

Multiple Drug Allergy

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Opinion statement

The tendency to develop multiple drug hypersensitivity (MDH), defined as a hypersensitivity to two or more structurally unrelated drugs, occurs in up to 10% of people who have a severe and proven immune-mediated drug hypersensitivity reaction (DHR). There are two subtypes of MDH: in the first type, MDH develops if different drugs are administered simultaneously; in the second, MDH develops if different drugs are administered sequentially, sometimes years apart. MDH presents clinically as immediate and/or non-immediate reactions. The main drugs responsible for MDH are antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), antiepileptics, hypnotics, antidepressants, corticosteroids, and local anesthetics. There are two pathogenic mechanisms of developing MDH: the first is T cell mediated and the second is IgE mediated. Activated T cells are directed against the culprit drug or its metabolites. MDH can be proven by positive responses to patch tests and/or delayed-reading intradermal tests as well as a positive lymphocyte transformation test. During the first DHR, the immune stimulation may lower the threshold of T cell reactivity to that drug and facilitate the immune response to the second drug, similar to viral infections. The drug-reactive T cells in patients with MDH display an enhanced state of activation. Less frequently, the pathogenic mechanism is IgE mediated. This can be proven by positive responses to an immediate-reading intradermal test and provocation test, as well as with positive specific IgE to culprit drug and a basophil activation test (BAT). A T cell-mediated reaction might be built on the IgE-mediated reaction. It is well-known that the tolerance mechanism to small molecular compounds fails in MDH patients, although the pathogenic mechanisms of this syndrome are still unknown.

Introduction

Drug hypersensitivity reactions (DHRs) are adverse reactions to drugs that are clinically and functionally heterogeneous [1]. Different sub-classifications have been proposed, based on the time of appearance of symptoms or type of immune mechanism involved.

There are three mechanisms that can be delineated: (1) allergic/immune reaction: some drugs have or gain the ability to bind covalently to proteins and form new antigens, and thus elicit immune reactions to hapten-carrier complexes; (2) pharmacological

interaction with immune receptors (p-i reactions): a substantial part of the immune-mediated DHR is due to a typical off-target activity of drugs on immune receptors such as human leukocyte antigen (HLA) and T cell receptors (TCRs); and (3) pseudo-allergy: symptoms of DHR can also appear if the drug stimulates or inhibits receptors or enzymes of inflammatory cells [2••].

Classification of Drug Hypersensitivity Reactions

In clinical practice, it is very important to classify DHRs as immediate or non-immediate according to the time interval since the last drug ingestion and the occurrence of the reaction. If reactions occur within the first hour of the last drug intake, it is an immediate reaction; these reactions are IgE mediated. Manifestations of immediate reactions are urticaria, angioedema, bronchospasm, rhinitis, conjunctivitis, gastrointestinal symptoms, and anaphylactic shock. This type of reaction can be proven by a positive response to an immediate-reading intradermal test and provocation test, as well as with positive specific IgE to the culprit drug and basophil activation test (BAT). If reactions occur more than 1 h after the last drug ingestion, it is a non-immediate reaction; these delayed reactions are T cell mediated. Manifestations of non-immediate reactions are maculopapular exanthemas and delayed appearing urticaria and/or angioedema, and as well as rare, severe reactions such as fixed drug eruption (FDE), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), and drug reactions with eosinophilia and systemic syndrome (DRESS). These reactions can be proven by positive responses to patch tests and/or delayed-reading intradermal tests as well as positive lymphocyte transformation tests (LTTs) and flow cytometric lymphocyte activation tests. Provocation tests are also necessary in the evaluation of non-immediate hypersensitivity reactions because the sensitivity of allergy skin tests is not 100%. Drug provocation tests are contraindicated in severe reactions such as SJS, TEN, DRESS, AGEP, FDE, etc. In non-allergic hypersensitivity reactions to drugs, inflammatory mediators are released by non-specific immunologic mechanisms. Non-steroidal anti-inflammatory drugs (NSAIDs) are most often responsible for this type of reaction. Provocation tests with the suspected drug are essential because skin tests and in vitro tests are usually negative [3••, 4–6, 7•, 8, 9].

