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Optimizing the State of the Immune System, Diagnosis and Treatment in Children with a Background of Hypersensitivity to Drugs

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Abstract: Drug use in children is–in most cases–supported by extrapolation of data generated from clinical trials in adult populations. This puts children at higher risk of developing adverse drug reactions (ADRs) due to "off-label" use of drugs and dosing issues. Major types of ADRs are drug hypersensitivity reactions, an idiosyncratic type of ADRs that are largely unpredictable and can cause high morbidity and mortality in a hard-to-identify specific population of patients. Lack of a complete understanding of the pathophysiology of DHRs and their unpredictive nature make them problematic in clinical practice and in drug development. In addition, ethical and legal obstacles hinder conducting large clinical trials in children, which in turn make children a "therapeutic orphan" where clear clinical guidelines are lacking, and practice is based largely on the personal experience of the clinician, hence making modeling desirable. This brief review summarizes the current knowledge of model-based evaluation of diagnosis and management of drug hypersensitivity reactions (DHRs) to antimicrobial drugs in the pediatric population. Ethical and legal aspects of drug research in children and the effect of different stages of child development and other factors on the risk of DHRs are discussed.

Keywords: children, adverse drug reactions, modeling, drug safety.

Introduction

An adverse drug reaction (ADR) is defined as any noxious and unintended response to a drug, which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or modification of physiological function. A conservative estimate of the rate of ADRs in the general population is 5% per course of treatment, however; it can be as high as 50%, for example, in the case of cancer chemotherapy. [1,2] ADRs are a leading cause of morbidly and mortality in patients from all age groups [3,4,5] Serious ADRs occur at a rate of 6.7% in hospitalized patients and 0.32% of them are fatal. A review of 17 prospective studies of incidence rate of ADRs in pediatric in- and out-patients estimated the incidence to be 9.5% (95% CI 6.81, 12.26) in in-patients and 1.5% (95% CI 0.7, 3.03) in out-patients [6,7]

Drug Hypersensitivity reactions (DHRs) including true "drug allergy" represent up to one third of all ADRs and can be severe and life-threatening requiring prolonged hospitalization and associated healthcare costs [8]. DHRs are classified, according to their onset and the immune mechanism involved, into immediate-type DHR (IDHRs) or delayed-type DHRs (DDHRs). IDHRs occur within an hour of drug exposure and are mediated by IgE antibodies generated against the drug or metabolite(s). On the other hand, DDHRs occur days or weeks after drug exposure and are IgG or T-cell-mediated [9,10]. Antibiotics are the most commonly prescribed

drugs in children and they are the second leading cause of ADRs resulting in emergency department visit and/or hospital admission in children (18%) after cancer chemotherapy [11,12,13]. DHRs represent a major clinical problem because of their potential seriousness and high morbidity. In addition, labeling a child with antibiotic allergy without confirmation has its consequences to both the patient and public health [14]. Approximately 10% of children are reported by their parents to have antibiotic allergy and 75% of them are diagnosed before their third birthday [15,16]. Unfortunately, this is frequently incorrect and over-Labeling of antibiotic allergy has been demonstrated to have a negative health impact both on the patient and the health care system. Unconfirmed childhood allergy labeling most often extends to the rest of the patients' life leading to unnecessarily depriving them from useful and safe drugs and exposing them to less safe and more expensive alternatives. In fact, studies have shown that when labeled children are challenged with the culprit drug, over 90% are able to tolerate the drug [17,18,19]. Current data shows that up to 10% of children are reported to have beta-lactam allergy and are the most common trigger of anaphylactic reactions in children [1,20]. The risk of fatal anaphylaxis due to penicillin use has been estimated at 0.0015–0.002% of treated patients [21,22]. Up to 75% of fatal drug-induced anaphylaxis in the United States are caused by penicillins, which corresponds to 500–1,000 annual fatality [23-26].

Prescribing medicines to children is challenging due to the lack of reliable safety data as a result of the limited number of clinical trials in the pediatric population. One example is dose. Dose calculation for pediatric patients based on weight and body surface area (BSA) can be both inaccurate and prone to errors. Children are not merely little adults; they have their own unique pharmacokinetics and pharmacodynamics and these parameters change dramatically especially during the first few years of life [27-31]. Dose estimation from adult studies can be extrapolated with allometric scaling but this may not always result in an optimal or safe dose due to the variability imposed by ontogeny.

In addition, "the pharmacological interaction of drugs with the immune system (p-i) hypothesis" postulates that drugs or their metabolites can directly and non-covalently interact and activate immune cells causing DHRs. Evidence also exist that supports the concept of drug-induced alteration in the self-peptide repertoire presented in the context of the major histocompatibility complex (MHC) molecules by antigen presenting cells to T-cells. This has provided explanation as to the role of human leukocyte antigen (HLA) genetic variation in the pathophysiology of DHRs (e.g., abacavir-induced DHRs). Understanding DHRs pathophysiology is crucial to the development and interpretation of in vitro tests for drug hypersensitivity as discussed further below.

