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LEADING ARTICLE

Vaccine–Drug Interactions: Cytokines, Cytochromes, and Molecular Mechanisms

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Abstract Vaccinations are recommended throughout life to reduce the risk of vaccine-preventable diseases and their sequelae. Vaccines are often administered in patients with chronic diseases who are likely to be treated with several drugs. A growing number of clinical observations have indicated the possibility of interactions between vaccines and drugs, leading to changes in drug metabolism after vaccination. These interactions represent a significant concern because of the increasing use of vaccines in older patients who are likely to be treated with several drugs. Because of the possible implications of adverse reactions in terms of public health, several studies were performed to verify the risk posed by these interactions and to clarify the biologic mechanisms that drive these events. Of the several mechanisms proposed to be at the basis of vaccine–drug interactions, the most convincing evidence suggests a role of inflammatory cytokines on the regulation of specific cytochrome P450 enzymes in the liver. Differences in the cytochrome P450 enzymes involved in the metabolism of these drugs could explain these contrasting results and provide important insights to fully understand the clinical importance of these events. Further studies are required to verify whether vaccine–drug interactions may occur in other clinical settings, especially the ones for which patients are required to be vaccinated against specific diseases.

Key Points

Vaccines may interact with cytochrome P450 enzymes and affect the metabolism of certain drugs in patients at risk.

Current evidence suggests that the mechanisms behind such interactions involve the effect of a number of inflammatory cytokines that are released after vaccination.

Further analyses are required to fully elucidate the clinical relevance of this phenomenon.

1 Introduction

Vaccinations are recommended throughout life to reduce the risk of vaccine-preventable diseases and their sequelae [1]. It is important to note that vaccines are administered to largely young and healthy children aged <5 years as well as patients with chronic conditions who are likely to receive already other medications. With the exception of the influenza vaccination, which is recommended for all adults each year, other vaccinations are recommended for specific populations based on a person's age, health conditions, behavioral risk factors (e.g., injection drug use), occupation, travels, and other indications [1]. In the USA, a

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number of vaccines, including those against herpes zoster, influenza, and pneumococcal infections are recommended for individuals aged older than 65 years [1]. Among these older adults, more than 76 % use two or more prescription drugs and 37 % use five or more, most of which on a daily basis [2]. Because of this, the vaccination of individuals who are receiving several drugs, some of which with a narrow therapeutically index, is a likely occurrence that may imply worsened safety and efficacy profiles of both the vaccine and the drug [3–10].

It is well accepted that several immunosuppressive drugs, such as the ones used for the treatment of multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis may affect vaccine response [10–13]. Concerns exist also for cancer patients, in whom immune responses are almost constantly depressed because of concomitant therapies [14] and for patients affected by human immunodeficiency virus or other conditions associated with a reduced immune response. The large majority of available reports on these interactions are focused on the effects of immunosuppressive drugs on vaccine efficacy and on the risks related to the administration of live-attenuated vaccines [10, 15]. A growing number of reports suggest that vaccines may influence drug metabolism, leading to significant changes in serum concentrations of specific drugs in the weeks following a vaccine shot [6–9]. This latter form of interaction, which will be referred to as "vaccine–drug", represents the main topic of this review and was investigated in several preclinical and clinical analyses [16].

The review of current evidence about vaccine–drug interactions we propose here explores the biologic mechanisms likely at the basis of the interactions as well as the genetic background of these events. Additionally, we explored other possible mechanisms behind such interactions, including cytokine response to simultaneous infections.

2 Method of Analysis

We conducted a PubMed search up to February 2015 using the terms "Drug" AND "Vaccine" or "Vaccine interaction" to retrieve all article dealings with a possible interaction between a generic vaccine and a generic drug. A second analysis was carried out using the terms "Warfarin", "anticonvulsants", "carbamazepine", "Theophylline", "chlordiazepoxide", "phenytoin", "phenobarbital", "lorazepam" AND "Vaccine" or "Influenza vaccine". These drugs were chosen based on previously reported cases. We then carried out a third literature analysis aimed at retrieving all articles describing the molecular mechanism of vaccine–drug interactions. This analysis was carried out using the terms "cytokines", "cytochromes", and "vaccines". For this analysis, we also considered studies reporting data derived from any preclinical setting.

We carried out an initial screening by reading each abstract to identify any articles meeting these inclusion criteria, which were assessed conclusively after a detailed analysis of their content. The retrieved studies were then read in their entirety to assess appropriateness. Citations from each included article were examined 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 biologic drugs or studies dealing with drug–vaccine interactions.

3 Cytokines and Cytochromes

An effective vaccine needs to mimic the "real" biological entity from which it is derived to be recognized and to initiate the cascade of molecular and cellular events required to induce an effective immune response and immunologic memory [17]. The immunologic mechanism behind vaccinations (extensively reviewed in [17]) includes the production of a series of cytokines, which mediate the communication between the T helper (Th) cells and the effector cytotoxic T cells or B cells. Functionally, Th1 cells produce interferon (IFN)-γ and interleukin (IL)-2, while Th2 cells produce IL-4, IL-5, and IL-10 [18–20].

