Correspondence

Aluminum exposure and toxicity in neonates: sources, absorption, and retention

Fanni et al[1] proposed a "guide to halt aluminum overload in the prenatal and perinatal periods" focusing on "aluminum exposure and toxicity in neonates". Their review addressed aluminum overload and risk of systemic intoxication beyond special circumstances of patients receiving intravenous fluid therapy and parenteral nutrition. Fanni et al[1] are commended for bringing into perspective the immature neurologic and immunologic systems of the premature/newborn in relation to aluminum exposure during pregnancy and infancy. Although their main questions were addressed and part of the discussion was summarized in the table, the respective recommendations deserve additional comments and clarification.

They urged that "neonatologists need to be much more concerned about aluminum content" that newborns may be exposed to during the first six months. They summarized total aluminum exposure from vaccines (4 mg), breast milk (10 mg), infant formula (40 mg), and soy-based formula (120 mg) in a very simple fashion, emphasizing that there is still too much aluminum in formulas. However they did not consider or discuss aluminum chemical forms, mode of exposure, bioavailability, or "biological activity".

When we compare total aluminum intake derived from feeding modes (breastfeeding and formula feeding), it is crucial that we consider constitutional/intrinsic (physiological) and extrinsic (bioavailabity) issues that affect aluminum exposure. In breastfeeding, aluminum concentrations decrease from colostrum (56.5 μg/L) to transitional milk (36.6 μg/L), reaching the lowest concentration in mature milk (13.4 μg/L) at the second month.[2] While breast milk aluminum concentrations may further decrease by six months of lactation, formula feedings are constant in aluminum concentrations, and are usually taken in higher quantities than breast milk. Therefore, aluminum intake by breastfed infants is relatively less than the aluminum intake by formula-fed infants. Although Fanni et al[1] mentioned factors that influence aluminum absorption ("assumption") in maternal diets, they didn't compare aluminum bioavailability in breast milk to that in formulas (cow's milk or soy based) fed to infants. Indeed, regarding total aluminum intake represented in the table, aluminum bioavailability (or retention) constitutes the most salient feature that was missing in the otherwise excellent review.

Fanni et al[1] correctly drew attention to "biologically active aluminum" but listed total aluminum exposure from vaccines (4 mg) as a fraction of the total aluminum exposures in milk feedings (10 to 120 mg). Without proper discussion, this can be incorrectly represented and understood. Indeed, an important difference exists between availability and/or reactivity of aluminum chemical forms in vaccines and infant feedings. Actually, when aluminum bio-availability (absorption and/or retention) is taken into consideration, the highest contribution of aluminum to the infant body load is that derived from vaccines. Keith et al[3] modeled these types (vaccines *vs.* infant feedings) of aluminum exposure, showing that the aluminum body burden from human milk and infant formulas (0.1 mg) during the first year was much less than that from vaccines (4 mg); there was 40-fold gradient that deserves consideration.

An important point concerning differences between the enteral and parenteral modes of exposure (oral feedings and vaccines) is that the aluminum intake by the nursing infant in colostrum and breast milk is proportional to the amount of milk nursed. Aluminum in milk is taken in small quantities proportional to infant's size, and spread evenly throughout the course of a day and during the entire lactation.[4] Exposure to aluminum in vaccines occurs as a "bolus" far exceeding the concentrations of bioavailable aluminum in breast milk or infant formulas.[4] Actually, the first aluminum-adjuvanted vaccine (hepatitis B) given to neonates at first post-natal day gives an aluminum load (250 mg) that is far in excess of that absorbed and retained from breast milk through the entire six months of lactation.[4] In circumstances where preterms and low birth weight neonates (<24 h and weighing >2000 g) may receive aluminum-adjuvanted hepatitis B vaccines, there are 20-fold differences in exposure depending on the vaccine maker.[5]

Fanni et al[1] pointed out that antacids are the most important source of adult human exposure as a possible cause of "embryonic and fetal toxic effects".To this we should add that adjuvant aluminum (intramuscular) is the most important source of exposure for newborns and infants. Indeed, in countries where the hepatitis B vaccine is administered at birth, the neonate aluminum dose exceeds by 25 times that recommended by the American Academy of Pediatrics (as informed by

Fanni et al[1]). Fanni et al[1] made a recommendation on advising pregnant women to limit intake of antacids, but gave no indication of doses that we could compare with aluminum adjuvants (phosphate and hydroxide salts) from vaccines taken during pregnancy.

