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AND DESENSITIZATION

Drug allergy occurs in fewer than 3% of the population. However, the causes are numerous. and the severity of reactions varies. When investigating a possible drug allergy, consider the following scenarios:

- Pharmaceutical side effect
- Toxic reactions due to overdose
- Idiosyncratic reactions or unique individual reactions
- Drug interactions
- Drug intolerance caused by increased sensitivity
 - to a specific medication
- Drug allergy and immunologic reaction

There are many forms of drug allergy or immunologic reactions to medications including IgEmediated anaphylaxis, IgG-mediated, such as serum sickness, and cellular or T-cell-mediated reactions, which can result in severe inflammation and damage to the liver, spleen, skin, neurologic system, heart and blood vessels (vasculitis).

Among the most common and manageable of these is the immediate allergic drug reactions or IgE-mediated reactions such as hives, angioedema, wheezing and severe anaphylaxis.



When drug allergy is IgE-mediated, our choices of treatment are limited to using an alternative medication or desensitization. But, when an alternative treatment is not available and the disease process is life-threatening, then desensitization to the necessary medication may be the best option.

Desensitization is a technique used by allergists to decrease a patient's hypersensitivity to a medication. To develop the patient's tolerance, the procedure is carried out over several hours. Over this period, the patient receives ever-increasing amounts of the reaction-causing medication. The incremental doses administered are small enough not to cause a severe allergic reaction, but large enough to induce immunologic changes associated with tolerance.

Patients undergo desensitization under consultation of an experienced physician, usually an allergist. A checklist including indications, contraindications and special risks (use of beta-blockers) using a protocol is prepared and reviewed in advance.

For example, patients with bacterial endocarditis associated with a *strep viridans* infection that is only sensitive to penicillin would be a candidate for desensitization. In this case, the benefits outweigh the risks and desensitization is perhaps the best and only course.

What about testing for drug allergy?

Most medications or drugs such as antibiotics, are low molecular weight molecules and therefore not large enough to elicit a positive skin test or be detected by other clinical testing. Allergy testing can be useful when the drug is of high molecular weight (usually greater than 10,000 Daltons), such as is found with insulin, monoclonal antibodies, vaccines, enzymes, or large molecular complexes.

Most drugs are low in molecular weight and are called *haptens* and only become complete allergens when metabolized in the body to be joined with larger molecules.

The combination of the hapten molecule plus a blood or tissue protein can create a high level of potential allergens that can cause an immunological or allergic reaction. This is why most low molecular weight medications are not suitable for testing.

Criteria for drug desensitization

The following factors need to be considered when reintroducing drugs known to have caused a previous allergic reaction in a patient:

- Probable IgE-mediated reaction to a drug or aspirin hypersensitivity
- Serious disease process without alternative medication (as confirmed by appropriate specialist)
- Obtain a complete medical history, including prior drug reactions
- Can the patient medically tolerate the desensitization procedure?
- There is no contraindication to desensitization (e.g. use of beta blocker)
- Well-equipped facility with appropriate monitoring equipment and treatment is available in case of severe anaphylaxis
- Experienced staff and skilled personnel present throughout the procedure.
- Fully inform patient of risks of re-introduction and have patient review and sign a comprehensive consent form.

A written desensitization protocol for each patient and medication is prepared and reviewed in advance. (See example below) In addition, with the administration of each dose, the time, and vital signs (blood pressure, pulse, pulmonary function, oximetry and clinical observations are recorded).

Figure 1: Levofloxacin (Levaquin) Oral Challenge/ Desensitization

Solution #	Dose (mg)	Cumulative dose (mg)	Vital signs and time
8	0.08	0.08	
7	0.8	0.88	
6	8	8.88	
5	16	24.88	
4	31.25	56.13	
3	62.5	118.63	
2	125	243.63	
1	250	493.63	
1/2 tablet	250	743.63	



Substances available by desensitization protocol

Patient hypersensitivity appears to result from IgE-mediated reactions.

- Antibiotics : penicillin and derivatives
- Vaccines: influenza, tetanus, measles, hepatitis B, MMR
- hepatitis B, MMR
 Chemotherapeutic agents (carboplatin, cisplatin, oxaliplatin, paclitaxel, liposomal doxorubicin, doxo-

rubicin, rituximab,

l-asparganinase, 6

mercaptopurine,

Antiplatelet therapy

Methotexate)

(clopidogrel)

D-penicillamine

Carbamazepine

- Heterologous sera
- Anti-venoms
- Heparin,warfirin
- Corticotropin
- Acetazolaminde
- Acyclovir
- Allopurinol
- Cyclosporine
- Omeprazole
- Pancreatic enzymes
- Opiates
- Seminal fluid
- Sulfasalazine
- Corticosteroids
- Antivirals
- Aspirin
- NSAIDs
- Peanuts *

*Early results of a recent Duke University pilot study involving 10 subjects indicated some success in peanut allergy desensitization. Additional studies are needed to confirm the validity of this study. Therefore, at this time, peanut desensitization has not yet been proven a safe and effective approach for clinical use.

