# ALUMINUM NEUROTOXICITY IN PRETERM INFANTS RECEIVING INTRAVENOUS-FEEDING SOLUTIONS

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## ABSTRACT

***Background*** Aluminum, a contaminant of commercial intravenous-feeding solutions, is potentially neurotoxic. We investigated the effect of perinatal exposure to intravenous aluminum on the neurologic development of infants born prematurely.

***Methods*** We randomly assigned 227 premature infants with gestational ages of less than 34 weeks and birth weights of less than 1850 g who required intravenous feeding before they could begin enteral feeding to receive either standard or specially constituted, aluminum-depleted intravenous-feeding solutions. The neurologic development of the 182 surviving infants who could be tested was assessed by using the Bayley Scales of Infant Development at 18 months of age.

***Results*** The 90 infants who received the standard feeding solutions had a mean (±SD) Bayley Mental Development Index of 95±22, as compared with 98±20 for the 92 infants who received the aluminum-depleted solutions (P=0.39). In a planned subgroup analysis of infants in whom the duration of intravenous feeding exceeded the median and who did not have neuromotor impairment, the mean values for the Bayley Mental Development Index for the 39 infants who received the standard solutions and the 41 infants who received the aluminum-depleted solutions were 92±20 and 102±17, respectively (P=0.02). The former were significantly more likely (39 percent, vs. 17 percent of the latter group; P=0.03) to have a Mental Development Index of less than 85, increasing their risk of subsequent educational problems. For all 157 infants without neuromotor impairment, increasing aluminum exposure was associated with a reduction in the Mental Development Index (P=0.03), with an adjusted loss of one point per day of intravenous feeding for infants receiving the standard solutions.

***Conclusions*** In preterm infants, prolonged intravenous feeding with solutions containing aluminum is associated with impaired neurologic development. (N Engl J Med 1997;336:1557-61.)

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ALUMINUM toxicity occurs in adults and children with renal insufficiency who are treated by dialysis with aluminum-contaminated solutions or oral phosphate-binding agents that contain aluminum.[1-7] The clinical manifestations of aluminum toxicity include hypochromic, microcytic anemia; bone disease[3,5,8-10]; and progressive dementia with increased concentrations of aluminum in the brain.[7,11,12]

Aluminum accumulates in the body when protective gastrointestinal mechanisms are bypassed, renal function is impaired, and exposure is high. These conditions are met in intravenously fed preterm infants, whose renal function is frequently compromised during their initial course; some have had high plasma aluminum concentrations.[13-17] We previously reported on a preterm infant who died unexpectedly and whose brain aluminum concentration was similar to that of adults who died with aluminum intoxication.[18]

We hypothesized that increased aluminum exposure in this vulnerable population would probably have detrimental effects on neurologic development in the long term. We undertook this prospective study in preterm infants to compare the effect on the infants' subsequent neurologic development of standard intravenous-feeding solutions, similar to those used in routine practice in the United States and Europe, and solutions whose aluminum content had been reduced.

## METHODS

### Subjects

We enrolled 227 infants from the neonatal intensive care unit of Rosie Maternity Hospital, in Cambridge, United Kingdom, from May 1988 to January 1991. The criteria for entry into the study were a clinical decision to initiate intravenous feeding, a birth weight of less than 1850 g, and a gestational age of less than 34 weeks. Infants whose mothers were not residents of the United Kingdom and infants with major congenital malformations were excluded from the study.

Each infant entering the study was randomly assigned by the pharmacy according to a multiple permuted-block method to receive either the standard or the aluminum-depleted intravenous solutions. Investigators and attending staff were unaware of the assignments, and no investigator served as an attending physician. The study was approved by the relevant ethics committees, and parental consent was obtained for each infant.

### Feeding Policy

Intravenous feeding was introduced (typically on postnatal day 2 or 3) and stopped at the discretion of members of the senior attending clinical staff. The proportion by volume of amino acid solution (Vamin Infant, Kabi Vitrum, now Pharmacia, Stockholm, Sweden) was increased at one- or two-day intervals from 15 percent to 30 percent in increments of 5 percent. Intravenous fat in-

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take (Intralipid 20 percent, Kabi Vitrum) was increased from 0.5 g per kilogram of body weight per day to 3 g per kilogram per day as the infant's clinical condition allowed. The volumes of calcium and phosphate solution administered depended on the amino acid concentration of the feeding solution. For solutions that contained 15 or 20 percent amino acids by volume, the calcium and phosphate contents were 36 and 18 mg per deciliter, respectively. For solutions that contained 25 or 30 percent amino acids by volume, the calcium and phosphate contents were 44 and 25 mg per deciliter, respectively.

