DRUG ALLERGY TRACK – Drug Allergy Evaluation and Management of Beta Lactam Allergy, 6th Dec 2012, 11:00AM – 12:30PM, HICC, G.03

DESENSITISATION PROTOCOLS IN BETA LACTAM ALLERGY

Chng Hiok Hee, Department of Rheumatology, Allergy & Immunology, Tan Tock Seng Hospital, Singapore

When a patient has had a hypersensitivity reaction to a drug and needs it again, either an unrelated alternative drug could be used or when appropriate, the same drug could be reintroduced using a desensitization procedure. Drug desensitization is defined as the induction of tolerance to a medication responsible for a hypersensitivity reaction. The procedure modifies a patient's response to a drug to temporarily allow treatment with it safely. Once the drug concerned is stopped, this tolerant state is lost within a few hours to a few days. This tolerant state can be maintained by continuous administration of the drug.

Desensitization should be differentiated from incremental drug challenge(also referred to as graded challenge) which is a diagnostic tool. The purpose of a graded challenge is to cautiously administer a drug to a patient who is unlikely to be allergic to it and there is no intention to induce tolerance to that drug.

In desensitization, increasing doses of the drug concerned are administered over a period of time, ranging from several hours to a few days, until the total cumulative therapeutic dose is achieved and tolerated. In a patient with IgE mediated beta lactam(BL) allergy, the full dose is usually reached within about 6-8 hrs. Doctors should be familiar with the indications, contraindications, and risks involved in desensitization. In general, desensitization is indicated in a person with BL allergy when the drug is irreplaceable (e.g. penicillin in pregnant women with syphilis), when a particular BL is more effective than other alternatives, and when a particular BL has fewer serious side effects than alternatives. The procedure should be avoided in hemodynamically unstable patients, when risk is higher because of co-morbidity, such as uncontrolled asthma (FEV1 < 70% of their normal value), or uncontrolled cardiac disease. In all cases, a decision is made after careful individual risk/benefit assessment, the reasons for desensitization are then documented, the procedure explained to the patient and consent obtained. Only doctors and nurses familiar with the procedure as well as the management of anaphylaxis should be administering the desensitization. BL desensitization is always carried out in a facility where close monitoring and resuscitation equipment is readily available such as in the intensive care or high dependency unit.

Before starting BL desensitization, beta-blockers, which can interfere with the treatment of a severe hypersensitivity reaction, should be discontinued whenever possible. However, indications for beta-blockers must be complied with, e.g., sudden withdrawal of beta-blocker therapy in a patient with arrhythmia may be life threatening and in this instance, it should not be stopped. Do not pre-treat

with antihistamines as they may mask early signs of a hypersensitivity reaction. Patients should always have an intravenous access during the procedure even when on oral desensitization..

BL desensitization can be performed via intravenous (Immunol Allergy Clin North Am 2004; 24: 425-43; Immunol Allergy Clin N Am 2009; 29: 585–606) or oral route (Allergy, Principles and Practice. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, editors. Drug allergy. St. Louis: Mosby Co 1993: 1726-46). The oral route is easier, less expensive, and has a lower risk for anaphylaxis. However, oral desensitization is not always advisable or feasible. There are protocols that combine oral and parenteral routes of administration (Allergy Clin Immunol 1982; 69: 275-82.). In the patient with history of severe anaphylaxis (such as hypotension with loss of consciousness or severe bronchospasm), it is advisable to modify the protocol by reducing the initial dose, decreasing the rate of infusion, increasing the time interval between doses in oral administration, and/or increasing the number of steps. The starting dose is always determined by taking into account the severity of the previous hypersensitivity reaction. When there was severe anaphylaxis in the past, the initial dose should be between 1/1,000,000 and 1/10,000 of the full therapeutic dose.

A standardized parenteral protocol used by Castells and colleagues at the Brigham and Women's Hospital in Boston, comprises a three-solution, 12-step infusion allowing the patients to receive full therapeutic doses after 5.8 hr (Immunol Allergy Clin N Am 2009; 29: 585-606). The solutions are made by 10-fold dilutions of the full target concentration (labeled solution 3). Each solution is administered in four different steps. The rate of each step is increased every 15 minutes to deliver approximately twice the dose of the previous step.

Breakthrough reactions are drug hypersensitivity reactions that occur during the desensitization procedure. They usually appear when a substantial increase in the dose is attempted. These reactions range from mild to severe. Mild reactions include warmth, tingling, pruritus, flushing, erythema, urticaria, and nausea. Severe reactions are generalized urticaria, bronchospasm, laryngeal obstruction, and hypotension. In general, unless reactions are very mild, it its advisable to interrupt the procedure, treat the reaction, and then modify the desensitization protocol by introducing intermediate dosing steps, going back one or two steps, or re-starting at the stopping point with a lower dose.

Once the full therapeutic dose is reached, subsequent doses must not be missed until the course of BL is completed so as not to breach tolerance. Even after successfully completing a course of the drug using desensitization, this procedure has to be repeated in the future if the patient requires the drug again. Thus the label of BL allergy for the patient should not be removed.

Suggested reading list:

Sullivan TJ, Yecies LD, Shatz GS, Parker CW, Wedner HJ. Desensitization of patients allergic to penicillin using orally administered beta-lactam antibiotics. J Allergy Clin Immunol 1982; 69: 275-82.

Stark BJ, Earl HS, Gross GN, Lumry WR, Goodman EL, Sullivan TJ. Acute and chronic desensitization of penicillin-allergic patients using oral penicillin. J Allergy Clin Immunol 1987; 79: 523-32.

Sullivan TJ. Allergy: Principles and Practice. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, editors. Drug allergy. St. Louis: Mosby Co 1993: 1726-46.

Solensky R. Drug desensitization. Immunol Allergy Clin North Am 2004; 24: 425-43.

Castells M. Rapid desensitization for hypersensitivity reactions to medications. Immunol Allergy Clin North Am 2009; 29: 585-06.

Castells M. Desensitization for drug allergy. Curr Opin Allergy Clin Immunol 2006; 6: 476-81.

Solensky R, Khan DA, Bernstein IL, Bloomberg GR, et al. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol. 2010; 105: 259-73.

Cernadas JR, Brockow K, Romano A, Aberer W, Torres MJ, Bircher A, et al, for the European Network of Drug Allergy and the EAACI interest group on drug hypersensitivity. General considerations on rapid desensitization for drug hypersensitivity - a consensus statement. Allergy 2010; 65: 1357-66.

Madaan A, Li JT. Cephalosporin allergy. Immunol Allergy Clin North Am 2004; 24: 463-76.