Updated aluminum pharmacokinetics following infant exposures through diet and vaccination

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A B S T R A C T
Aluminum is a ubiquitous element that is released naturally into the environment via volcanic activity and the breakdown of rocks on the earth’s surface. Exposure of the general population to aluminum occurs primarily through the consumption of food, antacids, and buffered analgesics. Exposure to aluminum in the general population can also occur through vaccination, since vaccines often contain aluminum salts (frequently aluminum hydroxide or aluminum phosphate) as adjuvants. Because concerns have been expressed by the public that aluminum in vaccines may pose a risk to infants, we developed an up-to-date analysis of the safety of aluminum adjuvants. Keith et al. [1] previously analyzed the pharmacokinetics of aluminum for infant dietary and vaccine exposures and compared the resulting body burdens to those based on the minimal risk levels (MRLs) established by the Agency for Toxic Substances and Disease Registry. We updated the analysis of Keith et al. [1] with a current pediatric vaccination schedule [2]; baseline aluminum levels at birth; an aluminum retention function that reflects changing glomerular filtration rates in infants; an adjustment for the kinetics of aluminum efflux at the site of injection; contemporaneous MRLs; and the most recent infant body weight data for children 0–60 months of age [3]. Using these updated parameters we found that the body burden of aluminum from vaccines and diet throughout an infant’s first year of life is significantly less than the corresponding safe body burden of aluminum modeled using the regulatory MRL. We conclude that episodic exposures to vaccines that contain aluminum adjuvant continue to be extremely low risk to infants and that the benefits of using vaccines containing aluminum adjuvant outweigh any theoretical concerns.

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1. Introduction

In the first year of life, infants receive vaccinations according to a schedule recommended by the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention [2]. Some of these vaccines utilize aluminum salts as adjuvants (for example, aluminum hydroxide, Al(OH)3, or aluminum phosphate, AlPO4). The particular vaccines (and therefore aluminum exposures) that an infant may receive at any point in the immunization schedule may vary depending on the vaccine chosen by the health care provider, parents, and caregivers from the available FDA-licensed vaccines. Potential aluminum exposures associated with vaccine administration, however, are different from dietary exposures to aluminum, since aluminum in vaccines does not have to pass through the walls of the gastrointestinal tract, which is a significant barrier to systemic aluminum absorption. Rather, it is expected that the whole amount of aluminum in the adjuvant will be absorbed from muscle into the blood following vaccination, albeit at some rate over time.

In an effort to evaluate the relative contribution to aluminum levels in infants from vaccines and from diet, Keith et al. [1] analyzed the pharmacokinetics of aluminum for infant dietary and vaccine exposures and compared these exposures to the level set by the Agency for Toxic Substances and Disease Registry, which is called the minimal risk level or MRL (ATSDR [29]). Exposures below this level are considered to be safe, but levels of exposure at or slightly above the MRL may also be safe due to safety factors that are built into the process of calculating the MRL. Keith et al. [1] concluded that the calculated body burden from aluminum exposures in infants from vaccines is below the MRL equivalent curve for all but a few brief periods during the first year of life. We updated the analysis of Keith et al. [1] with a current vaccination schedule, a more recent aluminum retention function from human volunteers, incorporation of infant glomerular filtration rates, an adjustment for the kinetics of aluminum efflux from the site of injection, contemporaneous MRLs, and the most recent infant body weight data for children 0–60 months of age [3].
1.1. Exposure to aluminum

Aluminum is a ubiquitous environmental metal with no known nutritional role in humans. Because of aluminum's abundance in the environment, it is frequently consumed as an incidental component of water or food, including infant formula [4]. Aluminum is also intentionally added to food as a caking or emulsifying agent. As a result, bread made with aluminum-based baking powder can contain up to 15 mg aluminum per slice, and processed American cheese can contain as much as 50 mg aluminum per slice [5]. Another potential means of exposure to aluminum in humans can occur through vaccination. Certain vaccines may contain specific aluminum salts (primarily aluminum hydroxide and aluminum phosphate) as an adjuvant. Aluminum adjuvants are important components of vaccines, since they stimulate the immune system to respond more effectively to protein or polysaccharide antigens that have been adsorbed to the surface of insoluble aluminum particles. Specifically, these coated particles are phagocytized by cells of the innate immune system (e.g., macrophages) and activate intracytoplasmic sensors of pathogen-associated molecular patterns located within the cells, such as the nucleotide-binding domain leucine-rich repeat-containing family of sensors [16].