In 19 infants, the decision to initiate intravenous feeding was reversed immediately after randomization on clinical grounds (typically, metabolic instability or improvement eliminating the need for parenteral feeding), and therefore none was given. These infants remained in the study and their results at the follow-up examination are included in the appropriate groups.

Enteral feeding was increased gradually to 180 ml per kilogram every 24 hours, according to tolerance. Mothers were encouraged to provide breast milk. If the mother provided no breast milk or an insufficient amount, a standard preterm formula was used (Farley's Health Products, Kendal, United Kingdom).

### Intravenous Solutions

The compositions of the two types of solution were identical except that the aluminum-depleted solutions contained less aluminum and more chloride, reflecting the use of calcium chloride instead of calcium gluconate (Table 1). The use of a mixed sodium–potassium phosphate solution in place of potassium acid phosphate minimized this increase in chloride.

### Data Collection

We collected data on the neonatal course of each infant, including data on intravenous fluid intake and the total volume and type of fluid given. Plasma concentrations of sodium, potassium, urea, creatinine, glucose, and calcium and acid–base status were measured daily, and plasma chloride weekly. Cranial ultrasonography was performed weekly. Extensive social, demographic, and obstetrical data were collected from the mothers by trained research nurses unaware of treatment-group assignments. Social class was coded according to the British Registrar General's Classification of Occupations, on the basis of the occupation of the income-providing parent or the father's occupation if both parents were earning. The mother's education was coded according to her formal educational attainment (1 for mothers with no certificates to 5 for those with a university degree or similar educational level).

**TABLE 1.** COMPOSITION AND ALUMINUM CONTENT OF THE STANDARD AND ALUMINUM-DEPLETED INTRAVENOUS FEEDING SOLUTIONS.

| SOLUTION* | STANDARD SOLUTIONS | | ALUMINUM-DEPLETED SOLUTIONS | |
|---|---|---|---|---|
| | VOLUME (ml) | ALUMINUM CONTENT ($\mu$g) | VOLUME (ml) | ALUMINUM CONTENT ($\mu$g) |
| Vamin Infant | 50 | 1.5 | 50 | 1.5 |
| Intralipid 20% | 15 | 0.1 | 15 | 0.1 |
| Vitlipid | 1 | 0.3 | 1 | 0.3 |
| Solivito | 1 | <0.1 | 1 | <0.1 |
| Neotrace | 1.6 | 1.2 | 1.6 | 1.2 |
| Potassium acid phosphate | 1.3 | 2.8 | — | — |
| Polyfusor phosphate | — | — | 14.4 | 0.3 |
| Calcium gluconate | 8.0 | 38.8 | — | — |
| Calcium chloride | — | — | 2.1 | 0.5 |
| Dextrose, sodium, potassium | 102 | <1.0 | 102 | <1.0 |
| Total aluminum intake at 180 ml/kg/day | 45 $\mu$g/kg/day | | 4.0–5.0 $\mu$g/kg/day | |

*Vamin Infant contained essential amino acids without added electrolytes. Intralipid 20% was a fat emulsion containing 20 g of fatty acids per deciliter. Vitlipid contained fat-soluble vitamins, and Solivito contained water-soluble vitamins. Neotrace was an in-house preparation containing copper and zinc only. Vamin Infant, Intralipid 20%, Vitlipid, and Solivito were manufactured by Kabi Vitrum.

### Neurodevelopmental Assessments

All the surviving children were invited to have a follow-up examination at the post-term age of 18 months. The examination consisted of a standard neurologic assessment[19] and an evaluation of development by a single experienced investigator unaware of the children's group assignments, using the Mental Scale of the Bayley Scales of Infant Development,[20] from which the Mental Development Index was derived (mean [±SD] for normal children, 100±16; possible range, 50 to 150).

A diagnosis of neuromotor impairment was made if the physical examination revealed abnormalities of tone or of the movement of limbs, trunk, head, or neck. The reference ranges used were from the schema of Amiel-Tison and Stewart.[19] Since any degree of impairment can influence the assessment of development with the Bayley Mental Scale (which depends heavily on age-appropriate fine-motor skills), the severity of the impairment was not taken into account in the analyses.

