Journal of Trace Elements in Medicine and Biology 49 (2018) 134–139

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb

Review

Low-dose Thimerosal (ethyl-mercury) is still used in infants` vaccines: Should we be concerned with this form of exposure?

José G. Dórea

Health Sciences, Universidade de Brasília, Brasília, 70919-970, DF, Brazil

ARTICLE INFO

Keywords:
Thimerosal
Ethylmercury
Methylmercury
Vaccines
Adjuvants
Children

ABSTRACT

In developing countries, Thimerosal-containing vaccines (TCV) are the main causes of organic Hg exposure for newborns, neonates, and infants immunized with TCV. This article addresses early-life exposure to this unique organic mercury compound (ethylmercury-EtHg) and the risks of its exposure. English language studies pertaining to Thimerosal/EtHg toxicity and exposure during early life were searched in PubMed; and, those publications judged to be relevant to the topic of this review were selected. The risk from the neurotoxic effects of pre- and post-natal Hg exposures depend, in part, on aggravating or attenuating environmental and/or genetic-associated factors. Health authorities in charge of controlling infectious disease dismiss the toxicology of mercury (immunological and subtle neurological effects as insignificant) related to low-dose Thimerosal. The review addresses the evidence that brings into question the safety of Thimerosal that is still present in vaccines given to pregnant women, infants, and children in developing countries, and recognizes the ethical imperative to extend the use of Thimerosal-free vaccines to developing countries, not just developed countries.

1. Introduction

During early development, exposure to mercury occurs by ingestion, inhalation and injection of this neurotoxic metalloid in its different chemical forms. Therefore, concerns about Hg exposure and neurotoxicity are justifiably heightened [1]. These forms of Hg exposure must be reduced and eliminated even if the established criteria for neurologic diagnosis are unknown for low doses. The worldwide effort to approve and enforce the Minamata convention is the best proof of the urgency of controlling mercury exposure and environmental contamination. This global concern resulted in a new Mercury International Legally Binding Treaty which was signed and adopted in 2013 [2]. To comply with the treaty and to safeguard neurological development in children, it is important that not only environmental but also iatrogenic organic mercury transmission be identified.

Organic mercury compounds – methylmercury (MeHg) and ethylmercury-EtHg (a Thimerosal metabolite) - are recognized as neurotoxic agents [3]; as such, their use needs to be limited, as a condition for preventing toxicity. It is especially during development that some neurological effects are more permanent [4]. Nevertheless, the WHO continues to recommend Thimerosal-containing vaccines (TCV) for global immunization of infants under the assumption that the benefits of using such products far outweigh any 'theoretical risk of toxicity' [5]. Considering the volume of toxicological research, the risks of EtHg toxicity are not theoretical and should be put in context. Indeed, it is not justifiable to put these risks on a par with those related to the intended antigens tested during the phases of vaccine production. Neurological reactions to antigens in licensed TCVs are indeed rare and are not the type of adverse events (or post-vaccination effects) expected from low doses of neurotoxic substances; however, risks of links with neurological disorders can be detected in large data-bases [6].

Vaccine policymakers pursue a strategy that focuses only on the target disease for prevention, control and/or eradication. The safety data on a specific vaccine follow a strict protocol intended only for the immune-related post-vaccine adverse events of the licensed product. Therefore, safety concerns about low-dose Thimerosal toxicity in pediatric vaccines are dismissed by the non-toxicologists (infectologists, vaccinologists, and public health professionals) in charge of immunization policies [5]. Nevertheless, toxicological science has prevailed in all industrialized nations where Thimerosal-free vaccines in young children are adopted [4].

The role of Thimerosal in immunogenic products is tied to vaccine development and carries implications beyond its claimed anti-bacteriological effects. From the regulatory point of view, experts on infectious diseases do not take into account the toxicology of EtHg and require 'compelling evidence' that "*vaccines from which thiomersal has been removed are as safe and efficacious as those products already licensed*" [5]. This has been a recurring issue related to vaccine formulation, and the data on Thimerosal in vaccines are conflicting and complicated. On the one hand, removing Thimerosal from 'Tick Borne Encephalitis

E-mail address: jdorea@unb.br.

https://doi.org/10.1016/j.jtemb.2018.05.010
Received 14 April 2018; Accepted 16 May 2018
0946-672X/ © 2018 Elsevier GmbH. All rights reserved.