1.2. Aluminum disposition and toxicity

Dietary exposure to aluminum (usually as the citrate) results in small amounts of aluminum being absorbed from the gut (<1%) and reaching the bloodstream [4]. Following enteral absorption, aluminum is transported mainly in the plasma in association with the iron-binding protein transferrin [8]. Aluminum is distributed well throughout the body with the skeleton and lungs (due to inhalation exposures) containing the highest mass of aluminum (approximately 50% and 25% of the body burden, respectively). As for many divalent and polyvalent metals, the skeleton can be a long-term storage depot for aluminum, with the half-life of aluminum in bone being on the order of years [5]. It is anticipated that bone will serve as a stable depot for aluminum in infants, as well as adults, due to the increase in bone mass and volume that takes place during an infant's rapid growth and development. With regard to the non-skeletal compartment, the half-life of aluminum in soft tissues such as the liver is short (<2 days), which indicates very little accumulation in these organs. The majority of bioavailable aluminum is excreted shortly after exposure, primarily in the urine [5], and there appears to be little difference in the renal clearance of aluminum in infants and adults at low exposures [9]. Although aluminum accumulates in the brain as well as bone over time, the concentration of aluminum in brain is lower than that in many other tissues of the body (e.g., liver, spleen), and only 1% of whole-body aluminum is present in the brain or central nervous system at any given time [8,5].

The toxicity of aluminum depends largely on the route and length of exposure. Following single injections, occasional irritation (dermal) at the site of injection is the only adverse effect that has been reported in the published literature. Neurotoxicity in rats has been demonstrated following long-term injections of aluminum leading to aluminum overload or aluminum toxicosis [10,11]. However, the doses tested in these studies were much higher than the maximal exposures that infants might be exposed to from vaccines, and the dosing schedules, the species of aluminum (soluble), and the routes of exposure (intraperitoneal) tested were not relevant to how infants might be exposed to aluminum through vaccination. There is no evidence for neurotoxic effects in humans who may be exposed to aluminum following single, episodic injections [12]. In addition, while aluminum hydroxide has been detected in biopsy samples of muscle obtained from some children with macrophagic myofasciitis (MMF), a rare inflammatory myopathy characterized by clinical symptoms of myalgia or arthralgia and an inflammatory infiltrate at muscle biopsy, this condition has not been shown to be caused by aluminum in vaccines [13]. The clinical symptoms that have been observed in the limited number of patients that have been diagnosed with this rare condition are considered to be due to separate, coincidental immune or neurological disorders that are unrelated to the presence of aluminum in vaccines [14,15].