### Measurement of Aluminum

The aluminum content of the intravenous-feeding solutions was measured by graphite-furnace atomic-absorption spectrometry, with the use of Zeeman-effect background correction (model Z3030, Perkin Elmer, Beaconsfield, United Kingdom). Analyte materials were diluted appropriately (with a minimum of a fourfold dilution) with 0.1 percent Triton X-100 and 0.1 M nitric acid (BDH AnalaR and Aristar grade, respectively) and calibrated by using a standard solution of aluminum (1 mg per liter) in 0.1 M nitric acid (coefficient of variation, 6 to 8 percent). All measurements were performed in quadruplicate.[21] Multiple batches of calcium gluconate (from four manufacturers) and calcium chloride (two manufacturers) were analyzed; concentrations of aluminum were consistently high for gluconate (4810±440 $\mu$g per liter) and low for chloride (210±10 $\mu$g per liter). All other components were analyzed on multiple occasions; the values shown in Table 1 are the mean values. Aluminum intake (component volume times component aluminum concentration) was calculated daily for each infant.

### Statistical Analysis

Our primary hypothesis was that neurologic development would be better in infants receiving the aluminum-depleted solutions. However, two factors were likely to confound the analysis: the difficulty of accurately assessing mental development in children with neuromotor impairment and the variation in the duration of intravenous feeding and hence in aluminum intake.

The Bayley Mental Scale, like most tests of mental ability in young children, requires age-appropriate fine-motor skills; therefore, scores do not usually reflect the level of intellectual ability of children with neuromotor impairment. For this reason, the main analyses were performed as reported previously[22] and as planned here by using Student's t-test, excluding the 25 children with evidence of neuromotor impairment at the time of testing. However, data on these infants were included in a separate analysis, in which children with neuromotor impairment arbitrarily received a score of 50 points and the data were analyzed as randomized by the Mann–Whitney–Wilcoxon test. Two infants could not be tested, because one was blind and the other completely uncooperative.

We also planned stratified analyses to take into account the



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duration of aluminum exposure — since once randomized, some infants would receive little intravenous feeding — and to seek threshold effects. The simplest stratification envisaged was to subdivide each group into two according to the duration of parenteral feeding (longer or shorter than the overall median), necessarily decreasing group numbers but maintaining similar numbers in each group. The effect of other variables known to influence developmental outcome was evaluated by multiple regression analysis.

## RESULTS

The characteristics of the infants in each group are shown in Table 2; daily aluminum intake was substantially greater in the infants receiving the standard solutions than in those receiving the aluminum-depleted solutions (mean [±SD], 19±8 vs. 3±1 μg per kilogram per day; P<0.001). The numbers of deaths, handicapped survivors, and children lost to follow-up are shown in Table 3.

Among the infants with no neuromotor impairment, the mean (±SD) Mental Development Index values for the groups receiving the standard and aluminum-depleted solutions were 98±20 and 101±18, respectively (Table 4). The Mental Development Index values for all the groups of infants who received intravenous feeding for 10 days (median duration of exposure) or less were similar. However, for the group of infants receiving the standard solutions for more than 10 days, the Mental Development Index was 10 points less than for those receiving the aluminum-depleted solutions (P=0.02). This difference was reflected in the significantly greater proportion of infants who received the standard solutions for more than 10 days and whose Mental Development Index values were below 85 points — 15 of 39 (38 percent) as compared with 7 of 41 (17 percent, P=0.03).

The corresponding analyses, including the children with neuromotor impairment, are also shown in Table 4. The results are weakened by the difficulty of obtaining realistic measurements of mental development in children with neuromotor impairment. Such children were thus given nominal scores of 50 points. When the results for the infants receiving intravenous feeding for more than 10 days were then compared by a nonparametric Mann–Whitney–Wilcoxon test, the difference between the groups was statistically significant (P=0.04).