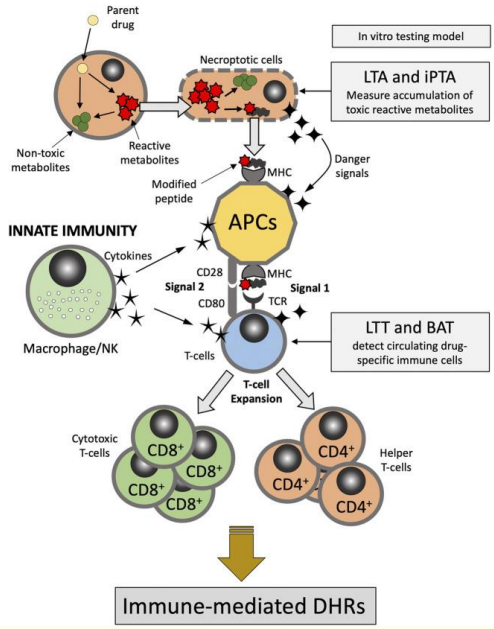

FIGURE 1

Pathophysiology of delayed-type DHRs. APC, antigen presenting cells; BAT, basophil activation test; DHRs, drug hypercreativity reactions; iPTA, *in vitro* platelet toxicity assay; LTA, lymphocyte toxicity assay; LTT, lymphocyte transformation test; MHC, Major histocompatibility complex; NK, natural killer; TCR, T-cell receptor.

Pathophysiology of delayed-type DHRs. APC, antigen presenting cells; BAT, basophil activation test; DHRs, drug hypercreativity reactions; iPTA, in vitro platelet toxicity assay; LTA, lymphocyte toxicity assay; LTT, lymphocyte transformation test; MHC, Major histocompatibility complex; NK, natural killer; TCR, T-cell receptor.

Modeling in Drug Therapy

Many drug regulatory agencies around the world have recently issued mandates to promote drug development for children use that is evidence-based [31,32]. However, conducting a large-scale detailed pharmacokinetics/pharmacodynamics (PK/PD) trials in children is a huge undertake even for major pharmaceutical companies and might not be feasible. In the United States, The Best Pharmaceutical for Children Act (BPCA), which became a law in 2002, has been put forward to encourage the pharmaceutical industry to perform studies to improve evidence-based pediatric drug therapy (NICHD, 2020). Model-based studies and application of simulation and pharmacometrics for pediatric therapy has gained momentum in recent years (Vinks et al., 2015). Pharmacometrics applies quantitative mathematical models of physiology, pharmacology and pathology to predict pharmacokinetics (PK) and pharmacodynamics (PD) parameters for the purpose of assessing drug efficacy and safety (Barrett et al., 2008). This recent concept has been applied in pediatrics to evaluate the influence of growth and development on drug disposition and toxicity (Anderson et al., 2006). However, data supporting model-based evaluation of antimicrobial-induced hypersensitivity reactions has been scarce and current guidelines do highlight this problem [33-34].

Thus, the model system employed should be tailored around the putative pathogenesis of the ADR of interest (Figure 1). The principle of the lymphocyte toxicity assay (LTA) and the in vitro platelet toxicity assay (iPTA) tests is based on the hypothesis that DHRs are developed as a result of accumulation of toxic reactive metabolites (RMs) resulting in induction of necroptosis and release of intracellular “danger signals”, and haptenation of endogenous peptides that can be recognized by the immune system [35]. The LTT and BAT tests detect circulating drug-specific immune cells (lymphocytes and basophil, respectively), which are thought to mediate the immune reaction [36-39]. Role of the in vitro testing model is discussed further below.

In vitro Testing Model

In vitro testing for DHRs has the advantage of carrying no potential harm to patients [40,41]. The selection of an in vitro diagnostic test for DHRs depends on the type of reaction (i.e., immediate vs delayed). Immediate IgE-mediated reactions are mediated by a specific IgE against the culprit drug and, therefore, quantification of those antibodies has been used to diagnose this type of reactions. Radioallergosorbent test (RAST), cellular fluorescent assay-IgE (CAP-IgE) and enzyme-linked immunosorbent assay (ELSA) have a good predictive value. A radioactive technique is no longer used but, “RAST” has become generic name for IgE quantification. These tests tend to have an excellent specificity but very poor sensitivity and have been validated only for a few very specific drug-induced reactions (i.e., classical allergy or Gell and Coombs Type I Hypersensitivity) and only for a few drugs [41,42]. The basophil activation test (BAT) has been found useful in diagnosing immediate-type reactions to muscle relaxants, beta-lactam antibiotics and NSAIDs [43]. The lymphocyte transformation test (LTT) measures drug specific T-cells in the circulation and it has been found to useful to aid diagnosis of delayed-type hypersensitivity reactions. However, due to its complected and expensive procedure, its clinical utility has been limited to highly sophisticated research center.

Conclusion

In terms of drug development, use of modeling for assessment of drug safety for antimicrobials has been hampered by both a lack of suitable animal models and by a lack of understanding of the putative pathophysiology of DHRs. As our understanding of the fundamental biology of DHRs expands and our ability to develop humanized animal increases it is hoped that this will enable better modeling of DHRs to antimicrobial therapy in children. This review summarizes the current state-of-the-art knowledge of model-based evaluation of DHRs to antimicrobials in children. Several key issues in the field have been highlighted, which include lack of animal model to study the molecular pathophysiology of DHRs and limited validated in vitro tests with good predictive values. We believe that further understanding of the exact pathophysiology underlying DHRs will allow the development of more predictive models to optimize the management of these ADRs.

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