Guest editorial

# Desensitization and test-dosing for the drug-allergic patient

Desensitization has been described as "neutralization of the antibody by small but increasing doses of a drug"[1] as would apply to IgE-mediated hypersensitivity where immediate cutaneous reactivity would disappear as the drug is administered. A broader definition for desensitization is "a procedure in which an allergic individual is exposed to increasing doses of allergen in hopes of inhibiting their allergic reactions."[2] During desensitization, most experience has been with beta lactam antibiotics where the patient is known to have IgE antibodies to major or minor determinants of penicillin, and these antibodies become bound to the drug and neutralized. Alternatively, mast cells may be activated, but the method of administration (very low initial dose with successive increments) avoids clinical responsiveness. For example, during a desensitization procedure in a penicillin-allergic patient, immediate cutaneous reactivity to the penicilloate derivative of carbenicillin went from 4+ to negative rapidly.[3] The patient had received 51.2 mg of carbenicillin which was the 11th dose administered every 15 minutes with a cumulative dose of 102 mg. The only clinical manifestation was generalized flushing which lasted 2 hours. The patient was skin-tested again and was negative. Carbenicillin was restarted and then successfully administered at 30 g daily without evidence of drug hypersensitivity.[3] Similarly, a penicillin-allergic child with cystic fibrosis who had immediate cutaneous reactivity to the major and minor penicillin determinants and ticarcillin itself experienced periorbital angioedema and ocular and pharyngeal pruritus during an attempted cautious infusion of ticarcillin when the 1:10 dilution was reached.[4] Oral penicillin was administered uneventfully, and immediate cutaneous reactivity became absent accompanied by successful administration of ticarcillin.[4]

Desensitization also can refer to unresponsiveness to a drug when there has been a clearcut allergic reaction previously but where IgE antibodies are not involved. Some examples include aspirin and nonsteroidal antiinflammatory drugs,[5,6] allopurinol,[7,8] and sulfonamides.[9-19] Desensitization is not without risk and could result in a fatality. Some dangers could be emergence of Stevens Johnson Syndrome, exfoliative dermatitis, profound neutropenia, status asthmaticus, or anaphylactic shock.[20] In the latter case, a step-wise challenge with trimethoprim-sulfamethoxazole (TMP-SMZ) resulted in blood pressure of 70/50, tachycardia, and pruritus requiring intravenous fluids and four injections of epinephrine.[20] Desensitization should be performed after it is established that the drug is essential (without suitable alternatives), the patient or authorized person can approve the risks of the procedure, plans for immediate treatment of adverse reactions are in place, and an appropriate location is available. For physicians who are inexperienced with drug allergy testing or uncomfortable with the risks, referral should be made. Protocols for drug allergy testing have been published[1,6] as has a practice parameter for drug hypersensitivity.[21]

The typical rash that a patient with HIV develops after administration of TMP-SMZ is morbilliform, pruritic and begins 8 to 12 days into therapy. Sometimes, a mild rash clears without stopping the TMP-SMZ. Administration of prednisone at relatively low doses such as 20 to 30 mg daily can help overcome or avoid a generalized morbilliform but non-blistering rash. Fever or bullae should be warning signs for a more severe problem such as Stevens Johnson Syndrome. The latter can be defined as erythema multiforme that becomes bullous accompanied by involvement of two areas of mucous membranes or skin and liver involvement with elevated temperature.[22] Renal impairment should not be overlooked. Whatever the mechanism is for the heightened sensitivity to sulfonamides,[17] an unresolved issue is why patients with HIV react to structurally dissimilar drugs such as sulfonamides, dapsone, pentamidine, penicillins, and antituberculous medications.[23,24]

In last month's issue (September) Yoshizawa et al[25] describe results with a 5 day test-dosing protocol for patients with HIV infection who had experienced "rash," "rash and fever," or "rash and leukopenia." An *in vitro* assay to detect serum IgE antibodies to sulfamethoxazole-guinea pig albumin was established but all 17 sera were negative. The positive control serum in that assay curiously was from a patient who had developed toxic epidermal necrolysis. Fourteen of 17 patients were desensitized successfully using the 5-day protocol. Two patients then developed cutaneous eruptions which necessitated repeated desensitization. The patients in this series had CD4 counts of $<200/\mu L$ which has been

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associated with apparent reduced likelihood of cutaneous reactions to TMP-SMZ.[26] Physicians attempting desensitization with TMP-SMZ in the US can utilize the pediatric suspension for oral testing. It contains 40 mg TMP and 200 mg SMZ per 5 mL. The equivalent starting dose to Yoshizawa et al would be 0.05 mL.

The AIDS epidemic and its associated high incidence of drug allergy have resulted in various desensitization or test-dosing protocols for various antimicrobial agents. Some contraindications include previous Stevens Johnson Syndrome, exfoliative dermatitis, blistering eruptions and drug-induced hepatitis. Some AIDS patients with such adverse drug reactions listed still may require desensitization or test-dosing as the previous reaction occurred when the patient was receiving multiple medications and it is not definite which drug might have been etiologic. Caution is advised with appropriate documentation in the medical record. Should a desensitization protocol result in the emergence of Stevens Johnson Syndrome, the protocol must be stopped, and systemic corticosteroids should be administered.[27]

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