Multiple drug hypersensitivity

Multiple drug hypersensitivity (MDH), first recognized in 1989 by Sullivan et al. [10], is defined as a hypersensitivity to two or more structurally unrelated drugs. There are two subtypes of MDH: in the first type, MDH develops if different drugs are administered simultaneously; in the second type, MDH develops if different drugs are administered sequentially, sometimes years apart [11]. MDH present clinically as immediate and/or non-immediate reactions. The drugs most commonly responsible for the development of MDH are antibiotics, NSAIDs, antiepileptics, hypnotics, antidepressants, corticosteroids, and local anesthetics [11, 12•, 13–23].

In some studies [11, 16, 19, 22], a T cell-mediated pathogenic mechanism of MDH was demonstrated in adults by positive patch tests, delayed-reading intradermal tests, and/or LTT and drug-induced interferon- γ release. Pichler et al. [24] found that the immune stimulation during the first DHR may lower the threshold of T cell reactivity to drugs and facilitate the immune response to the second drug, similar to viral infection. Daubner et al. [22] showed that the drug-reactive T cells display an enhanced state of activation in patients with MDH. In other studies, a positive autologous serum skin test (ASST) and/or autologous plasma skin test (APST) indicated an autoreactivity in adults with MDH [18, 20], which does not seem to be caused by functional circulating autoantibodies directed against IgE or Fc ϵ RI.

MDH should be differentiated from flare-up reactions, which occur in patients with an existing drug allergy whose therapy is changed to a second drug (early switch of therapy) but who still have a highly activated immune system. The second drug may worsen the current drug allergy in the form of appearance of more skin symptoms, elevation of liver enzymes, and a sudden increase in body temperature. These symptoms usually occur 1–2 days after starting a new drug. The appearance of new symptoms requires withdrawal of the second drug, and this then confirms the existence of allergies to both drugs. These reactions are common in patients with systemic drug allergies, drug-induced hypersensitivity syndrome (DiHS), and DRESS. In this condition, the T cell immune system is massively activated and these patients have a higher tendency to react to a new drug and might show a flare-up of their exanthema in reaction to a new drug. In remission, there are two possibilities regarding a second drug: (1) the second drug may remain negative in skin tests and might also be well-tolerated, because the co-stimulatory conditions do not exist anymore; or (2) a second sensitization to the second drug persists [24, 25].

So far, there are only four studies that have described MDH in children [12•, 13, 15, 21], two of which have described only hypersensitivity reactions to antibiotics [13, 15]. In the study by Park et al. [15], the diagnosis of multiple antibiotic hypersensitivity was based only on the patients' history, and 97 children did not undergo allergy tests. Kamada et al. [13] studied 120 children with multiple antibiotic hypersensitivity. In their study, only 98 of 115 children with a history of β -lactam hypersensitivity underwent allergy tests, and 31 had positive results. Adverse reactions to three classes of antibiotics were noted in 22 children. In two children, adverse reactions to four or more antibiotic classes were noted. The most frequent reactions were urticarial and polymorphous rash [13]. Buonomo et al. [21] studied 278 children with a history of MDH, and hypersensitivity was diagnosed in six children (2.2%); 64 (23.5%) of the remaining 272 children had negative results in the allergy work-up, although they had a history of adverse reactions to three drugs. In both the studies by Kamada et al. [13] and Buonomo et al. [21], challenges with the culprit drugs were not performed in children with negative results in allergy tests. In the study by Atanasković-Marković et al. [12•], MDH was diagnosed in seven (2.5%) of 279 children based on whole allergy work-up. Sensitivity to two chemically unrelated drugs was diagnosed in six children, while sensitivity to three chemically different drugs was diagnosed in only one child. Of the seven children with MDH, two had the first subtype (different drugs administered simultaneously), while five children had second subtype (different drugs administered sequentially). The main responsible drugs were antibiotics and NSAIDs, and the

most frequent reactions were maculopapular and urticarial rash. In five children, a T cell-mediated hypersensitivity was diagnosed by positive patch tests with the culprit drugs, two children were positive to immediate reading intradermal tests, and five children had negative results in allergy skin tests but positive drug provocation tests. The reactions observed after drug provocation tests were similar or identical to those reported in the history.

