RAISED SERUM NICKEL CONCENTRATIONS IN CHRONIC RENAL FAILURE

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Summary

We have measured serum nickel concentrations using flameless atomic absorption spectrophotometry. In 71 normals the median concentration was 1.0 μg/L, range <0.6–3.0 μg/L. Increased concentrations (p<0.05) were found in patients with chronic renal failure (CRF) treated conservatively (median 1.6 μg/L, range <0.6–3.6 μg/L).

Significantly increased concentrations (p<0.001) were found in patients treated by continuous ambulatory peritoneal dialysis (CAPD) (median 8.6 μg/L, range 5.4–11.4 μg/L) and haemodialysis. In patients on haemodialysis, post-dialysis concentrations (median 8.8 μg/L, range 3.0–21.4 μg/L) were significantly higher (p<0.001) than pre-dialysis values (median 8.6 μg/L, range 0.6–16.6 μg/L).

Introduction

In 1971 McNeely et al [1] reported diminished concentrations of nickel in patients with chronic renal failure (CRF) compared with healthy adults and they speculated that this was associated with reduced concentrations of serum proteins. Indeed, they found a positive correlation between the serum concentrations of nickel and albumin. Nickel was one of seven trace metals which Salvadeo et al [2] found to be reduced in dialysis fluid leaving the dialyser, suggesting transfer of nickel from dialysis fluid to blood. However, they were unable to demonstrate raised post-dialysis blood nickel concentrations, probably because of the low sensitivity of the analytical methods employed.

Interest in nickel as a cause of symptoms in renal failure was stimulated by Webster et al [3] who reported that symptoms of nausea, vomiting, weakness, headache and palpitations during haemodialysis were associated with nickel intoxication. This was attributed to the elution of nickel from a nickel-plated stainless steel heater in the water supply used to prepare dialysis fluid.

This study of serum nickel in patients with CRF, particularly those treated
by CAPD or regular haemodialysis, was undertaken to determine if long-term perturbation of serum nickel concentration is of clinical significance in renal failure.

**Materials and methods**

Nickel concentrations in normal subjects and patients with CRF were determined on a Perkin-Elmer 603 atomic absorption spectrophotometer fitted with an HGA-76B furnace and AS-1 autosampler. This was superseded by a Perkin-Elmer 3030 spectrophotometer fitted with an HGA-500 furnace and AS-40 autosampler for the determination of nickel concentrations in patients undergoing CAPD or haemodialysis.

Glass distilled water (nickel content <0.7μg/L) was used for washing and standard preparation. Aristar grade nitric acid was used to acid-leach containers. A dilute solution of Triton X-100 in distilled water (20ml/L) was used to prepare serum-based standards and to pre-treat serum samples. The diluted wetting agent was found to have a mean nickel content of 0.6μg/L.

Acid-leached 10ml polypropylene tubes for blood collection and storage, acid-leached 60ml polyethylene bottles for reagent storage, acid-leached volumetric flasks, syringes, venepuncture needles, autosampler cups and micropipette tips were all free of nickel contamination as judged by exposure to water, serum or whole blood for a time in excess of that expected in clinical or laboratory practice.

Samples of blood (5ml) from normal subjects, patients with CRF and patients on CAPD were obtained by venepuncture using stainless steel needles. Blood from haemodialysed patients was obtained from the arterial line before the patient was connected to the dialyser and at the end of dialysis. As a further precaution against contamination, 5 x 10ml aliquots of blood were withdrawn and reinjected through the line to flush the needle and syringe before blood collection.

The blood was allowed to clot in polypropylene tubes for 24 hours at room temperature. The tubes were centrifuged at 850g for 15 minutes, and serum decanted into polypropylene tubes and stored at −40°C. After vortex mixing for 30 seconds, 200μl aliquots of serum were mixed with an equal volume of Triton X-100 solution prior to analysis to prevent carbon accumulation in the furnace. Nickel concentrations were determined in triplicate by reference to a serum standard curve.

The instrumental conditions for the 603 spectrophotometer were as follows:

- Wavelength: 232.0nm
- Lamp current: 15mA
- Recorder: Integrate
- Background correction: Yes
- Slit: 0.2nm
- Mode: Peak Area
- Expansion: 0.4
- Sample volume: 50μl

The conditions for the 3030 spectrophotometer were similar except a lamp current of 25mA and an expansion of 2.5 were used.