2. Materials and methods

2.1. Baseline aluminum levels at birth

Rather than starting from a zero amount of aluminum in the body, we assumed a baseline level of aluminum in an infant at birth. Although whole-body aluminum levels have not been measured in human fetuses, they were measured in only one published animal study, i.e. Cranmer et al. [16], who measured “total” aluminum in fetal mice following maternal exposure to aluminum chloride or saline (control). In this study, saline-treated fetuses contained approximately 592 ppb aluminum. However, since the aluminum content of the saline was unreported and since we consider results in humans to be more relevant to human exposures, we estimated aluminum levels in newborns using the results of Moreno et al. [17], who measured background levels of aluminum in the serum of children at birth to be 0.16 ± 0.05 μmol/l, which is equivalent to a mean value of 4.32 ppb (MW, Al = 27 g). Next, we estimated levels of aluminum in whole blood to be 0.18 μmol/l (4.8 ppb), by taking into consideration published results indicating that approximately 90% of aluminum in blood resides in serum or plasma, with 10% of blood Al located in erythrocytes [5]. This value is in excellent agreement with a background blood concentration in newborns of 0.5 ± 0.11 μmol/l reported earlier by Sedman et al. [9]. Since aluminum in blood accounts for approximately 4% of total aluminum in the body at any given time [5] based on [18], a blood concentration of 4.8 ppb yields a total background concentration of aluminum in newborns of 120 ppb. Because a newborn infant weighs approximately 3.2 kg (50th percentile for girls; [19]), this concentration corresponds to an estimated body burden of 384 μg, or about 0.4 mg Al, at birth. This natal body burden of aluminum is considered to be low due to the fact that the placenta partially protects the developing fetus from exposures from the mother during pregnancy [20,16,28].

2.2. Schedule of vaccination

Using the most recent recommended immunization schedule for persons aged 0–6 years [2], potential combinations of FDA-licensed routine childhood vaccines were compiled and analyzed to determine the maximum doses (d) of aluminum that a child might receive over the course of a year. This information was derived from FDA-approved vaccine prescribing information, and the sequence of maximum exposures was determined to be as follows: 0.25 mg at birth, 0 mg at 30 days, 1.2 mg at 60 days, 1.2 mg at 120 days, 0.975 mg at 180 days, and 0.6 mg at 365 days of age. These amounts are summarized by vaccine in Table 1. By way of comparison, Keith et al. [1] calculated aluminum exposures as 0.25 mg at birth, 1.1 mg at 60 days, 0.85 mg at 120 days, 1.1 mg at 180 days, and 0.85 at 365.
days of age using an immunization schedule which is no longer current.

2.3. Aluminum retention in children

Aluminum retention in humans has been measured in adult volunteer studies using radioacive aluminum tracers following intravenous administration [21]. Priest [5] re-analyzed the retention of aluminum in the body using longer timecourse data and reported a retention function for adults that is a three-component exponential function of time:

\[ R = 29.3 \times e^{-0.595\times t} + 11 \times e^{-0.172\times t} + 6.5 \times e^{-0.000401\times t} \] (1)

where \( R \) refers to the percentage of administered aluminum in the body at time, \( t \), beginning approximately one day after injection. This retention function reflects three whole-body half-lives for aluminum of 1.4, 40, and 1727 days, respectively, which mirrors aluminum residence in three compartments in the body, with long-term storage in bone most likely responsible for the longest half-life [5]. The relevant adult rate constants in this 3-compartment model were determined from Eq. (1) using the method of Gibaldi and Perrier [22] and are presented in Fig. 1.

Because glomerular filtration, the primary pathway of excretion of aluminum from the body as well as the main process of renal elimination for xenobiotics in newborns, is not fully developed at birth [23,24], it is expected that aluminum is not cleared from the blood of infants as quickly as that of adults. As a result, the elimination rate constant, \( k_{10} \) (Fig. 1), would be expected to be lower in children than adults, but would also increase over time as renal function developed throughout childhood. We therefore modeled glomerular filtration in childhood based on aggregate mean creatinine clearance rates (\( C_{e} \)) measured in 122 children over the first thirteen years of life [25]. Since the data for \( C_{e} \) seemed to start out small and rise quickly and asymptotically approach a maximum between ages 5 and 13, we utilized a Michaelis–Menten function to describe the rapid increase in renal function. The functional form for \( C_{e} \) was estimated as follows:

\[ C_{e}(t) = \frac{a + b}{t + c} \] (2)

