ADJUVANTS AND ADDITIVES IN HUMAN AND ANIMAL VACCINES

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Abstract:

Vaccines typically contain immunologic adjuvants and other additives which act to accelerate, prolong, or enhance antigen-specific immune responses when used together with specific vaccine antigens. Nevertheless, despite ongoing questions about their efficacy and safety, millions of individuals have received these vaccines with relatively few documented adverse events. Vaccine pharmacovigilance is the term used to remind all of us that vaccines carry an inherent, albeit small, risk (CIOMS/WHO 2012).

Key words: *vaccine, adjuvants, additives*

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Introduction:

Countless individuals have been vaccinated routinely and repeatedly for the common, serious infectious viral and bacterial diseases without obvious untoward effects (Dodds WJ 1997, 1999, Tizard I 1990, Wellborn LV et al. 2011). But, medical professionals still need to be aware of the potential for adverse events (AE) and determine what constitutes "acceptable" harm (Dodds WJ 1997,1999, Tizard I 1990).

A variety of immunologic adjuvants and other additives are incorporated into today's human and animal vaccines; they are intended to accelerate, prolong, or enhance antigen-specific immune responses when used together with specific vaccine antigens (Aucouturier J, Dupuis L and Ganne V 2001, Cerpa-Cruz S et al. 2013, Heegaard PM et al. 2011, Nordly P et al. 2009, Sayers S et al. 2012, Spickler AR and Roth JA 2003). While these additives are incorporated into vaccines to enhance and prolong their immunogenicity, this increases the risk of autoimmune and inflammatory adverse events following vaccination (Cerpa-Cruz S et al. 2013). For the killed vaccines available for human and veterinary use, potent adjuvants and additives are included to produce a more sustained humoral immune response and compete favorably with the longer protection typically afforded by modified-live virus (MLV) products. But, these adjuvants and additives may also induce adverse effects (Cerpa-Cruz S et al. 2013, Cruz-Tapias P et al. 2013, Dodds WJ 1997, 2015, 2016a, Israeli E et al. 2009; Leventhal JS et al. 2012, Liu Y et al. 2012, Luján L et al. 2013, Perricone C et al. 2013, Shaw CA and Tomljenovic L 2013, Shaw CA, Li D and Tomljenovic L 2014, Spickler AR and Roth JA 2003, Stejskal V 2013, Tomljenovic L and Shaw CA 2012, 2016, Vogel FR 2000, Wilson-Welder JH et al. 2009).

While current vaccine adjuvants can successfully generate humoral antibody-mediated protection, other diseases such as tuberculosis and malaria require a cell-mediated immune response for adequate protection (Wilson-Welder JH et al. 2009).

Discussion:

1. Killed Inactivated vs Modified-Live Vaccines

Although killed or inactivated products make up about 15% of the veterinary biologicals used today, they have been associated with 85% of the post-vaccination reactions, mainly because of the acute adverse responses induced by the adjuvants and other additives used in companion animal, wildlife and livestock species (Dodds WJ, 1997, 2016 a,b, Luján L et al. 2013, Tomljenovic L and Shaw CA 2012, 2016). However, the debate about the relative merits and safety of the killed, inactivated versus the MLV vaccines, which are recognized to elicit a longer duration of immunity (DOI) (Dodds WJ 1999, Wellborn LV et al. 2011), has been ongoing, and was hotly debated in a comparison of the risks, costs, and convenience of killed versus modified live human polio vaccines (Stratton KR, Howe CJ and Johnston RB Jr, 1994). Documented AE from the adjuvants used in human vaccines, especially those containing aluminum and thimerosal (mercury salt), continue to appear in the

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literature (Perricone C et al. 2013, Shaw CA and Tomljenovic L 2013, Shaw CA, Li D and Tomljenovic L 2014, Stejskal V 2013, Tomljenovic L and Shaw CA 2012, 2016).

2. Potential Adverse Events and Toxicity

Published experimental studies have shown that simultaneous administration of even two or three adjuvants is capable of overcoming genetic resistance to autoimmunity (Tomljenovic L and Shaw CA 2012). Further, because vaccines are viewed as inherently safe and non-toxic, toxicity studies are often excluded from their regulatory safety assessment. Children are especially at risk being more vulnerable to toxicity than adults; and they are regularly exposed to more vaccine adjuvants and additives than adults (Stratton KR, Howe CJ and Johnston RB Jr, 1994). Adjuvants impact the central nervous system (CNS) at all levels and can do so by changing gene expression (Shaw CA, Li D and Tomljenovic L 2014), and play a key role in brain development and immune function Shaw CA and Tomljenovic L 2013, Shaw CA, Li D and Tomljenovic L 2014, Stejskal V 2013, Tomljenovic L and Shaw CA 2011, 2012). However, more recently, concerns have focused not only on the effects of vaccine antigens but also on the widespread use of aluminum and mercury-containing compounds in the vaccines given to humans and animals (Cerpa-Cruz S et al. 2013, Davis HL 2008, Perricone C et al. 2013, Shaw CA and Tomljenovic L 2013, Shaw CA, Li D and Tomljenovic L 2014, Spickler AR and Roth JA 2003, Stejskal V 2013, Tomljenovic L and Shaw CA 2011, 2012, 2016).