Results of the study by Atanasković-Marković et al. [12•], and those of other studies performed in adults [11, 16, 19, 22], demonstrate that a T cell-mediated pathogenic mechanism plays an important role in MDH. Gex-Collet et al. [11] presented seven adults with MDH who had documented positive LTT and patch tests to different drugs. Atanasković-Marković et al. [12•] showed that five of seven children with MDH were positive to patch tests with the culprit drugs. The study by Atanasković-Marković et al. [12•] and data from the literature suggest that an IgE-mediated reaction is less involved in the development of MDH. In addition, in that study only two of seven children with MDH had positive immediate-reading intradermal tests.

An IgE-mediated reaction might be followed by a T cell-mediated reaction. The pathomechanism of this syndrome is still unknown, but it is assumed that the tolerance mechanism to small-molecule compounds fails in these patients [25]. However, in the experience of Pichler et al. [24], multiple T cell reactions with distinct clinical pictures developed, but not IgE and T cell reactions together. On the other hand, Atanasković-Marković et al. [12•] noted a child who had had a T cell-mediated reaction to phenobarbital and an IgE-mediated reaction to amoxicillin.

Patients with severe symptoms of drug hypersensitivity may have a higher chance of developing a second drug allergy. In the study by Neukomm et al. [16], four of 44 patients with a very clear history of drug hypersensitivity, with positive LTT and skin patch test, showed sensitizations to more than one drug. They estimated that the tendency to develop MDH occurs in up to 10% of people with severe and proven immune-mediated DHR. That means that if patients with a previous severe drug hypersensitivity receive potentially sensitizing compounds such as antiepileptics or antibiotics, they may be at higher risk for another drug hypersensitivity, and therefore they should be carefully monitored [11, 26]. This was also confirmed in a study by Kanny et al. [27] in which six of 12 patients with well-documented delayed hypersensitivity to radio contrast media had had a previous drug allergy.

Daubner et al. [22] showed that a defect in the regulatory T cells (Foxp3+) cannot be detected in patients with MDH. In patients with MDH, drug-reactive T cells were found in the CD4⁺ CD25^{dim} T cell fraction and showed enhanced CD38 and PD-1 expression. The drug-reactive CD4⁺ T cells also show signs of a pre-activated state. This pre-activation seems to persist for years despite drug avoidance and may explain the enhanced readiness to react to new drugs that are not cross-reactive [24].

Conclusions

Patients with a severe and proven immune-mediated hypersensitivity reaction to drugs may be at higher risk of developing MDH if they receive a potentially sensitizing drug. During the first DHR, the immune stimulation may lower the

threshold of T cell reactivity to the drug and facilitate the immune response to the second drug. In patients with hypersensitivity to two or more structurally unrelated drugs, the drug-reactive T cells display an enhanced state of activation. An IgE-mediated reaction is less involved in developing MDH and might be followed by a T cell-mediated reaction. It is assumed that the mechanism of tolerance to small-molecule compounds fails for these patients. Flare-up reactions should be differentiated from MDH; the T cell immune system is massively activated in flare-up reactions, and these patients have a higher tendency to react to a new drug.

It is very important to perform both in vivo and in vitro allergy testing in patients with a history of MDH. This approach enables us to confirm the diagnosis of MDH in a very small percentage of these patients.

Compliance with Ethical Standards

Conflicts of Interest

Marina Atanasković-Marković declares that she has no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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