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Review

Aluminum in vaccines: Does it create a safety problem?

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ABSTRACT

For almost a century, aluminum (Al) in the form of Al oxyhydroxide (a crystalline compound), Al hydroxyphosphate (an amorphous Al phosphate hydroxide), Al phosphate, and Al potassium sulfate has been used to improve the immunogenicity of vaccines. Al is currently included in vaccines against tetanus, hepatitis A, hepatitis B, human papillomavirus, *Haemophilus influenzae* type b, and infections due to *Streptococcus pneumoniae* and *Neisseria meningitidis*. Official health authorities consider the inclusion of Al in most of the presently recommended vaccines to be extremely effective and sufficiently safe. However, the inclusion of Al salts in vaccines has been debated for several years because of studies that seem to indicate that chronic Al exposure through vaccine administration can interfere with cellular and metabolic processes leading to severe neurologic diseases. Children, who in their first years of life receive several vaccine doses over a reduced period of time, would be most susceptible to any risk that might be associated with vaccines or vaccine components. The main aim of this paper was to discuss the data presently available regarding Al neurotoxicity and the risk for children receiving vaccines or other pharmaceutical preparations containing Al. Analysis of the literature showed that no apparent reason exists to support the elimination of Al from vaccines for fear of neurotoxicity. The only problem that deserves attention is the suggested relationship between Al oxyhydroxide-containing vaccines and macrophagic myofaciitis or myalgic encephalomyelitis/chronic fatigue syndrome. Currently, definitive conclusions cannot be drawn on these risks and further studies must be conducted. Until then, Al remains the best solution to improve vaccine efficacy.

Contents

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1. Introduction

For almost a century, aluminum (Al) in the form of Al oxyhydroxide (a crystalline compound), Al hydroxyphosphate (an amorphous Al phosphate hydroxide), Al phosphate, and Al potassium sulfate has been used to improve the immunogenicity of vaccines [1]. Al is currently included in vaccines against tetanus, hepatitis A, hepatitis B, human papillomavirus, *Haemophilus influenzae* type b, and infections due to *Streptococcus pneumoniae* and *Neisseria meningitidis*. Official health authorities consider the inclusion of Al in most of the presently recommended vaccines to be extremely effective and sufficiently safe. In a workshop sponsored by the US National Vaccine Program Office, which was specifically planned to discuss the role of Al in vaccines, invited international experts concluded that Al salts were capable of directly stimulating the immune system through the activation of antigen-presenting cells, complement cascades, and the induction of chemokine secretion [1]. Consequently, when added to vaccine antigens, Al can lead to a significant increase in the immune response with higher and more persistent production of specific antibodies against antigens included in the vaccines, although its largest flaw is that Al usually only induces a Th2 immune response. Moreover, the same workshop demonstrated that Al adjuvants have an apparent wide margin of safety because adverse events following their administration were uncommon and showed poor clinical relevance. Although these and similar statements are shared by scientific authorities worldwide [2,3], the inclusion of Al salts in vaccines has been debated for several years, and it is one of the problems that might partially explain the vaccine refusals of some parents and physicians [4]. Studies that seem to indicate that chronic Al exposure through vaccine administration can interfere with several cellular and metabolic processes leading to severe diseases, including neurodevelopmental delay, autism spectrum disorder (ASD) and Alzheimer's disease (AD), are the basis for this debate [5–10].

Children, who in their first years of life receive several vaccine doses over a reduced period of time, are considered to be at the highest risk for Al-dependent, vaccine-related complications. Despite reassurances from health authorities, the question continues to be raised, and the elimination of Al from vaccines continues to be discussed, even through the mass media [11]. Recently, a study showing that subcutaneous injections of Al at vaccine-adjuvant levels activated homologous genes with biomarkers of autism in mouse brains has provided even more support for the opponents of vaccines. Practically, some supposed that this study might represent the final demonstration that Al induces the development of autism in predisposed individuals. The article was retracted a few weeks after its publication at the request of the editor-in-chief and the authors because the data and the results presented in the paper were clearly not reliable [12]. However, as has previously occurred for the supposed relationship between the measles, mumps and rubella vaccine and autism [13], negative data can have a greater resonance than their retraction, and the risk that fake news persistently supports vaccine opponents remains significant. The main aim of this paper was to discuss the data presently available regarding Al neurotoxicity and the risk for children receiving vaccines or other pharmaceutical preparations containing Al.