In their landmark book (Schoenfeld Y, Agmon-Levin N and Tomljenovic L, 2015) stated:

"because vaccines are delivered to billions of people without preliminary screening efforts and severe even fatal reactions can occur, there is concern about what this means for today's population of people".

Vaxjo is a newly published, web-based vaccine adjuvant database (Sayers S et al. 2012). Basic vaccine information stored includes: adjuvant name, components, structure, appearance, storage, preparation, function, safety, and vaccines that use this adjuvant. Currently over 100 vaccine adjuvants have been annotated in Vaxjo. These adjuvants have been used in over 380 vaccines against over 81 pathogens, cancers, or allergies.

2.1 The ASIA Syndrome

The term "autoimmune inflammatory syndrome induced by adjuvants" (ASIA) was first given to the disease symptoms that follow vaccinations in 2011 (Cruz-Tapias P et al. 2013, Perricone C et al. 2013, Stejskal V 2013). Many are vague and include arthralgia, myalgia, paraesthesia, and weakness. These signs are often considered deemed to be "insignificant" and are thus generally ignored by the treating doctors. The progression from mild symptoms to full-blown autoimmune disease can take months and is insidious. Aa acute clinical manifestation of the ASIA disease is usually seen after the second or anamnestic response to a mild or sub-clinical prior vaccinal event (Schoenfeld Y, Agmon-Levin N and Tomljenovic L, 2015).

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2.2 Clinical Symptoms

Vaccine AE have been linked to chronic fatigue syndrome, polymyalgia, polyarthritis, encephalitis, myocarditis, macrophagic fasciitis, rheumatoid arthritis, systemic lupus erythematosus and even "Gulf War Syndrome" (Schoenfeld Y, Agmon-Levin N and Tomljenovic L, 2015).

2.3 Ischemic Dermatopathy

Safety issues are commonly raised in cases of vaccine-induced ischemic dermatopathies, especially following rabies vaccination (Vitale CB, Gross TL and Magro CM 1999, Morris DO 2013). In dogs, ischemic dermatopathy is classified into three groups: post-rabies vaccination alopecia, dermatomyositis, and idiopathic, all three of which probably have a similar pathogenesis (Vitale CB, Gross TL and Magro CM 1999, Wilcock BP and Yager JA 1986). Clinically, these three forms exhibit variable alopecia, erosions, ulcers, crusts, and hyperpigmentation in a focal or multifocal distribution. In post-rabies vaccine alopecia, lesions are typically seen above the interscapular region, but can also involve the face, pinnae, foot pads, tip of the tail, and skin overlying bony protuberances. These other locations also are involved in dermatomyositis and idiopathic ischemic dematopathy, thereby confounding the diagnosis (Vitale CB, Gross TL and Magro CM 1999). Regardless of the inciting cause, the tissue injury occurs because of inadequate delivery of oxygen to the damaged area (Morris DO 2013).

2.4 Herpes Varicella- Zoster Issues

Another compelling situation exists with the prevalence of herpes virus varicella-zoster disease (Hambleton S and Gershon AA 2005). The varicella (chicken pox) and zoster (shingles) viral diseases are caused by a small alpha, herpes virus, that is similar to but distinct from the more common herpes simplex virus of cold sores. Shingles is due to reactivation of a latent varicella virus exposure in early life (Hambleton S and Gershon AA 2005). Complications of these virus diseases and potentially their vaccines can affect the CNS. However, vaccination against chicken pox (varicella) is highly effective, producing an 84-100% reduction in disease over the ensuing 2-8 years post-vaccination. Even among the non-vaccinated, chicken pox declined as an indication of the effect of so-called "herd immunity" within the region.

