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Elemental mercury exposure: peripheral neurotoxicity

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ABSTRACT Nerve conduction tests were performed on the right ulnar nerve of factory workers exposed to elemental mercury vapour. Time integrated urine mercury indices were used to measure the degree of exposure. Workers with prolonged distal latencies had significantly higher urine mercury concentrations when compared with those with normal latencies. Significant correlations between increasing urine mercury concentrations and prolonged motor and sensory distal latencies were established. Elemental mercury can affect both motor and sensory peripheral nerve conduction and the degree of involvement may be related to time-integrated urine mercury concentrations.

The neurological manifestations of inorganic mercury intoxication include symptoms (weakness, numbness, parasthaesia, muscle cramps) and signs (muscle atrophy, diminished muscle stretch reflexes, paresis, fasciculations, sensory loss) associated with peripheral nervous system dysfunction.[1-4] There is, however, limited information regarding the electrophysiological effects of elemental mercury on the human peripheral nervous system.

Barber[1] and Vroom and Greer[5] suggested that the clinical and electrodiagnostic abnormalities of inorganic mercury intoxication are best explained by anterior horn cell involvement with subsequent axonal degeneration. Both studies emphasised the similarity between inorganic and organic mercury intoxication; in the latter the existence of peripheral sensory nerve abnormality has been questioned.[6] Levine and Cavender (unpublished observations) found a significant correlation between prolonged motor distal latencies and urine mercury concentrations but did not perform sensory nerve conduction studies. Goldstein *et al*[3] indicated that mercurialism can be associated with a sensorimotor polyneuropathy and described a patient intoxicated by inorganic mercury in whom nerve conduction studies confirmed the clinical impression of sensory polyneuropathy. Similarly, Iyer *et al*[7] described a patient with a sensory polyneuropathy attributed to inorganic mercury intoxication.

We report here the results of an electrophysiological evaluation of the ulnar nerve in subjects exposed to elemental mercury vapour. Our goal was to ascertain whether the motor or sensory peripheral nerve, or both, were affected by exposure to mercury and, if so, whether the degree of abnormality could be related to the degree of exposure.

Methods

Eighteen male worker volunteers from a mercury cell chlorine plant were evaluated. The mean age was 31 (range 19-56). All subjects were asymptomatic, and results of routine physical examinations performed by the industrial physician at the time of testing were normal. The volunteers had no history of alcoholism, diabetes mellitis, or any known neurological abnormality.

Urine mercury concentrations were used to assess exposure.[8 9] Urinary mercury was determined once a month by cold, flameless atomic absorption.[10] Split samples were often used for intra-laboratory validation and the correlation was generally greater than $r = 0{\cdot}95$.[11] All subjects were included in a urinary mercury control programme at the plant whereby workers with spot sample urine mercury concentrations exceeding 0·50 mg/l were removed from exposure to mercury. Records of urine mercury concentrations were available for three years before

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evaluation or for the duration of employment if this was under three years.

The following time-integrated urine mercury indices were used as measures of body mercury concentrations and were designed additionally to detect any "threshold effect" that might exist:[10 12] spot sample urine mercury concentration (mg/l) at the time of testing; average urine mercury concentration during the previous three, six, 12, 24, and 36 months; and the number of months that urine mercury concentrations had exceeded 0·25 mg/l or 0·50 mg/l during the previous six, 12, 24, and 36 months.

The right ulnar nerve was studied in all subjects. Compound muscle action potential and sensory nerve action potential negative peak amplitude, motor and sensory distal latency, and maximum motor conduction velocity (max MCV) were measured by conventional techniques. Minimum motor nerve conduction velocity (min MCV) was measured by a collision technique.[13 14] The range of motor nerve conduction velocities (MCV range) was calculated as the difference between max and min MCV. A Teca TE-4 electromyograph was used in the testing. Evoked responses were recorded on the TE-4 fibreoptic recorder for subsequent analysis. Surface temperature was measured at the elbow and wrist (range 31-34°C).

Normal values had been obtained from individuals aged 21 to 50 who were in good health with no known neurological deficit by using techniques identical with those described in this study (J W Albers, W J Willems, unpublished observations). Ulnar motor nerve normal values were derived from 138 subjects and ulnar sensory nerve normal values from 82. No significant ($p < 0·05$) differences existed between men and women.

Urine mercury index values for subjects with abnormal nerve conduction studies (one or more abnormal values) were compared with those for the remaining subjects (*t*-test). Least square regression analysis was used to correlate urine mercury indices and nerve conduction test results.

Results

Average urine mercury concentrations ranged from 0·02 to 0·45 mg/l. The group mean for spot sample urine mercury concentration was 0·29 mg/l (range 0·02-0·70 mg/l). Five subjects had abnormal nerve conduction studies when compared with normal values; three had a prolonged sensory distal latency, one a prolonged motor distal latency, and one both prolonged motor and sensory distal latencies with a low-normal sensory nerve action potential amplitude. The mean compound muscle action potential amplitude was low (8·3 mv; $p < 0·005$) and motor distal latency long (3·0 ms; $p < 0·01$) when compared with normal values, although no individual amplitude was outside the normal range. No other mean measurements significantly differed from normal values.

