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Commentary

Classifying ADRs – does dose matter?

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Adverse drug reactions (ADRs) were originally defined as unintended responses to drugs that occur at doses used in treatment or prevention of disease. In some jurisdictions this has now been extended to include medication errors and unauthorized use of drugs such as drug abuse and misuse. For almost four decades a widely accepted classification has divided ADRs into type A reactions that are the result of augmented effects of the usual pharmacological action of the drug and therefore thought to be dose related, predictable and preventable reactions, and type B 'bizarre or idiosyncratic' ADRs that are exemplified by reactions which are less dependent on drug dose and unpredictable based on the pharmacological action of the drug [1]. The paradigm shift over the last 10 years has been recognition that predisposition to type A reactions is dependent both on dose and genetic factors and that the less prevalent type B reactions which include immunologically-mediated reactions can be both dose-related and predictable based on a defined effect outside of their primary pharmacological action (Figure 1). Hence as we increasingly move into the complex therapeutic arena of using small and large molecule drugs with complex on and off target effects, more contemporary classifications of ADRs which do not distinguish drug reactions based on their dose dependency, predictability or genetic basis are becoming more relevant and useful (Figure 1).

In thinking about dose dependency and laws of mass action not all immunologically mediated reactions are created equally. Although a certain threshold of exposure is required to prime an individual to both B-cell (IgE mediated) and T-cell mediated drug reactions the kinetics and dose responsiveness of these reactions is distinct. In the most extreme case of anaphylaxis, for instance, the immune system has been primed to recognize extremely small amounts of antigen which are highly effectively amplified through IgE leading to mast cell activation and culmination of a severe clinical phenotype through mediators such as histamine, leukotrienes, platelet activating factor, tumour necrosis factor and other cytokines. It was largely this exquisite sensitivity of patients with drug specific IgE to miniscule doses of drug, which gave rise to the concept of dose independence. It is noteworthy that non-IgE mediated mast cell activation associated with drugs such as vancomycin, opioids, fluoroquinolones and neuromuscular blocking agents can result in anaphylaxis-like reactions without prior drug sensitization which unlike IgE-mediated reactions do occur in a dose dependent fashion. The mechanisms for such reactions occurring with drugs such as NMBA and fluoroquinolones may be due to dose-dependent activation of specific G-protein coupled receptors on mast cells which leads to direct mast cell activation [2].

The dose-dependency of T-cell mediated reactions is evident both *in vivo* and *in vitro*. More recently this has been elegantly demonstrated with drugs like abacavir which causes a drug hypersensitivity reaction that is CD8 + T cell dependent and restricted by the class I MHC allele, HLA-B*57:01. In the clinic we saw the intensity of hypersensitivity symptoms increase after abacavir dosing with rapid offset of symptoms following abacavir discontinuation. This concentration effect was further reproduced *in vivo* with dose responsiveness seen on abacavir patch testing and *ex vivo* in ELISpot assays [3, 4]. It is now known that the specific mechanism by which abacavir causes hypersensitivity is through concentration dependent, non-covalent interactions with HLA-B*57:01 [5–7]. This interaction of abacavir with HLA-B*57:01 alters the repertoire of self-peptides bound and recognized by T-cells [5–7]. The crystal structure of abacavir bound to peptide and HLA-B*57:01 has now been solved [5–7]. The occurrence and severity of other HLA-restricted, T-cell mediated reactions such as allopurinol associated Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) is related to accumulation of the long-acting metabolite, oxypurinol, which occurs in the setting of renal failure [8]. More recent examples of phenytoin SJS/TEN/DRESS and nevirapine DRESS suggest that genetic variation in specific CYP enzymes leading to delayed clearance of the parent drug predispose to these reactions [9, 10]. For example, in the case of phenytoin the occurrence and severity of SJS/TEN/DRESS in Asian populations was associated with both CYP2C9*3 and phenytoin concentrations [9].