(TBE) vaccine' increased serious adverse events [5]; TBE vaccine without Thimerosal was shown to be reactive; restoring Thimerosal to the product abolished reactivity [5]. Indeed, Arjmand et al [7] also reported that electrophoresis bands prepared from Thimerosal freeze-thawed (*L. major*) vaccine were different from heat-killed autoclaved *L. major* preparations. Further reasons for continuing to use Thimerosal are provided by the fact that this metabolite can act as an adjuvant in some vaccines[8], while for others it can decrease vaccine antigenicity (i.e., anthrax, poliomyelitis) [9] or increase toxicity [10]. Given these two sides of the coin, Thimerosal use in immunologic products was not included in the Minamata Convention protocol [2].

In fact, world vaccine-policy-makers will only make a decision if a mercury poisoning incident were to occur post-vaccination. This unlikely event would certainly support a move to make all vaccines Thimerosal-free for all children. Such uncertainties and misinformation shared even among professionals make mandatory immunization a hotly debated topic that drives mistrust and vaccine hesitancy [11]. Therefore, it is crucial to address issues related to early-life exposure to organic mercury compounds now, in order to inform public health professionals of the unmeasured risks of EtHg exposure during early life. We need to reinforce the decision to keep vaccines Thimerosal-free and to recognize the ethical imperative to extend their use to all young children.

2. Toxicology of ethylmercury

Mercury is a toxic metalloid of concern to public health because of its various deleterious effects on organs and systems. Organic Hg is more toxic than its inorganic form; and both environmental-MeHg and iatrogenic-EtHg are the most prevalent forms of exposure for vulnerable fetuses, newborns, young children and pregnant and breast-feeding mothers. Although MeHg has received more scientific attention, studies have shown that EtHg toxicity is comparable to MeHg [12]; additionally, the early literature reported that organo-Hg compounds ('merthiolate') are more toxic for embryonic tissue cells than for bacterial cells [13].

The compared toxicity of ethyl- and methylmercury in experimental animals has been reviewed elsewhere [12]. Studies, dating back as early as 1985, showed consistently that EtHg was equally or more neurotoxic than methylmercury at a comparable dose. *in vitro* studies indicate a similar transfer mechanism by LAT1 for both MeHg and EtHg [14] and that compared to inorganic Hg, the blood–cerebrospinal fluid barrier is much more sensitive to both MeHgCl and Thimerosal [15]. Compared to inorganic HgCl2, organic mercury (MeHgCl and Thimerosal) can have easier access to the brain [16]; these compounds also can have stronger cytotoxic effects on neurons, with Thimerosal being the most cytotoxic of the three compounds [17]. It is worth noting that Hg half-life in the brain is now considered to be much longer than previously estimated; recent estimations place half-life at 27.4 years [18].

Exposure to Thimerosal in the formative stages of the central nervous system has been demonstrated experimentally [19]. Animal studies modeling exposure to EtHg (in TCVs) in developing infants have consistently shown that Thimerosal/EtHg affects neurobehavioral responses [19]. Animal studies with rats and primates, mimicking TCV-EtHg exposure, have shown that Hg stays longer in the brain [20]; in primates, neurobehavior may [21,22] or may not [23,24] be affected by Thimerosal-EtHg.

The mode of exposure dictates how much of the mercury that got into the body goes into the brain, thus, revealing how fast the brain levels can rise. In the case of the developing nervous system, an experimental one-time MeHg high-dose can be more harmful than a chronic low dose of MeHg [25]. A rapid rise in brain concentration of mercury is more likely to affect neurochemical structures. When predicting the risk of toxicity, it can be as important to consider how fast mercury gets to the brain as how much. Indeed, injected mercury reaches the brain much faster than mercury ingested in breast milk [26].