Table 1 *Comparison of urine mercury indices for subjects with normal versus abnormal conduction studies*

Urinary mercury index	*Group mean*		*Significance level of difference*
	Normal	*Abnormal*	
Average urine Hg (mg/l) in previous:			
1 month (spot sample)	0·18	0·17	0·86
3 months	0·12	0·22	0·55
6 months	0·12	0·19	0·17
12 months	0·13	0·29	0·02
24 months	0·10	0·21	0·006
36 months	0·10	0·18	0·10
No of months > 0·25 mg/l in previous:			
6 months	0·8	2·0	0·05
12 months	1·9	6·0	0·009
24 months	3·2	8·2	0·02
36 months	4·9	10·4	0·14
No months > 0·50 mg/l in previous:			
6 months	0·2	0·6	0·06
12 months	0·7	2·6	0·03
24 months	0·8	3·2	0·002
36 months	1·1	3·8	0·003

Results of the comparison between urine mercury index values for "abnormal" and "normal" subjects are displayed in table 1. Over half of the urine mercury indices were significantly ($p < 0·05$) higher in the abnormal group. The most significant differences between groups occurred using the number of months urine mercury concentrations exceeded 0·50 mg/l in the previous 24 and 36 months ($p < 0·002$ and $p < 0·003$, respectively). The significance of differences between the two groups tended to increase with time up to 24 months with a decrease at 36 months.

Correlation coefficients between urine mercury index values and nerve conduction test results are presented in table 2 with levels of statistical significance. Sensory distal latency was significantly correlated ($p < 0·05$) with over half of the urine mercury indices used. Motor distal latency also showed a significant correlation with urine mercury indices. In both cases positive correlations indicate an increase in distal latency with increasing mercury indices. The highest correlation obtained was between sensory latency and the number of months urine mercury exceeded 0·50 mg/l in the previous 24 months ($r = 0·72$, $p < 0·002$). Distal latencies tended to correlate best with six, 12, and 24 month time indices. Max MCV and min MCV were significantly correlated with a few urine mercury indices but no consistent relationship was shown. Compound muscle action potential amplitude, sensory

Table 2 *Correlation coefficients between urine mercury indices and selected nerve conduction measures*

Urinary mercury index	*Sensory distal latency*	*Motor distal latency*	*Max MCV*	*Min MCV*
Average urine Hg in previous:				
month spot sample)	+0·07	+0·07	−0·47**	−0·44*
3 months	+0·28	+0·32	−0·51**	−0·64***
6 months	+0·49**	+0·51**	−0·37	−0·44*
12 months	+0·67***	+0·36	−0·13	+0·05
24 months	+0·52**	+0·60***	+0·10	+0·18
36 months	+0·28	+0·44*	+0·36	+0·36
No months > 0·25 mg/l in previous:				
6 months	+0·51**	+0·61***	−0·42*	−0·47**
12 months	+0·61***	+0·44*	−0·21	−0·09
24 months	+0·43*	+0·46*	+0·13	+0·22
36 months	+0·22	+0·33	+0·32	+0·46*
No months > 0·50 mg/l in previous:				
6 months	+0·41*	+0·48**	−0·27	−0·50**
12 months	+0·68***	+0·35	−0·16	+0·09
24 months	+0·72***	+0·41*	−0·03	+0·16
36 months	+0·60***	+0·35	+0·16	+0·30

*p < 0·1; **p < 0·05; ***p < 0·01.

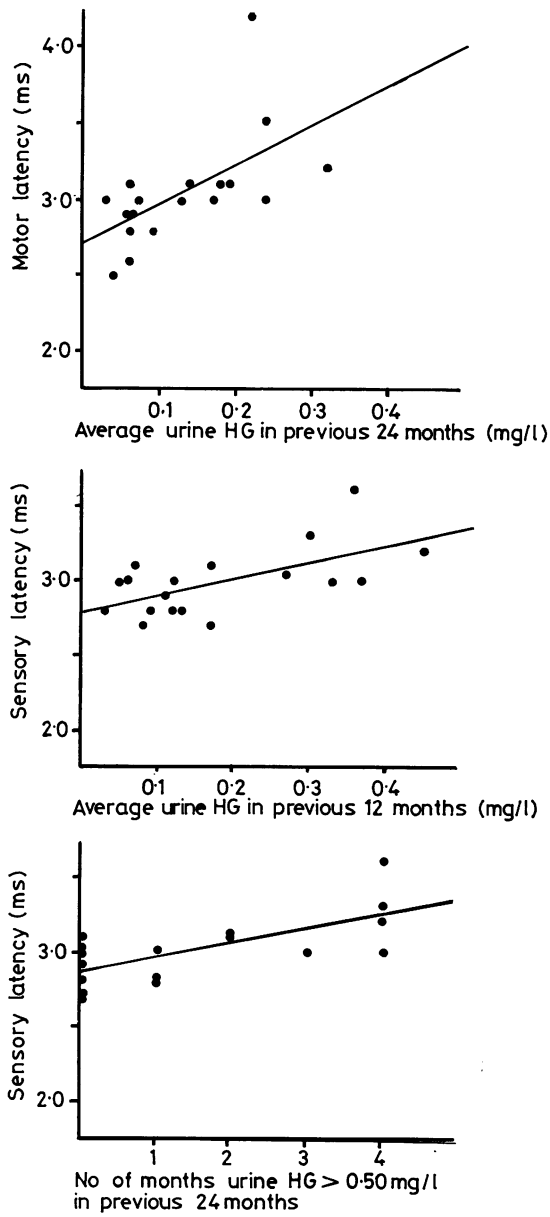
nerve action potential amplitude, and MCV range had no significant correlations with any urine mercury index. The figure shows three scatter plots illustrating the relationship between urine mercury indices and nerve conduction values.