Drug transporters and drug metabolizing enzymes likely evolved to protect man against xenobiotics and other

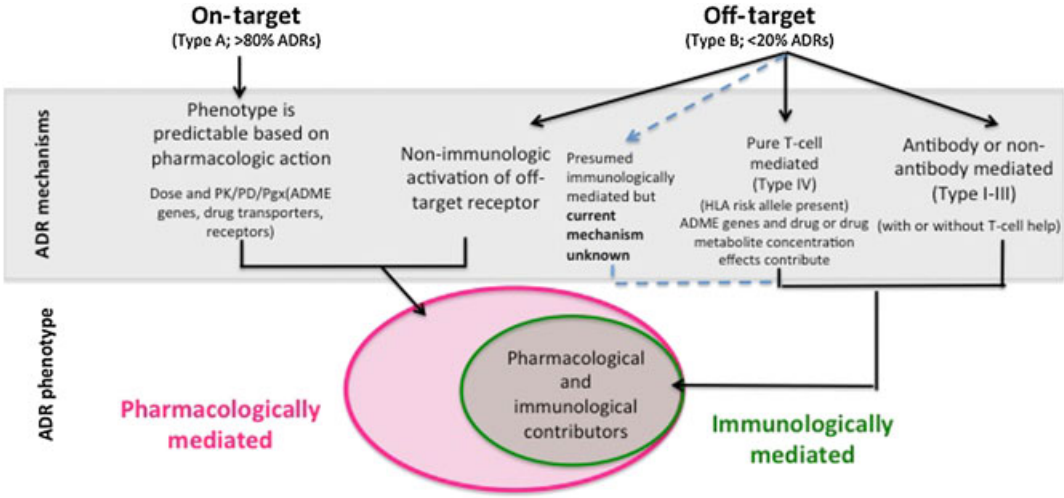

Figure 1

Classification of adverse drug reactions, Here adverse drug reactions are classified according to their on-target *vs*. off-target interactions between the drug and cellular components. Both on-target and off-target effects can demonstrate concentration–exposure relationships that may differ between individuals based on acquired or genetic host factors. The interaction between the drug and the target may relate to both the dose and/or duration of treatment. On-target reactions generally relate to an augmentation of the pharmacological action of a drug and off-target effects can occur by both immune mediated and non-immune mediated mechanisms (adapted from White *et al*. [13])

dangerous environmental exposures and these selective pressures have driven differential polymorphism of these proteins in different ethnically diverse and geographically separated populations [11]. It is therefore unsurprising, as Aronson *et al*. [12] point out, that not all individuals are equally at risk for ADRs at the doses of drugs usually prescribed. It is important to also emphasize that ecologic factors, such as organ function, disease states, pregnancy as well as pharmacogenomic factors are important drivers of interindividual differences in the pharmacokinetics and pharmacodynamics. It is therefore the combination of genetic and ecologic factors that leads to differences in drug exposure and response and both need to be incorporated into current strategies to study and implement individualization of drug therapy.

The review by Aronson *et al*. [12] highlights the imprecision of dose dependency as a criterion to categorize ADRs and the need to reformulate how they are classified. Drugs thus have on-target effects that are related to their primary pharmacological mode of action as well as off-target effects and the effect of drug dose and drug exposure is important for each of these. In addition, as we are now able to characterize the pathogenesis of many off-target ADRs the term 'idiosyncractic' has become erroneous. In cases where the pathogenesis of the ADR is as yet unknown marked intensification of an ADR on second exposure to the drug suggests immunological memory (Figure 1). It is now possible to predict many serious off-target ADRs by modelling drug–receptor interactions and in the case of immunologically-mediated reactions by identifying the immunopathogenesis of these reactions and their immunogenetic basis [13]. Success stories in prediction that have been translated into routine clinical practice to prevent morbidity and mortality from ADRs include HLA-B*57:01 screening to prevent abacavir hypersensitivity and HLA-B*15:02 screening in Southeast Asians to prevent carbamazepine SJS/TEN [14, 15]. In addition to advances in the prediction and prevention of off-target adverse drug effects, identification of these 'off-target effects' is also now also being used in positive ways to repurpose old drugs for new indications.

Competing Interests

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