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Tolerance induction in hypersensitivity reactions from drugs: a brief overview

Drug hypersensitivity reactions can occur with many drugs, are unpredictable, may affect any organ system and range widely in clinical severity from mild pruritus to exanthems to anaphylaxis. In most cases, the suspected drug must be avoided in the future. However, for certain patients, the particular drug may be essential for an optimal therapy. Under these circumstances, desensitization may be performed.

Key words: desensitization, drug hypersensitivity, tolerance induction

Drug hypersensitivity reactions can occur with many drugs, are unpredictable, may affect any organ system, and range widely in clinical severity from mild pruritus to exanthems to anaphylaxis. In most cases, the suspected drug must be avoided in the future. However, for certain patients, the particular drug may be essential for an optimal therapy. Under these circumstances, desensitization may be performed. It should be clearly differentiated between immediate type and delayed type hypersensitivity reactions. In the former this possibility is increasingly used [1], whereas in delayed exanthems the data is much scarcer. An extensive review has been recently published [2].
Therefore it is not a question of "yes or no", or "pro or con", but in which patients, with which type of adverse reaction, depending on the underlying pathomechanism and type of drug, such a procedure may be considered.

Definitions

Terminology considerably varies among different papers and in intensive discussions among experts experienced in the procedures some agreement has been reached and the following terminology has been proposed [2].
The term drug desensitization is generally used for the induction of a temporary state of tolerance to a compound responsible for a hypersensitivity reaction. It is performed by administering increasing doses of the medication concerned over a short period of time (from several hours to a few days) until the total cumulative therapeutic dose is achieved and tolerated. It is a high-risk procedure used only in patients in whom alternatives are less effective or not available after an acceptable risk/benefit analysis [1] (*table 1*).
In the context of diagnostic and therapeutic procedures in drug hypersensitivity reactions, different terms and definitions have been used, which are sometimes overlapping. Here we propose the following definitions:

Drug tolerance

This term defines a state in which a patient with drug hypersensitivity will tolerate a drug without an adverse reaction. The exact duration of the tolerance after desensitization in delayed drug hypersensitivity is unknown and may depend on the type of reaction, the drug and on patient-related factors. Drug tolerance neither indicates a permanent state nor that an immunologic mechanism can be demonstrated [3].

Table 1. Criteria and contraindications for desensitization in delayed hypersensitivity (according to Scherer, Brockow [2] and Cernadas, Brockow [1])

Considerations if desensitization might be indicated:
Drug therapy is essential
Drug is irreplaceable, more effective than alternatives or it has a unique mechanism
Unavailability of a non-cross-reacting drug
Previous reaction is clinically well documented
Previous reaction is not severe, e.g. maculopapular exanthema or fixed drug eruption
Pathomechanism is preferably identified after allergological workup
Benefits outweigh the potential risks
Contraindications:
Absolute:
Severe or life-threatening drug-induced diseases like SJS/TEN, DHS/DIHS/DRESS, signs of vasculitis, severe mucosal involvement
Drug-induced autoimmunity
Drug-induced general symptoms, such as drug fever, arthritis, generalized lymphadenopathy
Drug-induced organ involvement, such as hepatitis, nephritis, pneumonitis or cytopenia (platelets, lyphopenia, granulocytopenia), severe eosinophilia
Relative (after careful consideration):
Acute generalized exanthematous pustulosis
Preexisting clinical autoimmunity
Preexisting severe renal, hepatic, cardiac or respiratory dysfunction
Simultaneous treatment with potentially interfering drugs

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Treating through

"Treating through" is the continuation of a drug treatment in the presence of a drug hypersensitivity reaction. In some situations, patients have been treated through e.g. in a mild exanthema, sometimes under cover of anti-allergic medication such as corticosteroids and antihistamines [4-9], with or without dose reduction.

Provocation, Re-exposure, Graded drug challenge, Incremental test dosing, Dechallenge/Rechallenge

These terms have sometimes been used in the context of desensitization procedures. However, we consider them as diagnostic procedures, which are applied to confirm or exclude drug hypersensitivity [10, 11] and not to induce tolerance to the drug [1, 12].

Desensitization, Hyposensitization, Tolerance induction, Adaptive deactivation

These terms are used for procedures describing the induction of a clinical tolerance to a drug responsible for a previous hypersensitivity reaction. Here the term tolerance is used more in the sense of pharmacological tolerance and should not be confused with the same term used in immunology. In contrast to de-/hyposensitization with peptide allergens such as aeroallergens or hymenoptera venoms, in drug desensitization with xenobiotics there is usually only a state of temporary tolerance, as long as the patient is treated with the pharmacologically active substance [1]. After the cessation or interruption of the treatment, drug hypersensitivity may recur within some days, i.e. requiring a new course of desensitization [2].