Discussion

Significant differences in urine mercury indices among groups with prolonged versus normal distal latencies imply that peripheral nerve conduction can be affected by elemental mercury even when average urine concentrations do not exceed 0·50 mg/l. The number of significant correlations between both motor and sensory distal latencies and urine mercury indices (table 2) supports this concept.

Barber[1] reported considerably prolonged sensory distal latencies and decreased sensory conduction velocities in two patients who had been exposed to mercuric oxide. In these patients, motor conduction velocities were normal but needle electromyography showed frequent fasciculations. It was suggested that the clinical findings best resembled those found in organic mercury intoxication and amyotrophic lateral sclerosis.

Vroom and Greer[5] showed a mild slowing of motor and sensory conduction velocities, prolonged motor and sensory distal latencies, and a reduced compound muscle action potential in a group of nine patients with exposure to mercury vapour. Needle electromyography showed increased motor unit action potential amplitude, duration, and polyphasia. They attributed the reduced compound muscle action potential amplitude and prolonged sensory distal latencies to an inappropriately chosen



Selected scatter diagrams and regression lines for urine mercury indices versus ulnar motor and sensory latencies.

control group and concluded that inorganic mercury can cause abnormalities similar to organic mercury—namely, a disorder with both central and peripheral manifestations, the latter of which may mimic amyotrophic lateral sclerosis.

Similarly, we show a correlation between prolonged sensory and motor distal latencies and urine

mercury indices in the ulnar nerve of asymptomatic individuals. These findings are most consistent with a sensorimotor neuropathy and inconsistent with motorneurone disease alone. This would suggest that reported sensory symptoms of elemental mercury intoxication may be, at least in part, due to a peripheral abnormality.

Miglietta[15] reported a reduction of MCV range in amyotrophic lateral sclerosis without any change of max MCV. Seppalainen *et al*[16 17] found min MCV to be more sensitive than max MCV in detecting peripheral nerve dysfunction in individuals exposed to lead and carbon disulphide. We have reported a significant correlation between min MCV and urine mercury concentrations,[18] obtained by using multiple regression analysis techniques that included several seemingly independent variables. Further investigation has shown that these variables violate the independence assumption, thus invalidating this result. We were unable to show any consistent relationship between either min MCV or MCV range and urine mercury indices in the present study using simple regression analysis.

Urinary mercury determinations are commonly used to assess and control industrial elemental exposure to mercury. We have shown little correlation between spot sample urine mercury concentrations and electrophysiological data. This concurs with reports noting little correlation between spot sample urine mercury concentrations and neurological findings,[7 8] which may be due to the daily variation in urine mercury concentration.[19] We have attempted to overcome this problem by integrating urine mercury concentrations over time. The correlations shown in table 2 suggest that a dose-response relationship exists between the quantitative nerve conduction test results and time-integrated urine mercury indices. Reduction in the significance of results for 36-month compared with 24-month indices (tables 1 and 2) may be due to short-term effects or an artifact arising from the variability in the subjects' exposure over time, or both.

Urine mercury concentrations greater than 0·50 mg/l may be associated with increased central nervous system toxicity.[10 12] Results obtained in the present study, using the number of months that urine mercury concentration exceeded 0·50 mg/l as a measure of body mercury concentration, do not differ substantially from those obtained using concentrations exceeding 0·25 mg/l or average levels (tables 1 and 2) and offer no support for a threshold effect in the peripheral nervous system.

We conclude that exposure to inorganic mercury can affect both motor and sensory peripheral nerve conduction in a manner consistent with a mild sensorimotor neuropathy. The degree of involvement may be related to exposure to mercury as quantified by time-integrated urine mercury concentrations. Additional electrophysiological investigations, including needle electromyography, seem warranted on the basis of these results.

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