

# 3rd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV



23-26 October 2001, Athens, Greece

## Pathogenesis of drug hypersensitivity reactions

**Antiviral Therapy 2001; 6(Suppl. 4):9 (abstract no. 11)**

M Pirmohamed

*Department of Pharmacology and Therapeutics, the University of Liverpool, Liverpool, UK*

---

Drug hypersensitivity reactions are one form of type B or idiosyncratic drug reactions. Overall, they are thought to account for about 20% of all adverse drug reactions. In most cases, the pathogenesis of hypersensitivity reactions is unclear. The involvement of the immune system is surmised from the clinical manifestations, which may include rash, fever and eosinophilia. In addition, extra-cutaneous organs may also be involved either in isolation or in combination with the above. Typically, rechallenge leads to recurrence of the reaction, which may be quicker in onset and more severe than the primary reaction. In HIV patients, this is typified by abacavir hypersensitivity reactions. The metabolism of the parent drug to chemically reactive (or toxic) metabolites is thought to be important in the pathogenesis of drug hypersensitivity. Such chemically reactive metabolites can bind to proteins and by acting as haptens initiate an immune reaction. Recently, the hapten hypothesis of drug hypersensitivity has been challenged by the demonstration that an immune response can be directed towards the parent drug through a pathway that is MHC-restricted, but processing- and metabolism-independent. Which pathway is important *in vivo* is unclear, but it is likely that both may be important and should be regarded as complementary mechanisms by which drugs induce hypersensitivity reactions. It is interesting to note that drug rashes have been estimated to be 100 times more common in HIV-positive patients than in the general population. The reasons for this are not clear, but are likely to be multifactorial, and include changes in drug metabolism, oxidative stress, cytokine profiles and immune hyperactivation. HIV itself may also serve as a danger signal, leading to the development of an immune response rather than tolerance. Drugs implicated in causing hypersensitivity have changed since the advent of highly active antiretroviral therapy, largely as a result of: (i) a decrease in the use of antimicrobials such as co-trimoxazole; and (ii) the introduction of new drugs of different classes including abacavir, non-nucleoside reverse transcriptase inhibitors such

as nevirapine, and protease inhibitors such as amprenavir. Another factor that needs to be considered in the pathogenesis of these reactions is the issue of individual predisposition, which may be genetically determined. Genetic predisposing factors may reside in either the pathways controlling drug metabolism and/or the immune response. It is likely that predisposition to the hypersensitivity reactions is going to be polygenic in nature. Thus, in summary, the pathogenesis of drug hypersensitivity reactions is complex and multifactorial, and still not completely understood. Further research is needed not only to identify the mechanisms of drug hypersensitivity, but also the reasons why such reactions are more common in HIV-positive individuals. An understanding of the mechanisms is essential in order to develop evidence-based avenues to predict and prevent the occurrence of these potentially life-threatening adverse drug reactions.

011023  
11

Copyright © 2001 - [International Medical Press Ltd.](#) Reproduction of this abstract (other than one copy for personal reference) must be cleared through the International Medical Press Ltd. 2-4 Idol Lane, London EC3R 5DD UK.