In a further, explanatory analysis to assess the independent contribution of aluminum intake to the developmental outcome, multiple regression analysis with the Bayley Mental Development Index as the

**TABLE 2.** DEMOGRAPHIC CHARACTERISTICS OF THE PRETERM INFANTS IN THE GROUPS RECEIVING STANDARD AND ALUMINUM-DEPLETED FEEDING SOLUTIONS.*

| CHARACTERISTIC | INFANTS RANDOMIZED | | INFANTS TESTED NEURODEVELOPMENTALLY | |
|---|---|---|---|---|
| | STANDARD SOLUTIONS | ALUMINUM-DEPLETED SOLUTIONS | STANDARD SOLUTIONS | ALUMINUM-DEPLETED SOLUTIONS |
| Total no. | 112 | 115 | 90 | 92 |
| Sex (M/F) | 55/57 | 63/52 | 42/48 | 50/42 |
| Birth weight (g) | 1227±299 | 1216±318 | 1260±294 | 1234±295 |
| Gestation (wk) | 29.1±2.3 | 28.9±2.3 | 29.1±2.2 | 29.1±2.0 |
| Mechanical ventilation (days) | | | | |
| Median | 4.5 | 5 | 4 | 5 |
| Interquartile range | 2–8 | 2–8 | 2–8 | 2–7.5 |
| Birth weight (no.) | | | | |
| Appropriate for gestation | 89 | 92 | 75 | 73 |
| Small for gestation | 23 | 23 | 15 | 19 |
| Intraventricular hemorrhage | | | | |
| Total | 28 | 32 | 18 | 21 |
| Parenchymal | 6 | 8 | 4 | 1 |
| Periventricular leukomalacia | 4 | 7 | 3 | 2 |
| Parenteral nutrition (days) | | | | |
| Median | 9 | 10 | 9.5 | 10 |
| Interquartile range | 5–15 | 6–16 | 5–15 | 6–16 |
| Aluminum intake (μg)† | | | | |
| Median | 187 | 28 | 194 | 32 |
| Interquartile range | 70–350 | 11–49 | 82–360 | 14–48 |
| Mother's expressed breast milk (% of enteral intake) | 31 | 32 | 31 | 32 |
| Preterm formula (% of enteral intake) | 45 | 45 | 44 | 45 |

*Plus–minus values are means ±SD.

†There was no statistically significant difference (P<0.05) among the groups except for the difference in aluminum intake (P<0.001).



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dependent variable was carried out for the group of 157 infants with no evidence of neuromotor impairment at 18 months of age. The independent variables entered were birth weight, gestational age, sex, maternal educational attainment, social class, duration of intravenous feeding (days), duration of ventilation (days), aluminum intake (micrograms per kilogram), and the presence or absence of intraventricular hemorrhage (and whether parenchymal or not). The variables not significantly associated with the Mental Development Index in the model were removed stepwise. The duration of intravenous feeding was entered into the final analysis so that aluminum exposure did not become a proxy for the duration or severity of illness. Maternal educational attainment ($P<0.001$), birth weight ($P=0.01$), aluminum exposure ($P=0.02$), and sex (advantage for female sex, $P=0.02$) were the factors that, in combination, most strongly predicted the Bayley Mental Development Index. There was no interaction between aluminum intake and the other factors. Thus, the apparent effect of aluminum was unrelated to birth weight or sex; that is, for a given level of intake, the effect on the Mental Development Index was the same in large and small infants. Gestational age, duration of ventilation, and the presence or absence of intraventricular hemorrhage were not significantly associated with the Mental Development Index.

We estimate that for infants receiving full intravenous feeding with a mean aluminum intake of 45 $\mu$g per kilogram per day, the expected reduction in the Bayley Mental Development Index would be, on average, one point per day of intravenous feeding.

There was no significant difference in clinical course or plasma biochemical results between the two groups. Despite the increased chloride load attendant on the use of the aluminum-depleted solutions, there were no episodes of hyperchloremia among infants receiving these solutions. There was no difference in the number of episodes of extravasation resulting in cutaneous damage between the two groups. No infant required flushing of, or surgery on, an extravasation site.

**TABLE 3.** NUMBERS OF INFANTS IN THE GROUPS RECEIVING THE STANDARD AND ALUMINUM-DEPLETED FEEDING SOLUTIONS AT STUDY ENTRY AND AT THE TIME OF TESTING FOR THE BAYLEY MENTAL DEVELOPMENT INDEX.

| INFANTS | SOLUTIONS | |
|---|---|---|
| | STANDARD | ALUMINUM-DEPLETED |
| Total | 112 | 115 |
| Died | 14 | 14 |
| Lost to follow-up | 8 | 7 |
| Untestable* | 0 | 2 |
| Neurologically impaired | 12 | 13 |
| Never received intravenous feeding† | 8 | 11 |
| With normal neuromotor function, tested for Bayley Mental Development Index | 78 | 79 |

*One child was blind, the other completely uncooperative.