Because EtHg exposures occur acutely they require special consideration. The availability of pure Thimerosal and its direct route of exposure (injection) allow EtHg into the newborn brain not only faster but also in a more spiking pattern than that of mercury in breast-milk; thus increasing the risk of Hg toxicity. Blood EtHg surges post-injection [27], bypassing gastro-enteric barriers, and it is a risk factor for crossing the blood-brain barrier (BBB) to affect neurological integrity. Thimerosal-EtHg has been shown to reach the brain of experimental animals [28]. Furthermore, at the site of the injection, Thimerosal can damage or kill cells; it is speculative that these changed materials may induce the formation of autoantigens [29]. Evaluated evidence indicates that unintended effects of EtHg should be expected, including both neurological [4,30] and immunological effects [4].

The role played by exposure mode, both acute (EtHg) and sustained (MeHg in breastmilk), in increasing the risk of delays in optimal neurodevelopment depends also on genetic susceptibility. Recent research indicates that polymorphisms of the genes regulating coproporphyrinogen oxidase, metallothionein and catechol-O-methyltransferase can increase susceptibility to mercury and neurotoxic outcomes in the form of neurodevelopmental disorders in children [31,32].

Multiple acute doses of Thimerosal-EtHg in pediatric TCVs are the most widespread form of organic Hg exposure and represent the most important toxic challenge to the most vulnerable individuals – fetuses, newborns, infants, and young children. Small doses of EtHg have consistently been found to be harmful in isolated neuronal tissues and experimental animals [33]. Therefore, the developing target organs and systems (brain and immunological system) represent a considerable health risk for clinical issues or permanent disability.

Wren [34] affirmed that Hg toxicity may be modified by (a) Se:Hg ratio of accumulation and (b) dealkylation of organic Hg to the relatively less toxic inorganic Hg. The presence of co-occurring attenuating and aggravating factors poses challenges to studying Hg neurotoxicity. However, we know that preventing Hg exposure during developmental stages can reduce the risk of lowering the intelligence quotient for both MeHg [35,36] and EtHg [37]. In these cases, TCV and diets rich in predatory fish are the main causes of organic Hg exposure at levels that are markedly higher than current recommendations [12].

3. Ethylmercury co-exposure with Al and other neurotoxicants

Of the six recognized toxic elements, Al and Hg are found in the TCV formulations. Aluminum and Thimerosal-EtHg are of different chemical classes, but both are neurotoxic and are used in pediatric TCVs as adjuvant and preservative (respectively) on a fixed ratio (Al:Hg - 50:1 in most vaccines); through the injected route of exposure, they both possess equal bioavailability [38]. As such, this type of co-occurrence and bioavailability differs substantially from the common causes of infant exposure to Al and Hg – breast milk. In breastfeeding, Al and Hg occur as contaminants, and neither has an essential role for the developing human. However, due to low absorption from the intestinal tract, their appearance in cord blood is 10.9 μg/L and 4.4 μg/L respectively [39], thus showing a much lower ratio for Al:Hg (2.5:1).

During infancy, compared to vaccine-Al, bio-available Al from breastfeeding (absorbed and/or retained) represents a fraction of the contribution of adjuvant-Al to the infant body load [38]. Furthermore, in relation to six-month lactation, the amount of vaccine-EtHg (in current TCV schedule of developing countries) represents close to 60% (of total Hg), and adjuvant-Al represents more than 100% of the Al encountered in breast milk [40]. Depending on the route of exposure, once in the body the two contaminants have different metabolism. *Per se*, Al and EtHg are both neurotoxic and their respective risks of neurological disorders have been studied for TCV-EtHg [4,6] and adjuvant-Al [41,42]. However, in combination, their effects on the CNS need further evaluation.

EtHg and adjuvant-Al are usually considered to represent low doses

Download English Version:

https://daneshyari.com/en/article/7638660

Download Persian Version:

https://daneshyari.com/article/7638660

Daneshyari.com