Indications

As outlined in review articles [1, 2], drug desensitization can be considered when: (1) the drug concerned is irreplaceable (e.g. penicillin in pregnant women with syphilis or platinum salts in patients with platin-sensitive ovarian cancer); (2) the drug concerned is more effective than the alternatives (e.g., an antibiotic in cystic fibrosis or tuberculosis, cotrimoxazole in HIV-positive patients for *Pneumocystis jirovecii* prevention, aspirin in patients with cardiovascular complications), or it plays a particular role in the pathomechanism in a disease (e.g. aspirin in aspirin-exacerbated respiratory disease). [1]

Contraindications

Desensitization to culprit drugs should generally not be performed in patients at increased risk due to a co-morbidity, such as those with uncontrolled asthma (FEV1 < 70% of normal value), hemodynamically unstable ones, or those with uncontrolled cardiac diseases. In patients treated with beta-blockers and subjects who have experienced severe anaphylaxis, as well as in patients with hepatic, renal, or other diseases, in which exposure might provoke a potentially harmful complication, desensitization should also only be considered after a careful individual risk/benefit evaluation. Desensitization is absolutely contraindicated in patients who have experienced severe, potentially life-threatening reactions such as vasculitis, or bullous skin diseases such as SJS/TEN, and DIHS/DRESS, cytopenias, and internal organ involvement [10, 13-17].

Protocols

Immediate hypersensitivity reactions

Most desensitization protocols have been developed for immediate type reactions and are used in patients with allergic reactions to antibiotics (mainly penicillin), insulins, sulfonamides, chemotherapeutic and biologic agents, aspirin and many other drugs [18-26]. Desensitization is mainly performed in IgE-mediated reactions, but also in reactions where drug-specific IgE have not been demonstrated [1]. Desensitization induces a temporary tolerant state, which can only be maintained by continuous administration of the medication. Thus, for treatments like chemotherapy, which are typically given in intervals of 4 weeks between cycles, the procedure must be repeated for every new course [1].

Delayed hypersensitivity reactions

While desensitization is better documented in immediate reactions, an analogous procedure in delayed reactions, some of them T cell mediated, is controversial [2].
Although efficacy, at least in a few successfully treated cases, has been documented, its mechanism of action is not elucidated. In most reports of successful desensitization in delayed hypersensitivity, a preexistent sensitization has not been documented and to the best of our knowledge, in the few cases of documented sensitization, no investigation on the post interventional status of sensitivity has been performed. Thus many cases of successful desensitization may represent a low-risk re-exposure of patients who were not truly sensitized.
Despite the pathophysiology being often ill defined, it is sometimes possible to induce a state of temporary tolerance to the drug causing a hypersensitivity reaction. This can be achieved by the administration of increasing doses of the offending drug over an extended period of time until the therapeutic dose is reached.
However, if at all indicated, desensitization in delayed hypersensitivity reactions should be restricted to uncomplicated exanthemas and fixed drug eruptions, due to the possible complications and the limited therapeutic options in more severe systemic hypersensitivity reactions. In certain clinical situations, such as sulfonamide hypersensitivity in HIV-positive patients or hypersensitivity to antibiotics in cystic fibrosis patients, published success rates exceed 80%. However, desensitization success rates are at least questionable in patient series without a confirmed diagnosis of drug hypersensitivity by prior allergological testing. Still, even among these patients, there are those who cannot be successfully desensitized even with premedication and a very slow increase of doses.

Pre-treatment with antihistamines and corticosteroids has been proposed for delayed reactions and there is some evidence that it may suppress or at least diminish a hypersensitivity reaction, although controlled clinical studies are lacking. The published success rates vary greatly between different case series, drugs and clinical presentations, without obvious clinical predictors. Slower protocols tend to be better tolerated than rush-protocols, with the disadvantage of a longer period to reach therapeutic doses. An underreporting of unsuccessful outcomes has to be assumed.

The decision to desensitize a patient with a delayed hypersensitivity reaction to a drug is very individual and influenced by a number of factors. These include the availability of alternative drugs, the type and pathophysiology of the reaction, the clinical situation and the availability of protocols. At present, drug desensitization has to be considered as an empirical therapeutic option for the use of an essential drug in serious clinical situations.

The most extensive literature exists on patients who have been desensitized with cotrimoxazole, particularly HIV positive patients [7]. Other successfully desensitized sulfonamides include diaminodiphenylsulfone (dapsone), sulfadiazine, sulfasalazin and mesalazine. Desensitization with antibiotics, especially in patients with cystic fibrosis, includes betalactams and a few cases with ciprofloxacin, clindamycine, tetracyclines and others [27].

There are a few reported cases on one or several tuberculostatic drugs, such as ethambutol, isoniazid, rifampicin, streptomycin and p-amino salicylic acid, but also with antimycotics, such as fluconazol and itraconazol, as well as virostatics (amprenavir, efavirenz, nevirapine, zidovudine) [28-31]. Other medications, such as pentamidine and pyrimethamine, were used in protozoal infections. Some patients have been successfully brought to a state of clinical tolerance with the anti-epileptics carbamazepine, oxcarbazepine and phenobarbital.

Miscellaneous drugs include allopurinol, clopidogrel bisulfate, methylphenidate, mesalazin (5-amino salicylic acid), nitrogen mustard, penicillamine, leflunomide and epoetin-α.

In summary, desensitization in drug hypersensitivity may be considered in some selected clinical situations. However, the most important issue in treating patients should still be the maxim: first do no harm. ■

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