Since the horizontal asymptote of the creatinine clearance represents the adult rate of clearance, the function:

\[ f(t) = \frac{a + b}{a + b + \left( \frac{t}{t + c} \right)} = 0.361 + 0.639 \left( \frac{t}{t + 231.46^2} \right) \] (3)

which has a horizontal asymptote of unity, should roughly represent the filtration efficiency of the renal system relative to the adult efficiency. Since the primary means of aluminum removal is through the kidney, it follows that the rate of aluminum removal in children should be:

\[ k_{10}(t) = \hat{k}_{10} \times f(t) = 0.41095 \left( 0.361 + 0.639 \left( \frac{t}{t + 231.46^2} \right) \right) \] (4)

where \( \hat{k}_{10} \) is the estimated elimination rate constant in adults based upon the equation from Priest [5] and \( f(t) \) represents the fraction of adult aluminum removal for children at age \( t \). Upon substitution of the function from Eq. (4) into the ordinary differential equations that describe the 3-compartment model for aluminum it follows that:

\[ \frac{dx_1}{dt} = -k_{10}(t)x_1 + k_{21}x_2 + k_{31}x_3 - k_{12}x_1 - k_{13}x_1 \] (5)

\[ \frac{dx_2}{dt} = k_{12}x_1 - k_{21}x_2 \] (6)

\[ \frac{dx_3}{dt} = k_{13}x_1 - k_{31}x_3 \] (7)

Because this set of differential equations includes a non-constant coefficient, \( k_{10}(t) \), the exact solution is non-tractable. Therefore, we utilized numeric Runge–Kutta type methods to solve the set of differential equations numerically using the statistical program R (R Foundation for Statistical Computing [31]).

2.4. Infant body weight

Because the safe, oral daily dose of aluminum (i.e., MRL = 1 mg/kg bw/day) is expressed by ATSDR [4] as normalized to body weight, it was necessary to multiply this MRL value by infant body weight to obtain safe doses (\( d \)) of aluminum over the first year of life. Because infant body weight is not constant and increases rapidly after birth, it was necessary to determine the relevant mathematical functions that describe infant body weight during this time. We, therefore, modeled the most recent infant body weight data for US children 0–60 months of age [3]. We estimated the 5th and 50th percentiles of infant body weight (kg) for age (months) for males and females combined using quantile regression. The model describing the relationship between weight and age was estimated using the best-fitting polynomial functions of age, since the data indicate that this relationship is non-linear. The degree of the polynomial was determined by minimizing a cross-validation criterion, and the following functions were calculated from the NHANES [3] data:

\[ BW_{5th} = 2.65899 - \frac{1.86774}{(1 + age)^{0.5}} + 1.59926(1 + age)^{0.5} \] (8)

\[ BW_{50th} = 3.35319 + (1.74026(1 + age)^{0.5}) + 0.618471(0.1 + 0.1 age) \] (9)

2.5. Calculations of aluminum body burdens

The ATSDR MRL of 1 mg/kg bw/day was multiplied by the relevant functions for infant body weight [Eqs. (8) and (9)] and corrected for the low absorption of aluminum from the gastrointestinal tract (0.78%; [26]), to estimate correspondingly safe oral doses (\( d \)) of
aluminum. The following dietary exposures of infants to aluminum, published previously by Keith et al. [1] and adjusted for 0.78% oral absorption, were utilized in our model: (1) age 0–6 months: 0.03 mg (breast milk) and 0.15 mg (formula); (2) age >6 months: 0.7 mg (breast milk or formula). Retention of aluminum following infant dietary exposures, exposures from vaccines according to the 2011 ACIP schedule, and safe doses of aluminum were then estimated over the first 400 days of life using Eqs. (1)–(7). Retention curves were generated using the publicly available statistical modeling software, R (R Foundation for Statistical Computing [31]).