The drug desensitization is carried out over a period for 4 to 8 hours under constant supervision. If patients exhibit symptoms of itching, hives, shortness of breath, or hypotension, then the progression of the protocol is stopped until symptoms resolve with or without treatment. Then, the protocol is restarted at a lower dose and the progression is reduced to a more gradual pace with careful monitoring. Such an approach is almost always successful for IgE-mediated allergic drug reactions.

Unfortunately, drug desensitization is not long-lasting. Once the patient discontinues treatment for a period longer than 24 hours, hypersensitivity may recur. Therefore, once beginning a desensitization protocol, it is imperative to continue treatment without interruption until the complete therapeutic course is fully executed.

Most common sensitivities treated

- Antibiotics (IgE-mediated reactions)
- Aspirin (Aspirin and related NSAIDs hypersensitivity can result in life-threatening reactions including anaphylaxis, hives, angioedema, and severe asthma, even though these reactions appear to be non-IgE-mediated. Aspirin desensitization may require hours or days between doses and may take many days to complete the protocol.)
- Local anesthetic allergy

Desensitization method

Desensitization requires preparing a series of dilutions of the drug suspected of causing the reaction. We begin with administering a very small volume of the most dilute concentration of the drug (see Figure 1). The drug is administered via an intravenous, subcutaneous or oral route. The intravenous route is most popular for antibiotic desensitization. Aspirin desensitization is usually performed orally.

Following the first dose, a specific time interval passes before the second dose. If no reaction occurs, a second and higher dose is administered. The time between doses varies according to the medication used for desensitization and the patient's history of prior allergic reaction. For intravenous administration, the interval is usually 20 - 30 minutes. However, for oral desensitization, the interval can be at least an hour for each successive dose. With aspirin or NSAID desensitization, the dose interval may take many hours or even days for completion.

During the desensitization, the patient remains in a facility under the direct observation of a nurse and the specialist physician. Blood pressure, pulse oximetry,

Figure 2: Mast cell

Ig-E antibodies on the surface of mast cells, when activated by a medication, cause the mast cell to release chemical mediators into the tissue and blood.





physical assessment, and breathing tests, are monitored during each interval to assess tolerance for the next dose.

If the patient begins to develop allergy symptoms during the procedure, the treatment and the procedure protocol are modified according to the patient's response. This may include dropping back to a previously tolerated dose, increasing the time between doses, or increasing doses at a lower increment.

Finally, once desensitization is successfully completed, the patient is reminded that he or she cannot interrupt the continuous treatment until the program is fully complete. An interruption of 24 hours or more in daily dosing may lead to resensitization to the administered medication and therefore requires a new desensitization procedure.

Desensitization does not help with most

- Non-lgE-mediated reactions
- Non-hive-like rashes (erythema multiformae)
- Drug intolerances
- Delayed or cellular drug reactions (e.g. Steven Johnson's Syndrome)

Test dosing

In a low-risk scenario with a vague history of drug reaction, one could consider a test dosing, but only in cases where careful investigation indicates that true drug allergy risk is very low or improbable.

A test dose, or graded challenge is a method—such as in the case of a local anesthetic—that can be used to determine whether a patient can tolerate the needed medication without undergoing the more involved desensitization.

Risk of an allergic reaction to a medication

The risk is increased by:

- Subcutaneious or intravenous administration
- Repeated courses of the same or related medication
- Prolonged administration

Patient considerations

A complete drug allergy history is essential. If a question of drug allergy exists, this needs to be correlated with any existing medical records. Failure to adequately document a thorough history of pre-existing drug reactions and review appropriate records prior to prescribing medications may be the basis of a successful malpractice suit.

Drug considerations

A wise way to avoid serious drug reactions is to take a careful drug allergy history and prescribe only those medications that are absolutely essential. Although this approach appears obvious, in the hustle and bustle of a busy practice, a lack of discipline in this area may increase the risks of serious drug allergy reactions.

In one study of penicillin allergy related patient deaths, only one third of the patients had a clear indication for treatment with penicillin.

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