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Werner J. Pichler

Approach to the Patient with Drug Allergy **405**

Benno Schnyder

Drug allergies are adverse drug reactions mediated by the specific immune system. Despite characteristic signs (eg, skin rash) that raise awareness for possible drug allergies, they are great imitators of disease and may hide behind unexpected symptoms. No single standardized diagnostic test can confirm the immune-mediated mechanism or identify the causative drug; therefore, immune-mediated drug hypersensitivity reactions and their causative drugs must be recognized by the constellation of exposure, timing, and clinical features including the pattern of organ manifestation. Additional allergologic investigations (skin tests, in vitro tests, provocation tests) may provide help in identifying the possible eliciting drug.

The Pholcodine Story **419**

E. Florvaag and S.G.O. Johansson

Anaphylactic reactions to neuromuscular blocking agents during general anesthesia constitute a major cause of concern and a great source of debate among anesthesiologists. The authors' recent investigations, taking the striking differences of incidence between Norway and Sweden as the point of departure, have provided valuable insights into the pathogenetic mechanisms and the highly uneven geographical distribution of these rare, but dramatic and notoriously unpredictable, events. Eventually, a cough syrup containing pholcodine emerged as the most likely suspect. This new knowledge led to the withdrawal of the drug from the Norwegian market and to the examination of the role of pholcodine-containing drugs in other countries. The present article is a brief summary of the research behind this development.

Perioperative Anaphylaxis **429**

P.M. Mertes, M. Lambert, R.M. Guéant-Rodriguez, I. Aimone-Gastin, C. Mouton-Faivre, D.A. Moneret-Vautrin, J.L. Guéant, J.M. Malinovsky, and P. Demoly

The incidence of immune-mediated anaphylaxis during anesthesia ranges from 1 in 10,000 to 1 in 20,000. Neuromuscular blocking agents represent the most frequently involved substances, followed by latex and antibiotics,

but every drug or substance used may be involved. Diagnosis relies on tryptase measurements at the time of the reaction and skin tests and specific IgE or basophil activation assays.

Immediate and Delayed Reactions to Radiocontrast Media: Is There an Allergic Mechanism?

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Knut Brockow

Radiocontrast media can cause immediate (1 hour) and nonimmediate (>1 hour) hypersensitivity reactions that remain unpredictable and a cause of concern for radiologists and cardiologists. Immediate hypersensitivity reactions resemble anaphylaxis, whereas nonimmediate ones clinically are predominated by exanthemas. Increasing evidence indicates that immediate reactions and nonimmediate skin exanthemas may be allergic reactions involving either contrast media-reactive IgE or T cells, respectively. Skin testing is a useful tool for the diagnosis of contrast media allergy. It may have an important role in the selection of a safe product in previous reactors, although validation data are still lacking. In vitro tests to search for contrast media-specific cell activation are currently under investigation.

Heparin Allergy: Delayed-Type Non-IgE-Mediated Allergic Hypersensitivity to Subcutaneous Heparin Injection

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Axel Trautmann and Cornelia S. Seitz

Itching erythematous or eczematous plaques around injection sites are quite frequent side effects of heparin treatment and clinical symptoms of delayed-type non-IgE-mediated allergic hypersensitivity (DTH) to heparin. For diagnosis, intradermal, patch, and subcutaneous challenge tests with heparins are suitable. In most cases, changing the subcutaneous therapy from unfractionated to low molecular weight heparin or treatment with heparinoids does not provide improvement because of extensive cross-reactivity. Hirudin polypeptides, which exhibit a different chemical structure, are a safe therapeutic alternative for subcutaneous application, however. Importantly, despite DTH to subcutaneously injected heparins, most patients tolerate heparin intravenously. Moreover, in case of therapeutic necessity and DTH to heparins, the simple shift from subcutaneous to intravenous heparin administration without prior testing may be justified.

The Variable Clinical Picture of Drug-Induced Hypersensitivity Syndrome/Drug Rash with Eosinophilia and Systemic Symptoms in Relation to the Eliciting Drug

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Yoko Kano and Tetsuo Shiohara

Drug-induced hypersensitivity syndrome (DIHS)/drug rash with eosinophilia and systemic symptoms (DRESS) is a life-threatening adverse reaction characterized by skin rashes, fever, leukocytosis with eosinophilia or atypical lymphocytosis, lymph node enlargement, and liver or renal dysfunction. The syndrome develops 2 to 6 weeks after initiation of administration of a specific drug. It has been demonstrated that various

herpesvirus reactivations, in addition to human herpesvirus 6, contribute to internal organ involvement and the relapse of symptoms observed long after discontinuation of the causative drugs. A better understanding of the interplay in the development of DIHS/DRESS has implications for safer and more efficient treatment of this syndrome.