It is widely accepted that the most likely mechanism by which vaccines interact with drugs, the so-called vaccine–drug interaction, relies on the effects of inflammatory cytokines on cytochrome P450 (CYP) regulation in the liver [16, 21].

CYP isoforms constitute a superfamily of haem-thiolate proteins, with functions ranging from the synthesis and degradation of endogenous steroid hormones, bile acids, vitamins, and fatty acid derivatives to the metabolism of foreign compounds such as drugs, environmental pollutants, and carcinogens [22].

The first evidence about the effects of cytokines on drug metabolism has been described in patients with natural infections such as influenza, in which theophylline elimination was significantly reduced during the acute phase of the infection [23]. These data were further strengthened by indications that cytokines could down-regulate P450 expression in cultures of rodent and human hepatocytes [24]. A number of cytokines, including IFNγ and IL-10 have been reported to reduce the activity of several cytochromes relevant to drug metabolism both in vivo and in vitro [24–28]. Additionally, mice with null mutations in cytokine or cytokine receptor genes displayed diminished

CYP down-regulation in response to some inflammatory stimuli [24, 28]. Similar correlations have been reported for IL-6, for which plasma levels have been linked to the reduction in P450-dependent drug clearance in several clinical settings, including cancer [25] and congestive heart failure [26].

The amount of evidence on the effect of cytokines following natural infections was extended further to include the effects of the same cytokines following vaccinations, as it was shown that antigen-specific production of IFNγ was highly correlated with changes in drug metabolism following vaccination [29]. These and other observations [21, 27] strongly suggest an immune-mediated mechanism by which vaccines interfere with drug metabolism.

4 The Molecular Mechanism

While firm evidence exists about the effects of cytokines on the down-regulation of the expression of cytochromes of the P450 family, the mechanism by which such phenomena occur remains debated.

Increasing evidence suggests that a decrease activity of nuclear hormone receptors such as CAR and PXR represents a likely mechanism to explain these phenomena [4, 30–32]. These two members of the nuclear hormone receptor superfamily of ligand-activated transcription factors are highly expressed in the liver [33, 34] and have been associated with increases in gene expression of several CYPs in humans, rats, and mice. The PXR has also been proven to bind a response element in the CYP3A4 promoter after activation by a range of drugs known to induce CYP3A4 expression [35].

The mRNA expression of both CAR and PXR was found to be markedly reduced following the injection of bacterial lipopolysaccharide (LPS). This down-regulation was dose dependent and lasted for over 16 h in mice. Additionally, treatment with LPS was also reported to reverse up-regulation of CYP3A in mice pre-treated with the PXR ligand RU486 [31].

Along with CAR and PXR, other mechanisms have been put forward [36]. The peroxisome proliferator activated receptor-α mediates the induction of hepatic CYP4A and other genes by peroxisome proliferators [37] and negatively regulates the human fibrinogen gene in both constitutive and inflammatory conditions [38]. However, analyses on down-regulation of CYP1A2, 2A5, 2C29, 2E1, and 3A11 by LPS treatment in the livers of wild-type and proliferator activated receptor-α-null mice did not highlight any significant difference [39].

Another important factor that has to be taken into account to explain the biologic mechanism behind this interaction is the presence of a significant inter-individual variability in both CYP activity and immune response to a given vaccine [5, 40]. The presence of single nucleotide polymorphisms (SNPs) may increase the risk for vaccine–drug interactions. Variability in CYP activity owing to SNPs has been indeed widely described and is now beginning to be introduced in clinical practice to improve drug efficacy and safety by tailoring patient's therapy [41–43].

The presence of SNPs within genes associated with immune responses has been proven to influence also vaccine efficacy, thus also indicating the presence of a genetic variability in vaccine response. A number of studies have been reported on this topic, including significant evidence about the role of several SNPs in cytokines production following vaccinations [44–50].

However, inter-individual variability as a result of SNPs in several key metabolic genes has already been employed in a number of clinical setting, including oncology [51, 52], infectivology [53], and other diseases [54–56]. As a number of genes and SNPs are known to potentially influence the risk of vaccine–drug interactions by interfering with both immune response [44–50] and CYP activity [41–43], further studies are required to fully explore this topic.

5 Evidence from Clinical Practice

The regulation of CYPs mediated by cytokines appears to be gene specific; this would explain why some drugs appear to be influenced by vaccines and others do not.

In a recent analysis, Aitken and Morgan explored the effects of several inducing agents on the expression of various CYPs and found that IFNγ was active in reducing the mRNA level of CYP2C8, 3A4, and 2B6, but not CYP2C9, 2C19, and 2C18 [32].

Such an evidence suggests that only drugs metabolized by CYPs affected by IFNγ are interested by the vaccine–drug interaction phenomenon, thus explaining the conflicting results retrieved from the literature [16, 21].