Breakthrough varicella cases are usually mild and can occur due to exposure to the wild type varicella-zoster virus. But, immunity from either the MLV or killed inactivated vaccines can last up to 20 years. Breakthrough clinical signs are either primary or secondary events: primary being due to genetic vaccine non-responders or improper vaccine storage conditions, whereas secondary cases show a decreased in immune protective response over time. The 10-year breakthrough rate in children is 2-34% (Hambleton S and Gershon AA 2005). In immunocompromised groups, the rate of herpes zoster breakthrough infection is 4-20 times higher. One suggested option to reduce the breakthrough rate is to give two doses of vaccine 4-8 weeks apart to increase the amount of induced cell-mediated immunity (Hambleton S and Gershon AA 2005).

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3. Heavy Metals as Adjuvants and Additives

Aluminum and mercury (thimerosal salts) are Exposure to aluminum and mercury (thimerosal saltsa) is widespread; these metals are found in many sources of drinking water, as a food additive especially in processed "fast" convenience foods, in many cosmetics, field, lawn and garden fertilizers and herbicides, and in pharmaceuticals including vaccines; they thus can accumulate in the bodies of humans and most, if not all, species. They are linked to both neurological and neuropsychiatric disorders (Shaw CA and Tomljenovic L 2013, Shaw CA, Li D and Tomljenovic L 2014, Stejskal V 2013, Tomljenovic L and Shaw CA 2012, 2016). Studies have shown that adjuvant nanoparticles can cross the blood-brain barrier and enter the cerebral spinal fluid resulting in harmful inflammatory responses within the CNS (Tomljenovic L and Shaw CA 2011, 2016).

They not only are neurotoxins, but also are immunotoxic, genotoxic, pro-oxidant, and pro-inflammatory (Dodds WJ 2016 a, b, Tomljenovic L and Shaw CA 2016). Further, they are recognized to be endocrine disrupters, depress glucose metabolism, and interfere with calcium homeostasis, and mitochondrial and other biochemical pathways (Tomljenovic L and Shaw CA 2016). Other metals like nickel, chromium, silver and gold can also elicit AE (Stejskal V 2013).

4. Human Illness from Use of Animal Vaccines

Another potential and important vaccine is occupational when humans are internationally or unintentionally exposed to animal vaccines (Berkelman RL 2003). This typically involves occupational exposures of veterinarians, veterinary technicians and livestock handlers to brucellosis vaccines during immunization of cattle, as well as veterinarians, their staff and pet caregivers when intranasal or oral Bordetella or kennel cough vaccines are given and create a surrounding aerosol (Berkelman RL 2003).

5. Other Vaccine Safety and Efficacy Issues

Vaccines are expected to undergo rigorous review and both experimental and field challenge testing for safety and efficacy before receiving licensure for use in their intended locales. Some vaccines may be given provisional or temporary licensure pending completion of challenge trials, when an emergency need arises (e. g., Asian H3N8 strain of canine influenza). Does this oversight guarantee safety and efficacy? The obvious answer is not; despite the effort involved, especially when acceptable vaccine performance for a fatal disease like rabies only requires survival of 88% of the live rabies virus challenged vaccinates (Dodds WJ 2016 c.)

The safety of vaccine ingredients has not been adequately studied for potential long term adverse effects. Vaccine contents are either the whole, weakened infectious agents or synthetic peptides, and genetically engineered antigens of the infectious agents with adjuvants and other additives. In addition, they contain diluents, preservatives (thimerosal, formaldehyde, aluminum hydroxide), detergents (polysorbates, Tween), other residuals of culture media like

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yeast (*Saccharomyces cerevisiae*), porcine and bovine gelatin, bovine serum and fetal calf extract, egg proteins, soy, antibiotics (neomycin, gentamicin, polymixin B, amphotericin B, streptomycin), EDTA, *E. coli*, chick embryo cell, human albumin, porcine circovirus 1 and 2, xanthum gum, and monkey and canine cells and protein. A detailed list of the vaccine contents of the commonly given human vaccines can be found in Appendix B-8 – B-10 of the 13th Edition of "Epidemiology and Prevention of Vaccine-Preventable Diseases" from the US Centers for Disease Control and Prevention (CIOMS/WHO Working Group 2015).

Safety issues have not been studied with most of these ingredients because of presumably incorrect "assumptions" that trace amounts are insignificant!

Conclusion:

Medical professionals are confronting increasing numbers of human and animal patients exhibiting signs of immunologic dysfunction and disease. In a number of these cases, the onset is associated within 30-45 days of a vaccination. The evidence implicates vaccines and their adjuvants as potential triggering agents combined with the genetic predisposition of the vaccinated host. The number of adjuvants used in human and animal vaccines should be re-examined. At the same time, discovery and implementation of new types of vehicles that enhance the immune response to vaccines should be encouraged. A multifaceted approach to furthering the recognition of this situation, along with alternative strategies for containing infectious disease and reducing the environmental impact of conventional vaccines is clearly needed.

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