.2 µg per L). To ascertain the source of the patient's hypernickelemia, nickel concentrations were analyzed in i.v. al-
bumin solutions from three manufacturers; the following results were obtained: Vendor A: 207 μg per L; Vendor B: 234 μg per L; and Vendor C: 204 μg per L. Assuming that the nickel concentration in the albumin solutions averaged 0.2 mg per L and that 12.7 L of albumin solution was administered, the author estimates that this patient received an aggregate i.v. dose of 2.5 mg of nickel.

A recent assessment of nickel metabolism in humans indicates that the body burden of nickel in normal adults averages 0.5 mg (7 μg per kg for a 70 kg adult person). Oral intake of nickel averages 170 μg per day, of which approximately 5 percent is absorbed (8.5 μg per day). Inhalation of nickel averages 0.4 μg per day for urban dwellers and 0.2 μg per day for rural dwellers, of which 35 percent is retained (0.07 to 0.14 μg per day). This assessment involves the assumptions that 70 percent of the nickel absorbed into the blood is promptly excreted by the kidneys and that the remaining 30 percent is deposited in the tissues with a mean retention time of 200 days. Such assumptions are in general agreement with results of toxicokinetic analyses of 63Ni2+ metabolism following parenteral administration of 63NiCl2 to rats and rabbits, based upon a three-compartment model, and following intratracheal administration of 63NiCl2 to rats, based upon a three-compartment model. Hogetveit et al suggested that 10 μg per L be set as the critical point, or cut-off value, for plasma nickel concentrations in nickel refinery workers; they recommended that workers with plasma nickel concentrations greater than 10 μg per L be closely supervised, required to wear masks, or furloughed until the plasma nickel concentrations had dropped: In a subsequent paper, Barton and Hogetveit established a new plasma nickel limit of 7.5 μg per L, and they proposed an ultimate goal of 5 μg per L. These values for plasma nickel concentrations were proposed for healthy industrial workers and may not be applicable to hospitalized patients who receive intravenous fluids.

Based upon all of these considerations, the present author recommends that the maximum permissible level of nickel be set at 5 μg per L for common i.v. solutions, and 10 μg per L for solutions that contain albumin or amino acids (e.g., histidine) which avidly bind Ni2+. These nickel concentrations are proposed for the diluted solutions that are normally infused in one-litre bottles. The permissible concentration of nickel in trace element concentrates that are put up in 10 ml vials would depend upon the nickel concentration in the diluent. Analyses of nickel concentrations in the i.v. fluids should be performed by a sensitive and reliable method, such as the IUPAC Reference Method, which employs electrothermal atomic absorption spectrometry. Furthermore, the present author recommends that the maximum permissible amount of nickel administered to infants, growing children, and adults as a contaminant in i.v. fluids should not exceed 0.5 μg per kg per day (35 μg per day for a 70 kg adult). This daily dosage is equal to 10.6 percent of the single i.v. dose that was reported by Rubanyi et al to cause increased coronary artery resistance in anesthetized dogs and is equal to 7 percent of the estimated body burden of nickel.

References

4. Bennett, B. G.: Summary exposure assessment


