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Review

Can vaccines interact with drug metabolism?

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ABSTRACT

Vaccines are safe and efficacious in reducing the burden of several serious infections affecting children and adults. Due to their efficacy, vaccines are often administered in patients with chronic diseases, likely to be under poly-therapy.

Because of several case reports indicating changes in drug metabolism after vaccination, the hypothesis of an interaction between vaccines and specific drugs has been put forward. These interactions are conceivably of great concern, especially in patients treated with molecules characterised by a narrow therapeutic index.

Herein, we review and systematise the available evidence on vaccine–drug interactions. The picture that emerges indicates that reduction in the activity of specific CYPs following vaccination may occur, most likely via interferon γ overproduction, and for specific drugs such as anticonvulsivant and theophylline may have significant clinical relevance. Clinical interaction between vaccines and drugs that are metabolised by cytochromes uninfluenced by INFγ levels, such as warfarin, are instead unlikely to happen. Further studies are however needed to gain a complete picture of vaccine–drug interactions and define their relevance in terms of possible negative clinical impact.

Contents

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Introduction

The introduction of vaccines represented a vital step for public health, resulting in significant reductions in mortality and morbidity in the general population as well as in subjects with severe risk factors [1–3], such as patients in poly-therapy or receiving drugs with a narrow therapeutic index.

Occasional reports highlighted the possible risks of interactions between vaccines and drug metabolism leading to significant changes in serum levels and/or pharmacodynamics parameters of specific drugs after a vaccine shot [4–10]. These interactions represent a notable concern mostly in view of the large utilisation of influenza and pneumococcal vaccines in patients older than 65 years, which are more likely to be under poly-therapy and have often reduced drug metabolism.

A recent analysis identified about 30 cases of suspected drug–vaccine interactions reported to the Vaccine Adverse Event Reporting System (VAERS) database, the United States of America-based national vaccine safety surveillance programme [4], but this number could be significantly higher because the VAERS database is affected by underreporting issues that may limit its detection power [4,5]. In addition, reliable causal link are often lacking [4–10], making it difficult to discern if other factors may have caused the specific adverse event.

Causality assessment of post vaccine adverse events is indeed difficult or even misleading [11–13], especially when the clinical manifestation occurs weeks or months after vaccination [14–18].

The aim of our analysis was to assess the possible interference of vaccines with drug metabolism, considering all evidence available to date from published case reports, large safety databases and results of clinical studies. For some of these vaccine–drug interactions we are also able to provide tentative molecular mechanisms.

Materials and methods

We carried out a PubMed search up to 2013 using the terms: “Drug interaction” AND “Vaccine” or “Vaccine interaction” to retrieve all article dealing with a possible interaction between a generic vaccine and a generic drug. The name of each identified drug was then searched using the terms “drug name” AND “Vaccines”. We considered studies that included case reports and case series, case–control studies, post-marketing surveillance programmes and published analyses by the VAERS. We carried out an initial screening by reading each abstract to identify the articles meeting these inclusion criteria, which were conclusively assessed after a thorough analysis of their content. The retrieved studies were then read in their entirety to assess appropriateness. Citations from each included article were examined in order to identify any other published study potentially meeting inclusion criteria. We limited the research to articles written in English.

We did not include studies dealing with interactions between vaccines and biological drugs or studies dealing with drug effects on vaccine efficacy.

Results

The mechanism behind: how a vaccine can modify drug metabolism?

After reports of anecdotic cases of vaccines interacting with drug metabolism, several studies were aimed at identifying biological mechanisms possibly explaining these observations. A role for immune modulation in interactions with drugs was unveiled, based on several converging pieces of evidence. Vaccine immunisation elicits an immune response that mimics the response to the natural disease in order to provide protection against subsequent challenges, including the production of cytokines such as interferon-γ (INFγ) [19,20]. A major role of inflammatory cytokines as regulators of the expression of members of the cytochrome P450 family of oxidising enzymes (CYPs) was described in the liver. Cytokines can down-regulate expression of (CYPs) in cultures of rodent and human hepatocytes [18,22,23] and in mice with null mutations in cytokine or cytokine receptor genes displayed diminished P450 down-regulation in response to some inflammatory stimuli [24,25]. Moreover, changes in drug metabolism, measured with the erythromycin breath test, highly correlated with antigen specific production of INFγ after a vaccination [21]. This cytokine, along with pro-inflammatory cytokines such as IL-10, has been reported to reduce the activity of several CYPs relevant to drug metabolism both *in vivo* and *in vitro* [22–26]. A correlation between the reduction of P450-dependent drug clearance and levels of plasma interleukin-6 (IL-6) has also been documented in patients with tumours [26] and congestive heart failure [27].

Taken together, these observations, complemented by other examples also from the clinical practice [21,28], suggest an immune-mediated mechanism by which vaccines interfere with drug metabolism.

How cytokines down-regulate expression of CYPs, however is still debated. Whereas several pathways have been proposed, the most likely action is to be ascribed to a decreased activity of nuclear hormone receptors such as the constitutive androstane receptor CAR and the pregnane X receptor PXR [5,27–29]. The regulation of CYPs mediated by cytokines appears to be gene specific; this would explain the reasons why some drugs appear to be influenced by vaccines and others do not. In a recent analysis, Aitken and Morgan explored the effects of different inducing agents on the expression of several CYPs and found that INFγ was active in reducing the mRNAs level of CYP2C8, 3A4 and 2B6, but not CYP2C9, 2C19 and 2C18 [29].

Another important factor to compound to explain the biological mechanism behind the effect of vaccines on drug metabolism is the presence of a significant inter-individual variability in CYP activity and immune response to vaccines [6,30]. The presence of single nucleotide polymorphisms (SNPs), rare and unknown mutation as well as the presence of concomitant therapies may increase the risk for vaccine–drug interactions. Variability in CYP activity due to SNPs has been widely described and is now beginning to be introduced in clinical practice to improve drug efficacy and safety by tailoring patients’ therapy [31,32].

The presence of SNPs within genes associated with immune responses has been proven to influence also vaccine efficacy [33], thus indicating the presence of a genetic variability also in vaccine response.

Chronic warfarin therapy: can vaccines affect the INR?

Analysis of the data in the literature revealed that in spite of concerns on vaccine–drug interactions having been raised for several vaccines and drugs, most of the consolidated information regard the interaction between influenza vaccine and warfarin [34]. This topic is of high interest as warfarin sodium represents the mainstay of anticoagulation therapy for millions of patients in treatment and prophylaxis of various thrombotic events [35]. Warfarin has a narrow therapeutic range and requires regular monitoring for anticoagulation response via the international normalised ratio (INR) [35]. Several factors such as food or other medications may cause an INR fluctuation by interacting with hepatic metabolism [35].

The influenza vaccine was firstly associated with the risk of increasing anticoagulation in 1984, as the result of the report of the case of an 81-year-old patient who experienced gastrointestinal bleeding 10 days after vaccination [36]. In a subsequent study,