Concerns on vaccine–drug interactions have been raised for several vaccines and drugs, with particular emphasis on the possible interaction between influenza vaccine and warfarin [57]. This topic is of significant concern as warfarin has a narrow therapeutic range and several factors such as food or other medications may interact with its hepatic metabolism [58]. This drug requires regular monitoring for anticoagulation response via the international normalized ratio, and fluctuations in these parameters as well as significant clinical adverse reactions have been reported following vaccination. A number of studies were carried out to verify such a correlation, yielding mainly null findings [59–65].

These results could be explain by considering the findings reported by Aitken et al., who did not find any effect of IFNγ production on CYP2C9 or any other cytochrome involved in warfarin metabolism [66].

6 Discussion

While vaccine–drug interactions involving warfarin are unlikely, this occurrence could be suspected for drugs metabolized by cytochromes known to be inhibited by IFNγ production. This was the case for carbamazepine, which is metabolized by the liver's CYP3A4 enzyme and for which a concomitant administration of drugs that inhibit this cytochrome is known to increase plasma concentrations and cause toxicity [67, 68]. The possibility of an interaction was therefore suspected and reported in cases in which signs and symptoms of carbamazepine toxicity were observed a few days after immunization [69]. Vaccination has also been reported to influence serum concentrations of other drugs including theophylline [70–75], chlordiazepoxide, phenytoin, phenobarbital, and lorazepam [16].

It is noteworthy to mention that several clinical situations could reduce the metabolism of specific drugs with the same mechanism described for vaccine–drug interactions [4]. This was recently highlighted by Raaska et al., who reported an increase in clozapine serum concentration in two patients who developed minor infections [76]. In all these cases, cytokine plasma levels were linked to the reduction of P450-dependent drug clearance.

The presence of concomitant diseases including mild and frequently under-reported cases of infections could have a significant etiologic role and represents an important challenge in the evaluation of possible cases of vaccine–drug interactions.

Increasing evidence suggests that in certain subjects, vaccines modify the metabolism of a number of drugs, possibly resulting in clinically significant adverse reactions. The individuals who may be at risk for these interactions include older patients and individuals harboring specific SNPs in genes coding for drug metabolism or for vaccine response [16].

These interactions represent a significant concern because of the increasing use of vaccines in older patients who are likely to being treated with several drugs. Because of the possible implications of adverse reactions in terms of public health, several studies were carried out to verify the risk posed by these interactions and to clarify the biologic mechanism that drives these events [59–65].

Of the several mechanisms proposed to be at the basis of vaccine–drug interactions, the most convincing evidence suggests a role of inflammatory cytokines on CYP regulation in the liver [16]. Cytokines are released after vaccination and were found to reduce the expression of several CYPs by modulating the levels of CYP2C8, 3A4, and 2B6, but not CYP2C9, 2C19, and 2C18 [66]. This could explain the contrasting results observed in several studies, in which authors were able to prove the occurrence of vaccine–drug interactions for some drugs such as carbamazepine and theophilline, while not for other ones such as warfarin. As mentioned above, differences in the CYPs involved in the metabolism of these drugs could explain these contrasting results and provide important insights to fully understand the clinical importance of these events.

An important point to be evaluated in further analyses is represented by the genetic and non-genetic predisposition of patients to develop a vaccine–drug interaction. Increasing evidence indicating that specific risk factors exist have been provided in the literature, including the role of age, sex, and SNPs [3, 5, 16, 39, 44, 45, 47].

The role of genetic predisposition in the risk of occurrence of vaccine-related adverse reactions has been discussed largely in recent years [21, 50, 77, 78], with special emphasis on the "ASIA-Autoimmune/inflammatory Syndrome Induced by Adjuvants" [79]. The term "ASIA-Syndrome" was coined in 2011 to describe the spectrum of immune-mediated diseases triggered by an adjuvant stimulus [79–86]. This syndrome comprises an "umbrella" of clinical conditions including post-vaccination phenomena caused by vaccine adjuvants [87–90]. These recent observations describing the role of SNPs as a risk factor for vaccine-related adverse reactions provide important insights that could be applied in the context of a vaccine–drug interaction. Further analyses should be carried out to verify whether common SNPs may predict the risk of these events.

A special emphasis during the evaluation of a suspected vaccine–drug interaction should be reserved to the concomitant clinical conditions. Such a concept was clearly defined in a recent article by Raaska et al., who pointed out that a minor infection could also modify drug metabolism, thus creating a clinical condition similar to those described for vaccine–drug interactions [76].

7 Conclusion

Taken altogether, these findings suggest that interactions between vaccines and drugs are possible and likely to be caused by interactions of inflammatory cytokines and CYPs, leading to a reduction in drug metabolism. Further studies are required to verify whether vaccine–drug interactions may occur in other clinical settings, especially those for which patients are required to be vaccinated against specific diseases [91]. Finally, clinicians should be

made aware of the possibility of these interactions and their implications.

Compliance with Ethical Standards

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Conflict of interest Paolo Pellegrino, Cristiana Perrotta, Emilio Clementi and Sonia Radice have no conflicts of interest that are directly relevant to the content of this study.

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