Additionally, Fanni et al[1] summarized animal data regarding aluminum exposure during pregnancy. To this, we should add equally interesting results from intramuscular dosing (as in aluminum-adjuvanted vaccines) of aluminum and its metabolism and neurological effects, pointing out that aluminum can find its way to the brain (as compared to liver increases highlighted by Fanni et al[1]). Recent experimental research has shown susceptibility of young rats to aluminum toxicity,[6] and that aluminum (from aluminum-containing vaccines) translocates from intramuscular injection site to the brain.[7] Indeed, adjuvant aluminum can produce neurological effects.[8]

Finally, in their conclusion, Fanni et al[1] made a long list of food and kitchen utensils that should be avoided during pregnancy. However they failed to inform readers of aluminum bioavailability, a fundamental part of interpreting and recommending provisional levels necessary for hazard and risk assessment.

Although I share Fanni et al's[1] concerns about halting aluminum overload during pregnancy and lactation, I have not found evidence-based support for linking aluminum kitchen utensils (and respective maternal aluminum overload) with breast milk aluminum concentrations. Actually, Chao et al[2] found no significant correlations between tested food items (that included canned food and Chinese herbal teas) and aluminum concentrations in breast milk of Taiwanese mothers. I also share the cautious approach of Fanni et al[1] regarding aluminum-adjuvanted vaccines for pregnant mothers and infants. However, recent findings on the toxic effects of aluminum doses modeling pediatric vaccines are worth comment and contextualization for neonatologists.

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First of all we want to thank the authors for their additional comments on our article, focusing on bioavailability of aluminum. The aim of our article was restricted to lay stress on the possibility that aluminum exposure might be at the basis of toxicity in neonates, alerting perineonatologists and pediatricians to halt aluminum overload in the prenatal and in the perinatal period. To this end, we suggested some practical points of management and prevention in a "very simple faction" (as the authors write), in order to reach the cooperation of the major part of perineonatologists and pediatricians, even of those are not particularly informed on this field of human perinatal pathology. The debate opened in this journal on this topic, and in particular this letter, reinforces our concern on aluminum content in many products our newborns are exposed to, and lays stress on the need of opening a debate on this topic in the neonatological community.

Regarding the relative risk for aluminum overload of infant formulas and vaccines, the authors state that "the highest contribution of aluminum to the infant body load is that derived from vaccines". In the article from Keith and coworkers,[1] it is reported that "the calculated body burden of aluminum from vaccinations exceeds that from dietary sources", but the authors also state that "however, it is below the minimal risk level equivalent curve after the brief period following injection". Moreover, in the article of Dòrea and Marques cited in the letter,[2] the authors state that their study "does not dispute the safety

of vaccines but reinforces the need to study long-term effects of early exposure to neuro-toxic substances on the developing brain". These data taken together, we think that considering "vaccines versus infant formulas" in the evaluation of aluminum exposure in neonates is not correct. On the contrary, we should consider all the multiple factors involved in causing aluminum overload and toxicity in infants, including but not restricted to vaccines and infant formulas, that are usually characterized by higher aluminum levels as compared with breast milk.[3]

The recommendation suggested in the letter for pregnant women to take care of vaccines taken during pregnancy could be added to our practical guide, reinforcing the statement that exposure to aluminum in the general population probably primarily occurs through the consumption of antacids, food and buffered analgesics, without excluding that exposure to aluminum might also occur through vaccination.[4]

The final part of the letter regards the concern on the use of aluminum kitchen utensils, particularly in pregnant women. The beverage preparation method has been shown to influence significantly the aluminum content in coffee infusions, the highest amount of aluminum being found in coffee infusions brewed in aluminum single-cup filter.[5] This simple datum may justify, in our opinion, the suggestion that caution should be taken in using aluminum kitchen utensils, particularly for pregnant women, given the risk that the excess aluminum absorbed might interfere with development of fetal tissues. Even in the absence of data linking the use of aluminum utensils with the metal concentrations in breast milk. As for the cited article of Chao et al,[6] it should be underlined that the study was carried out on a limited number (45) of lactating women, invited to complete a questionnaire regarding their dietary habit during pregnancy, including the use of canned food, but in the absence of any data regarding the use of aluminum pots for cooking foods.

Whereas we may agree on the vast part of critical observations contained in the letter, we must admit that the sentence stating that we "failed to inform readers on aluminum bioavailability" does not find our approval: we did not fail simply because an extensive discussion on aluminum ions bioavailability was not our goal. The aim of our paper was "simply" that of alert the community of perineonatologists and pediatricians about the risk of aluminum exposure in newborns, extending the information to pregnant women and to mothers about the vulnerability of infants to early exposure of aluminum ions.[3] For readers interested to go in deep on aluminum bioavailability, a recent statement of the European Food Safety Authority[7] might give the right answers to their questions.

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