The temperature programme used for the 603 spectrophotometer was as follows (3030 programme in parenthesis):
<table>
<thead>
<tr>
<th>Temperature °C</th>
<th>Hold time Sec</th>
<th>Ramp time Sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry</td>
<td>120 (90)</td>
<td>60</td>
</tr>
<tr>
<td>Char</td>
<td>700 (1300)</td>
<td>20</td>
</tr>
<tr>
<td>Atomise</td>
<td>2200</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Clean</td>
<td>2500</td>
<td>5</td>
</tr>
</tbody>
</table>

Pyrocoated graphite tubes were used with both instruments. During the atomisation stage 'maximum power' and 'gas stop' were used. The detection limit was 0.6µg/L.

There was no significant difference in the nickel concentrations in 31 samples determined on both the 603 and 3030 spectrophotometers (paired 't' test, p>0.05).

Results

The results are displayed in Figures 1 and 2. Statistical calculations were performed using the Mann-Whitney U test unless otherwise stated.

In 71 normal subjects (39 males, 32 females, age range 19–64 years) the median serum nickel concentration was 1.0µg/L, lower quartile 0.6µg/L, upper quartile 1.4µg/L, range <0.6–3.0µg/L. There was no significant difference (p>0.05) between the concentration of nickel in males (median 1.0µg/L) and females (median 1.1µg/L).

Increased concentrations (p<0.05) were found in 31 patients with CRF treated conservatively. The median value was 1.6µg/L, lower quartile 1.0µg/L, upper quartile 2.0µg/L, range <0.6–3.6µg/L. The serum creatinine range in these patients was 135–1116µmol/L.

No significant correlation was found between serum nickel and the extent of renal failure as assessed by serum creatinine concentrations (Spearman's rank correlation coefficient rs=0.10, p>0.05). There was no significant correlation between serum nickel and serum albumin concentrations (rs=0.01, p>0.05).

In 13 patients on CAPD the median serum nickel concentration was 8.6µg/L, lower quartile 7.5µg/L, upper quartile 9.7µg/L, range 5.4–11.4µg/L; a significant increase (p<0.001) over patients with CRF.

Increased concentrations (p<0.001) of serum nickel compared to patients with CRF were found in 25 haemodialysed patients. Post-dialysis serum nickel concentrations (median 8.8µg/L, lower quartile 7.3µg/L, upper quartile 13.8µg/L, range 3.0–21.4µg/L) were significantly higher (paired 't' test, p<0.001) than pre-dialysis values (median 8.6µg/L, lower quartile 5.9µg/L, upper quartile 12.1µg/L, range 0.6–16.6µg/L).

Initial analysis of nickel in tap water, water treated by deionisation and reverse osmosis and dialysis fluid indicated that the highest concentrations were present in the dialysis fluid (2–3µg/L).

Discussion

We conclude that serum nickel is elevated in patients with CRF, especially those treated by haemodialysis or CAPD. Preliminary observations suggest
Figure 1. Concentrations of nickel in normal subjects, patients with CRF, patients treated by CAPD and patients maintained on haemodialysis, before (Pre-HD) and after (Post-HD) one dialysis.
Figure 2. Correlation between serum nickel concentrations and plasma creatinine and serum albumin concentrations.
that dialysis fluid is the likely source of the rise in serum nickel that occurs across one dialysis and may be responsible for the permanent elevation of serum nickel in dialysed patients. We suspect that the source of nickel in dialysis fluid is the chemical concentrate.

The concentrations we have detected in haemodialysed patients are two orders of magnitude lower than those described by Webster et al in intoxicated patients (3000 μg/L) [3]. However, the symptoms described by Webster remain a problem of dialysis and warrant a further, wider study to see whether nickel intoxication is a commoner problem than the single report in the literature suggests. It is also possible that the eightfold increase in serum nickel, compared with normals, that we have detected in patients treated by haemodialysis or CAPD, is accompanied by as yet unrecognised symptoms of chronic intoxication. Further studies are in progress to test this hypothesis.

Acknowledgments

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References