Book review

Drug hypersensitivity

Edited by W. J. Pichler. Published by Karger, Basel, 2007, 460 pages, \$249.25. ISBN-10: 3805582698

This is an important book for all those interested in drug allergies. Werner Pichler has assembled an excellent team of authors, all of whom are authorities in their areas. The book is well organized and contains groups of chapters under the headings, Epidemiology, Basic Mechanisms, Clinical Manifestations, a section which is practically very useful on Diagnosis and Diagnostic Tests and finally a practical guide to Desensitization.

Many works that consider some aspects of adverse drug reactions (ADRs) put it into context by reminding readers of different classification systems. In his Foreword Pichler does not do this, but simply puts all drug hypersensitivity reactions into the Type B (idiosyncratic) group of ADRs. This reviewer agrees with this approach, as attempts to subdivide idiosyncrasies on the basis of whether they are immunological or non-immunological (enzymatic or pseudo-allergic) do not really contribute usefully to the classification.

The opening section on Epidemiology sets the scene on the magnitude of the problem of drug hypersensitivities by summarizing a lot of literature covering the frequency, prevalence and incidence of drug hypersensitivity reactions. A chapter on Risk Factors reviews the genetic associations looking at HLA, immune response genes such as cytokines and their receptors, as well as some drug detoxifying enzymes.

The section on Pathomechanisms starts with a description of how the immune system develops responses to small molecules. The model which has yielded the most information is the experimental contact hypersensitivity system. S. Martins describes the immune response in mice and covers many of the mechanisms at a good level of detail. However, the murine immune system differs from the human counterpart in several respects – thus, in murine models, mast cells, B-1 B cells, $\gamma\delta$ T cells and NKT cells have all been claimed to be important in the manifestation of contact hypersensitivity. The evidence for these mechanisms in human responses to contact sensitizers is generally lacking. Their role in drug hypersensitivity is still totally cryptic. There are some excellent chapters covering how small molecules (drugs and contact sensitizers) become antigens, acting as haptens and binding either to proteins which can be presented via MHC or by direct binding to the framework structure of MHC. An excellent chapter by Cavani and De Pità discusses tolerance mechanisms to small molecular compounds. The authors give a nice overview of the mechanisms by which immunological

tolerance is induced and maintained in mice. There is an educational overview of the different types of regulatory/suppressive T cells, drawing from tolerization studies in which mice are fed immunogens or they are applied to ultraviolet-irradiated skin.

There is a very instructive series of chapters relating to HIV infection and ADRs to the antiretroviral drugs. Chapters like these are where the reader really gains the benefit of the experience of the authors. It would take a lot of reading to gain the overview that is so clearly presented in these chapters. An excellent chapter by Pirmohamed gives a feel of the frequency of ADRs to the range of antiretrovirals. The metabolic explanations are educational. For example, a main contribution to the increased susceptibility to ADRs in HIV+ patients is the reduction in antioxidant defences. The ability of the HIV-1 tat protein (involved in viral penetration into cells) to reduce the intracellular glutathione levels results in increased susceptibility of cells to toxic effects of drugs, leading to cell death by necrosis. This in turn is thought to give danger signals to the immune system. Whereas the toxicity is covered very nicely, it is a pity the immune responses to drugs in HIV+ patients are not included at the same level to give a fuller picture.

This group of chapters is supplemented by a very good account of how Abacavir interacts with HLA-B* 5701 to be presented to T cells. There is also a fascinating account of Nevirapine hypersensitivity investigated in the brown Norway rat model.

An interesting and contemporary topic is that of adverse reactions to biological drugs. Pichler himself gives a very useful account of this area, presenting an overview of information that would otherwise be widely scattered in case reports and potentially obscure, inaccessible clinical journals. The chapter is educational regarding the nomenclature of biological drugs in relation to their content of mouse or human components. The authors have developed a classification based on mechanisms; it will be interesting to see how this classification is adopted into general use and whether it stands the test of time. There is also a series of tables laying out the clinical patterns of ADRs induced by the different agents. Overall, this is a chapter that would be of great value as a freestanding copy in most hospital wards.

There is a section of 13 chapters on the clinical manifestations of drug hypersensitivities. Some of these focus on particular drugs and patterns such as urticaria and anaphylaxis due to antibiotics, drugs used in anaesthesiology

and contrast media. Three chapters cover different patterns of skin reactions from maculopapular rashes to Stevens–Johnson syndrome and toxic epidermal necrolysis. There is an excellent chapter on viral reactivation in drug hypersensitivity. This is a feature to which many clinicians dealing with severe drug reactions have still to be alerted. The recognition that members of the herpes family, including human herpesvirus-6, -7, cytomegalovirus and Epstein–Barr virus, can suddenly become activated is of great importance in the management of patients with severe drug hypersensitivities. The viral reactivation often occurs just as the patient is starting to recover from a severe reaction. This plunges the patient back into a crisis with leucocyte/lymphocyte counts either dropping precipitously or shooting up the scale, raising anxieties about new bacterial infections. In addition, these changes are accompanied by critical dysfunction in many organ systems. It is important that the syndrome is recognized and appropriate treatment started with antivirals such as Ganciclovir.

There is a group of chapters covering specific organ involvement in hypersensitivity reactions, including liver, kidney and blood systems, and there is a chapter on Allergy and Pseudoallergy to drugs and vaccines in children.

Drug hypersensitivity reactions present to virtually all hospital clinical departments, yet there is still remarkable uncertainty among the medical teams on how to approach the diagnosis of these conditions and how to identify the culprit drug. There is a good chapter by A. Bircher on how to assess patients with drug hypersensitivity reactions. Annik Barbaud gives an excellent account of how to do

skin tests – prick tests, patch tests and intradermal tests. She also reviews evidence on the usefulness of the tests in the different types of clinical reactions. *In vitro* tests to determine drug-induced T-cell activation are described by Beeler and Pichler. The problem with such tests is that, apart from their general lack of availability, the question of when, in relation to the adverse drug reaction, they can be used to detect positive responses is also important and is discussed. One of the problems with tests of T-cell activation is that they take time – lymphocyte proliferation takes 7–9 days to deliver results. Shorter duration assays, including release of cytokines and expression of cell surface markers such as CD69, are described. The use of basophil activation and degranulation tests is described in relation both to immediate type hypersensitivity and non-immunological intolerance reactions.

Finally, the book closes with chapters on desensitization with antibiotics and drugs used in oncology.

The one small adverse comment that can be made about the book is one of the style in diagrams and figures. Diagrams are totally heterogeneous in their approach and there does not seem to have been an editorial attempt to achieve a standardized style. Indeed, some figures look as though they were constructed by an amateur using Powerpoint for the first time. One might have imagined the publisher would have helped improve their quality. However, this is a very minor detraction from the book, which is a really important and welcome contribution to the field. This book is a ‘must have’ for everyone involved with and dealing with drug hypersensitivities, whether as clinicians caring for patients or as researchers investigating these problems.

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