2. Aluminum (AL) disposition

Al is an environmental metal that is the third most abundant element in the earth's crust and represents approximately 8% of the crust's total mineral components. Moreover, it is largely used in many human activities, including food and drug preparation. Finally, the release of Al to the air from industrial processes and acidic precipitation, which mobilizes the metal from natural sources, is common [14]. This airborne Al can pass to the water or be inhaled. Thus, humans are continuously exposed to Al, and it can be found (although in different concentrations) in all of the body tissues and fluids beginning at birth. Starting with the evidence that the mean Al blood level of term neonates is 0.19 ± 01 1 μmol/L [15] and that the Al in the blood accounts for approximately 4% of the total Al in the body [16], the total body content of this metal at birth has been calculated to be approximately 400 μg [17].

Total body Al concentrations increase with exposure and are generally significantly higher in adults than in children. The highest levels are found in the skeletal system and the lungs, which contain approximately 50% and 25% of the body burden, respectively. Significantly lower concentrations, 10%, 3% and 1%, are usually detected in the muscle, liver and brain, respectively [18].

Food and vaccines are the most important sources of Al for infants and young children. However, vaccines play a major role in this regard because Al absorption from the gastrointestinal tract is poor. Approximately 0.2–0.4% of the ingested Al is absorbed and reaches the bloodstream, with variations based on the type of Al salt [19,20]. During infancy, general fluid consumption varies from approximately 600–900 mL per day, and Al intake depends on the dietary source. Breast milk contains a mean of 40 μg/L, whereas Al levels in formula are significantly higher, ranging from 225 μg/L to 1150 μg/L because food industries use Al components in processing facilities and add Al to food preparation to improve mixing and reduce caking [21–25]. After weaning, Al intake increases and reaches a mean of approximately 700 μg per day [26]. Thus, no more than 2–3 μg per day of Al derived from food enter the systemic circulation during the first year of life. In contrast, almost the full amount of Al included in vaccines given intramuscularly is bioavailable, albeit at a rate over time and with differences among Al salts [27]. It has been calculated that only 51% of Al phosphate and 17% of Al hydroxide reach the bloodstream after a single intramuscular (i.m.) injection in the first 28 days after injection, and the remaining amount is absorbed in 28 and 137 days, respectively [17]. In vaccines, the maximum amount of Al per dose varies from vaccine to vaccine, with a maximum in combined preparations that can range from slightly more than 800 μg per dose, a value that matches the US regulations that limit the amount of Al in the recommended individual dose of biological products (including vaccines), to not more than 850–1250 μg. An FDA study found that the maximum amount of Al an infant should be exposed to over the first year of life is 4225 μg when the recommended ACIP vaccine schedule is used for calculation. This finding was confirmed by Glanz et al., who examined the cumulative and episodic vaccine Al exposure in a sample of 408,608 children ranging in age from birth to 24 months [28]. The mean cumulative Al exposure from the vaccines varied from 1110 ± 320 μg to 4000 ± 800 μg between 92 and 730 days of age. In 2002, an attempt was made to evaluate whether intakes due to food and vaccines could be excessive and lead to clinical problems. Keith et al. compared the calculated body burdens with those expected for exposure at a level considered safe for intermediate-duration exposure according to the minimum risk level (MRL) established at that time (2000 μg/kg/day) by the Agency for Toxic Substances and Disease Registry [29]. These authors found that during the first year of life, the calculated body burden from Al exposure from food was always below the MRL curve, suggesting that diet could not cause clinical problems. The same findings were reported for vaccines for all but a few brief periods following injection. Recently, the analysis of Keith et al. was updated, and new parameters were included [29]. Contemporaneous MRLs (1000 μg/kg/day) and some variables capable of better evaluating the retention and excretion of Al in younger children were introduced [27]. In this study, previous data

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