3. Results and discussion

Fig. 2 shows the amount of aluminum that is retained by an infant following exposure from vaccines (assuming complete and instantaneous absorption) or the diet (formula or breast milk) throughout the first 400 days of life. The two upper curves show the amount of aluminum retained by infants of median or low birth weight, if the infant consumed the MRL of aluminum (1 mg/kg bw/day) every day over the first year of his/her life. The MRL is based on the infant’s weight, so the upper curve shows the body burden of aluminum associated with infants at the median or 50th percentile weight, and the lower curve shows the level associated with infants at the 5th percentile of weight. Both curves assume intestinal absorption of 0.78% [26] and retention according to Eq. (1) that was modified to reflect glomerular filtration rates in infants. Fig. 2, as well as the equivalent curve published previously by Keith et al. [1], demonstrate that there are brief “excursions” of bodily aluminum levels above the MRL following vaccination, when complete and instantaneous absorption of aluminum from the site of injection is assumed; however, due to the rapid elimination of aluminum, the levels quickly fall back below the MRL. The curves for aluminum retention associated with formula and breastmilk show a slight change at six months that is due to the assumption that infants switch from breastmilk or formula to solid food on this date and therefore begin to receive a higher aluminum dose from baby food.

The determinations of the kinetics of aluminum retention by Priest [21] were based on experiments where human volunteers were given an intravenous injection of aluminum citrate. For vaccines, the injection is intramuscular, the aluminum is in an insoluble form (e.g., as the phosphate or hydroxide of aluminum), and muscle at the site of injection is considered to be a storage depot for aluminum. Over time the insoluble aluminum hydroxide or aluminum phosphate particles are solubilized by citrate ions in the interstitial fluids of muscle. After solubilization, the uptake and distribution kinetics of aluminum will likely be similar to the kinetics determined by the human volunteer studies. However, it is unlikely that the process of absorption from the site of intramuscular injection into the blood is instantaneous, as is assumed for intravenous exposures and as presumed by the retention functions used to generate Fig. 2 and by Keith et al. [1].

Flarend et al. [27] investigated the absorption into the blood of aluminum hydroxide and aluminum phosphate following intramuscular injection into New Zealand White rabbits. Two important observations were made in their experiments: (1) only a fraction of the injected aluminum was taken up from the site of injection into blood over the 28-day experimental period, and (2) absorption of neither adjuvant was instantaneous. Specifically, blood concentrations of aluminum hydroxide decreased to a minimum by the end of the experiment (reached a terminal phase), where as aluminum phosphate blood concentrations were relatively constant over the 28-day period and did not reach a terminal phase. These results likely reflected differences in the rate of absorption of each adjuvant from the site of injection and not differences in excretion, since all other experimental conditions were equivalent in each group. By comparing with the area under the curve of the blood concentration-time curve for an intravenous administration of 0.85 mg aluminum citrate, the authors determined that only 17% and 51% of injected aluminum hydroxide and aluminum phosphate, respectively, was absorbed into the blood over 28 days. If the results of the rabbit studies by Flarend et al. [27] are reflected in similar kinetics in humans, then the dose of aluminum that enters into the bloodstream after intramuscular injection of vaccines in infants is at best only one half of what has been modeled in Fig. 2.

Therefore, based on the results of [27], we assumed: (1) that only 51% (for aluminum phosphate, AP) or 17% (for aluminum hydroxide, AH) of injected aluminum would be absorbed into the blood following a single intramuscular vaccine injection over the first 28 days after exposure, and (2) that absorption of the remaining adjuvant at the site of injection would take place at a constant rate over the next 28 days for AP and 137 days for AH, rather than instantaneously, as modeled in Fig. 2. In order to make this calculation, we assumed that the rate of absorption after 28 days was the same as that during the 28-day experimental period in [27], i.e., 0.51/28 day⁻¹ for AP and 0.17/28 day⁻¹ for AH. These rates are considered to be highly conservative, since blood concentrations of AH approached zero by the end of the experiment, thereby implying a very low rate of uptake into blood, and the blood concentration–time curve for AP appeared to be entering a terminal phase 28 days post-injection. Using these assumptions for the absorption of aluminum from intramuscular injection of vaccines, we repeated our analysis.

