

## Clinical applications of drug desensitization in the Asia-Pacific region

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Drug desensitization is the induction, within hours to days, of a temporary state of tolerance to a drug which the patient has developed a hypersensitivity reaction to. It may be used for IgE and non-IgE mediated allergic reactions, and certain non-allergic reactions. The indication for desensitization is where no alternative medications are available for the treatment of that condition, and where the benefits of desensitization outweigh the risks. Desensitization is a therapeutic modality for drug allergy (similar to allergen specific immunotherapy for allergic rhinitis and insect venom anaphylaxis). In contrast, the drug provocation test is a diagnostic modality used to confirm or refute the diagnosis of drug allergy. This review discusses the clinical applications of desensitization for the treatment of common infectious, metabolic and cardiovascular diseases, and oncological conditions in the Asia-Pacific region.

**Key words:** Anaphylaxis; Desensitization; Drug hypersensitivity; Stevens Johnson syndrome; Toxic epidermal necrolysis

### INTRODUCTION

Although many classes of drugs are presently available to treat various medical conditions, certain drugs with the potential to cause allergic or non-allergic drug hypersensitivity reactions [1] may be the therapeutic drug of choice as no better alternatives are available. Examples of drugs with a propensity to cause drug allergy include isoniazid, rifampicin and pyrazinamide for the first-line treatment of tuberculosis (TB); allopurinol for the treatment of tophaceous gout, and trimethoprim-sulfamethoxazole (TMP-SMX) for the treatment and prophylaxis of *Pneumocystis jiroveci* infection and toxoplasmosis in human immunodeficiency virus (HIV) infected patients [2, 3]. As for

drugs causing non-allergic drug hypersensitivity, aspirin remains an important anti-platelet agent in those with cardiovascular diseases, in particular individuals with coronary artery disease following percutaneous coronary intervention to prevent in-stent thrombosis.

Drug desensitization is the induction, within hours to days, of a temporary state of tolerance to a drug which the patient has developed a hypersensitivity reaction to [4]. Although in the strictest sense, this term/procedure should only be applied to tolerance induction in IgE-mediated allergic drug hypersensitivity, it is now also used in tolerance induction for non-IgE mediated allergic reactions (e.g. non-immediate reactions like maculopapular exanthema and fixed drug

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eruptions), and non-allergic reactions (e.g. aspirin intolerance or hypersensitivity). The indication for drug desensitization is where no better alternative medications are available for treatment of that condition, and where the benefits of desensitization outweigh the risks. Desensitization is a therapeutic modality for probable or definite drug allergy based on the results of validated allergological tests or drug imputability (similar to specific immunotherapy for allergic rhinitis and insect venom anaphylaxis) [5]. In contrast, the drug provocation test is a diagnostic modality used to confirm or refute the diagnosis of drug allergy [6].

### Mechanisms in drug desensitization

Various studies have proposed different mechanisms for IgE-mediated desensitization: internalization of antigen/IgE/ FcεRI and cross-linking of inhibitory receptors on mast cells [7]; reduced levels of up-stream signal transducing molecules, such as Syk which are necessary for activation and mast cell IgE-signalling [8]; negative regulation of IgE mediated allergic responses by Lyn kinase in mast cell responses both *in vivo* and *in vitro* [9]; and elevated levels of the signal transducer and transcription activator STAT-6 involved in transcription of IL-4 and IL-13 necessary for desensitization of murine mast cells [10, 11].

The mechanism for desensitization in non-immediate reactions remains unknown. This is because of the many mechanisms involved in non-immediate reactions prior to T cell activation, including haptentation, biotransformation of inert prohaptens to reactive haptens [12], and direct interaction of non-haptens with T-cell receptors [13]. For instance, interference with SMX haptentation, but not SMX-specific antibodies, appear to be important in the development of clinical sensitivity (i.e. failure of desensitization) in patients with AIDS who have undergone SMX desensitization [14]. At the site of the target organ, CD25+CD4+ T regulatory cells in the epidermis of lesions of fixed drug eruptions (FDE) appear to be important in the induction of desensitization to allopurinol FDE [15].

In non-allergic drug hypersensitivity reactions like acetylsalicylic acid (ASA) or aspirin intolerance, abnormal metabolism of arachidonic acid results in a decrease in the levels of the anti-inflammatory prostaglandins, especially prostaglandin E<sub>2</sub>, and an increase in the synthesis of cysteinyl leukotrienes, particularly leukotrienes C<sub>4</sub>, D<sub>4</sub> and E<sub>4</sub>. The excessive production of leukotrienes results in urticaria, angioedema, bronchospasm and occasionally non-allergic anaphylactic (anaphylactoid) reactions in such pre-disposed individuals [16]. These patients often develop

aspirin exacerbated respiratory disease (AERD) which comprises aspirin intolerant asthma with chronic rhinosinusitis and/or nasal polyposis, or aspirin induced urticaria (AIU)/ aspirin-exacerbated chronic urticaria [17, 18]. High dose aspirin desensitization (650-1,300 mg/day) has been shown to ameliorate AERD symptoms through various postulated mechanisms including direct mast cell inhibition [19], direct modulation of the intracellular biochemical pathways of inflammatory cells, reduced production of thromboxane A<sub>2</sub>, reduced leukotriene B<sub>4</sub> levels [20], increased LTE<sub>4</sub> levels [21], inhibition of activation of transcription factors like NFκB [22], and inhibition of IL-4 and IL-13 induced activation of STAT6 [23]. During acute desensitization in AERD, significant elevation in exhaled nitric oxide and serum tryptase levels have been demonstrated; in long term treatment with ASA, IL-4 is suppressed, the pro-inflammatory matrix metalloproteinase-9 is down-regulated, while the T<sub>H</sub>1 marker FMS-like tyrosine kinase 3 ligand increases [24]. It is likely that a similar mechanism exists in patients with coronary artery disease successfully desensitized to low-dose (81-325 mg/day) aspirin [24-26].