†These infants entered the study but were found not to need intravenous feeding. They were tested developmentally.

## DISCUSSION

The results of this study suggest that aluminum intake in preterm infants is associated with reduced developmental attainment at the corrected postterm age of 18 months. The infants who received the standard intravenous feeding solutions (providing 25 $\mu$g of aluminum per deciliter) had a lower mean Bayley Mental Development Index than those who received aluminum-depleted solutions (providing 2.2 $\mu$g of aluminum per deciliter), although this difference did not reach statistical significance. How-

**TABLE 4.** VALUES ON THE BAYLEY MENTAL DEVELOPMENT INDEX FOR INFANTS WITHOUT NEUROMOTOR IMPAIRMENT AND FOR ALL INFANTS ACCORDING TO THE DURATION OF INTRAVENOUS FEEDING.*

| GROUP | VALUES FOR INFANTS WITHOUT NEUROMOTOR IMPAIRMENT | | | | VALUES FOR ALL INFANTS | | | |
|---|---|---|---|---|---|---|---|---|
| | STANDARD SOLUTIONS | ALUMINUM-DEPLETED SOLUTIONS | DIFFERENCE | P VALUE | STANDARD SOLUTIONS | ALUMINUM-DEPLETED SOLUTIONS | DIFFERENCE | P VALUE |
| As randomized | 98±20 (n=78) | 101±18 (n=79) | 2.9 | 0.34 | 95±22 (n=90) | 98±20 (n=92) | 2.7 | 0.39 |
| ≤10 days TPN | 105±19 (n=39) | 101±20 (n=38) | −3.9 | 0.36 | 99±23 (n=50) | 100±20 (n=47) | 1.0 | 0.83 |
| >10 days TPN | 92±20 (n=39) | 102±17 (n=41) | 9.9 | 0.02 | 90±21 (n=40) | 96±21 (n=45) | 5.4 | 0.24 |

*Values are given as means ±SD. TPN denotes total parenteral nutrition. Ten days was the median duration of total parenteral nutrition for the whole population as randomized (see Table 2).



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ever, a substantial number of infants received little or no intravenous feeding after randomization, and explanatory analysis showed that the effect of aluminum exposure was dose-related. Aluminum exposure from the standard intravenous solutions was calculated to be associated with a mean loss of one point on the Bayley Mental Development Index per day of full intravenous feeding, after adjustment for potentially confounding factors. In infants fed intravenously for 10 or more days, those receiving the standard solutions had a major (10 point) deficit in their Mental Development Index and were twice as likely to have a Mental Development Index below 85. These results provide support for our hypothesis that intravenous aluminum may have neurotoxic effects, with longer-term consequences for neurologic development.

Aluminum is the most common metallic element in the earth's crust[23] but has no clear biologic role. When intake is not controlled, aluminum causes severe neurotoxic effects in adults and children with renal failure.[6,7,11,12] Previous studies of aluminum exposure in preterm infants revealed increased plasma concentrations or urinary excretion of aluminum, and those who died had high tissue aluminum concentrations.[13-18,24-26] Our findings are therefore plausible in the light of the previous work on aluminum neurotoxicity and on the deposition of aluminum in tissues, including the brain, of preterm infants.

We chose to carry out a randomized study because in a nonrandomized study it would have been difficult to identify any effects of aluminum among the many other factors that could influence neurologic development in preterm infants. Indeed, manifestations of aluminum toxicity — anemia and bone disease — arise frequently in premature infants for reasons other than aluminum exposure. In our previous studies of preterm infants we found that by 18 months of age, cognitive performance on the Bayley Mental Development Index has some value in predicting the later intelligence quotient. However, the correlation is considerably greater for group mean scores than for individual infants (>0.9 rather than >0.5, unpublished data). Whether exposure to aluminum affects intelligence later in life is unknown.

In conclusion, aluminum has no known biologic role and is potentially neurotoxic. Some degree of aluminum exposure in preterm infants fed intravenously seems unavoidable; the duration of such exposure is necessarily uncertain. Our findings suggest that the use of aluminum-depleted solutions for intravenous feeding in these infants may result in improved neurologic development.

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