Figs. 3 and 4 demonstrate that modeling the slower release of aluminum from the injection site eliminates the “excursions” of whole-body aluminum above MRL levels shown in Fig. 2. The body burden of aluminum is less than 50% of the oral safe level for either AP (Fig. 3) or AH (Fig. 4) at all times during the first year or so of life. Using the assumptions of slower release of aluminum adjuvant from the site of injection, the estimated level of aluminum in infants exceeds the MRL (safe) body burden at no time, and the margin of exposure between aluminum body burden from vaccine and the
MRL increases with age. It was also observed that the body burden of aluminum following injection of AH increased more gradually than that for AP. This was due to the slower rate of efflux of AH from the site of injection reported in rabbits.

Although based on the most recent data available, there are several uncertainties in our analysis. First, the published retention function for aluminum (Eq. 1) is based on results for only one person, albeit data have been acquired from this adult for twelve years [5]. Ideally, the retention function would have been derived from pharmacokinetic data in infants or in more than one adult; however, an expansion of this analysis is unlikely. An infant monkey study could provide these data, however, given the present lack of evidence of harm due to the current aluminum levels, such studies may be a low priority. Second, the results of Flarend et al. [27], from which we obtained our estimate of the rate and extent of absorption of aluminum hydroxide and phosphate following intramuscular injection, are based on data from only two rabbits per adjuvant tested. The low number of animals in that study is not surprising, given that it was primarily an exploratory investigation into the disposition of injected aluminum, utilizing, at that time, a new method for detecting radioactive Al in the body (accelerator mass spectrometry). Ideally, the results of that study should be confirmed using a larger number of animals, in order to increase our confidence in the results. Nevertheless, the study clearly showed that the absorption of aluminum, at least in rabbits, is neither instantaneous nor complete up to one month following intramuscular injection [27]. We consider this behavior to be more biologically plausible than complete and instantaneous absorption from the site of injection, and more consistent with the view of muscle tissue being a storage depot for aluminum adjuvant following intramuscular vaccination. A third uncertainty in the analysis is the extent to which the use of maximum aluminum exposures (modeled here) is relevant to aluminum body burdens estimated following more typical exposures to aluminum adjuvant, which are considered to be lower. Ideally, one would like to model aluminum exposures to reflect typical exposures in the population. However, modeling body burdens following maximum exposures to aluminum provides a “worst case” scenario, since more typical exposures to aluminum will obviously lead to a lower body burden and therefore a greater margin of exposure (safety), the distance between safe and expected body burdens of aluminum. Our results indicate that body burdens following maximal exposure to aluminum adjuvant do not exceed those based on an accepted regulatory standard of safe aluminum levels, i.e., the MRL established by ATSDR.

4. Conclusions

Using the previous work of Keith et al. [1] as our starting point, we re-evaluated aluminum levels in infants using a number of updated parameters, including a current pediatric vaccination schedule, baseline aluminum levels at birth, a recent aluminum retention function from human volunteers that incorporates glomerular filtration rates in infants, an adjustment for the kinetics of aluminum efflux at the site of injection, the most recent MRL for aluminum, and up-to-date infant body weight data for children 0–60 months of age. Assuming slow release of aluminum adjuvant from the site of injection into the systemic circulation, we have demonstrated that aluminum levels in infants are well below the minimal risk level curves for either median or low-birth weight babies. We also compared the body burden of aluminum contributed by vaccines with that contributed by diet. The body burden of aluminum from vaccines is not more than 2-fold higher than that received in the diet. While the contribution of vaccines to an infant’s aluminum body burden can be slightly higher than that of the dietary contribution in our model, the fact that the primary pool where the aluminum is residing, as a long-term storage depot, is likely to be skeletal and not a more sensitive soft organ system is reassuring [5]. Although aluminum toxicity is known to occur in humans, it is found exclusively in individuals suffering from kidney disease or in those exposed to high levels of aluminum via occupational inhalation. However, for infants, our study demonstrates that there is little risk for aluminum toxicity following immunizations administered according to ACIP recommendations even
with maximal exposures to aluminum adjuvant. For the general population of infants, who receive less than the maximal dose, the risk is even lower.

References