Skin Testing for IgE-Mediated Drug Allergy

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Birger Kränke and Werner Aberer

Skin tests with drugs help determine the cause and mechanism of drug hypersensitivity reactions. The diagnosis of adverse drug reactions is based primarily on history and clinical presentation. In type I, IgE-mediated allergic drug reactions, skin prick test and intradermal testing may provide rapid and supportive evidence for diagnosis or exclusion of IgE-mediated reactions. These tests often are more sensitive than laboratory assays for IgE antibodies to drug allergens, which are available only for a few drugs. Because intradermal skin tests occasionally induce adverse events, they should be performed by experienced personnel in an adequate environment.

Skin Testing in Delayed Reactions to Drugs

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Annick Barbaud

Drug skin tests (eg, patch tests, prick tests with delayed readings, intradermal tests [IDT], especially with delayed readings) are used to investigate cutaneous adverse drug reactions (CADR) in delayed hypersensitivity reactions caused by a particular drug. Their value depends on the clinical features of the CADR and on the drug tested. In maculopapular rash (MPR), drug skin tests are of value, beginning with patch tests, and followed: 1) if negative by prick tests (with delayed readings at 24 hours); and, 2) if the injectable form of the drug is available, with IDT with immediate and delayed readings. This article discusses details of the use of patch tests as they apply to patients with various drug reactions. Drug skin tests are useful to study cross-reactivity between suspected drugs. False positive results can occur. The negative predictive value of drug skin tests is approximately 90%.

In Vitro Tests in Drug Hypersensitivity Diagnosis

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Priska Lochmatter, Anna Zawodniak, and Werner J. Pichler

The diagnosis of a drug hypersensitivity reaction (DHR) is a challenging task because multiple and complex mechanisms are involved. Better understanding of immunologic pathomechanisms in DHRs and rapid progress in cellular-based in-vitro tests can help to adjust the correct diagnostic strategy to individual patients with different clinical manifestations of drug allergy. Thus, drug hypersensitivity diagnosis needs to rely on a combination of medical history and different in vivo and in vitro tests. In this article, the authors discuss current in vitro techniques, most recent findings, and new promising tools in the diagnosis of T-cell-mediated drug hypersensitivity.

The Basophil Activation Test in Immediate-Type Drug Allergy

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and Didier G. Ebo

Diagnosis of drug allergy involves first the recognition of sometimes unusual symptoms as drug allergy and, second, the identification of the eliciting drug. This is an often difficult task, as the clinical picture and underlying pathomechanisms are heterogeneous. In clinical routine, physicians frequently have to rely upon a suggestive history and eventual provocation tests, both having their specific limitations. For this reason both in vivo (skin tests) and in vitro tests are investigated intensively as tools to identify the disease-eliciting drug. One of the tests evaluated in drug allergy is the basophil activation test (BAT). Basophils with their high-affinity IgE receptors are easily accessible and therefore can be used as indicator cells for IgE-mediated reactions. Upon allergen challenge and cross-linking of membrane-bound IgE antibodies (via Fc-epsilon-RI) basophils up-regulate certain activation markers on their surface such as CD63 and CD203c, as well as intracellular markers (eg, phosphorylated p38MAPK). In BAT, these alterations can be detected rapidly on a single-cell basis by multicolor flow cytometry using specific monoclonal antibodies. Combining this technique with in vitro passive sensitization of donor basophils with patients' serum, one can prove the IgE dependence of a drug reaction. This article summarizes the authors' current experience with the BAT in the diagnostic management of immediate-type drug allergy mediated by drug-specific IgE antibodies.

Provocation Tests in Drug Hypersensitivity

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Werner Aberer and Birger Kränke

Provocation tests are regarded as the "gold standard" to establish or exclude the presence of hypersensitivity to a certain drug because they reproduce not only allergy symptoms but other adverse manifestations, irrespective of their pathomechanism. Provocation testing is potentially harmful and should be considered only after balancing the risk-benefit ratio in the individual patient. The reasons for false-positive and false-negative results are numerous, including loss of sensitization, cofactors not being included in the diagnostic procedure, and the potential induction of tolerance during provocation. When conducted by experienced clinicians in a carefully monitored setting, however, drug provocation testing is a safe method to confirm or exclude drug hypersensitivity.

Rapid Desensitization for Hypersensitivity Reactions to Medications

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Mariana Castells

Drug desensitization is the induction of temporary clinical unresponsiveness to drug antigens to which patients have presented severe hypersensitivity reactions. It is typically achieved by gradual reintroduction of small doses of drug antigens at fixed time intervals, and it is aimed at providing increased safety and protection from side effects, including anaphylaxis. Delivery of full therapeutic doses is achieved during desensitization, allowing patients to receive firstline chemotherapy, antibiotics, or monoclonal

antibodies, as well as other drugs such as insulin, aspirin, and iron. Desensitizations are high-risk interventions. Inhibition of cellular activation mechanisms occurs during drug desensitization, allowing for the protective clinical outcomes and lack of side effects in the majority of cases, but the cellular and molecular inhibitory mechanisms are incompletely understood. The indication for desensitization protocols can only be done by trained allergists and immunologists and should be implemented as standard of care because of their high success rates and outcomes-demonstrated safety profile.

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