### Principles in drug desensitization

Several cardinal principles in drug desensitization [4, 5, 27] for drug allergy/hypersensitivity are as follows:

- There is no alternative drug available for the treatment of the underlying condition (e.g. allopurinol in chronic tophaceous gout, penicillin in pregnant women with syphilis, platinum salts in recurrent ovarian cancer).
- The drugs for the treatment of the underlying condition are superior to the alternatives (e.g. isoniazid for tuberculosis).
- The initial reaction should not be potentially life-threatening reaction. Drug induced hypersensitivity syndrome (DiHS), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) are absolute contraindications to desensitization. However, anaphylaxis is not a contraindication.
- The benefits of desensitization outweigh the risks of recurrence of drug hypersensitivity/ allergy.
- Starting doses are at 1:1,000,000 to 1:100 of the target therapeutic dose depending on the severity of the initial reaction, or based on end-point intradermal skin testing to a non-irritative concentration of the drug.
- Dose escalations are doubled at 15-30 min intervals for immediate reactions, or at intervals of up to 24 h for non-immediate reactions.
- Close monitoring and resuscitative equipment with staff

trained in resuscitation should be available for rapid desensitization.

- Pre-medications with systemic corticosteroids or anti-histamines should be avoided.
- Concomitant medical conditions should be stable (e.g. asthma, cardiac insufficiency).
- The patient is still deemed allergic to the drug to which he/she has been successfully desensitized.
- The patient must adhere to the drug daily in order for tolerance to be maintained, unless breakthrough reactions occur where dose escalations may need to be interrupted/slowed down.
- In desensitization for non-immediate reactions, periodic monitoring of complete blood count and liver enzymes should be considered prior to interval dose escalations.

The European Academy of Allergy and Clinical Immunology [4] has recently drawn up guidelines on desensitization in drug allergy. The American Academy of Allergy Asthma and Immunology and the American College of Allergy Asthma and Immunology have also addressed the topic of desensitization or “temporary induction of drug tolerance” in its recent 2010 Updated Practice Parameter on Drug Allergy [27]. Both academies are in the midst of establishing databases of desensitization protocols for which sufficient evidence for the effectiveness/adverse events for each protocol exists.

In this review, we will focus on drugs for which desensitization protocols have been described for 4 major classes of diseases highly prevalent in the Asia-Pacific region: infectious, metabolic, cardiovascular diseases and oncological conditions.

### Desensitization for betalactam allergy

Betalactams are the most common cause of drug allergies in most prospective epidemiological studies on adverse drug reactions/drug allergies [28-32] including studies originating from the Asia-Pacific region [33, 34]. The majority of the studies on betalactam desensitization to date have been in patients with cystic fibrosis who require anti-microbial therapy, of which betalactams are the antibiotics of choice [35, 36]. Rapid desensitization protocols using oral [37] and intravenous penicillins, cephalosporins [38] (ceftriaxone, cefepime [39], ceftazidime [40], cefotaxime [41], and cefazolin [42]) have been described and in general found to be effective and safe. Successful desensitization protocols to the carbapenems

including meropenem [43] and imipenem/cilastatin [44] have also been well-described with no adverse reactions, even when used in patients with renal impairment [45]. Adverse effects where they occur, are usually mild comprising flushing, pruritis, rash or urticaria, with no serious reactions or late reactions in most studies [46].

### Anti-tuberculous drug desensitization

*Mycobacterium tuberculosis* infection remains endemic in certain parts of Asia, with one-third of the world's burden of TB, or about 4.9 million prevalent cases, found in the World Health Organization South-East Asia Region [47]. Treatment of TB infection involves combinations of anti-tuberculous drugs including isoniazid, rifampicin, ethambutol and pyrazinamide. Non-immediate reactions to anti-tuberculous drugs are much more common than immediate reactions, with hypersensitivity reactions that lead to discontinuance of antituberculous agents and to switch of therapy seen in 4-5% of the general population [48]. Drug eruptions in the form of maculopapular eruptions (MPE), lichenoid drug eruptions [49], haematological reactions, hepatitis, DiHS, SJS/TEN [50] have all been reported in the literature [51]. In practice, it is often difficult to determine which of the anti-tuberculous drugs resulted in the allergic drug reaction. Although patch tests and lymphocyte transformation tests would be useful in such situations to help identify the putative drug, these tests are not readily available in the Asia-Pacific region, are often drug- and reaction-specific (hence negative tests may not be useful), and it is usually not possible to defer TB treatment for 4-6 weeks pending the outcome of results of these tests [52-55]. Drug provocation tests although useful in helping to determine the putative drug, are not without risks especially in DiHS, SJS and TEN. Second-line drugs like fluoroquinolones, aminoglycosides, cycloserine and clofazamine, are not encouraged as alternative therapy for patients with drug allergy to first-line TB drugs as they are usually reserved for multi-drug-resistant (MDR)-TB [56]. Even though MDR-TB although only occurs in fewer than 3% of new cases and 18% of re-treatment cases in the south-east Asia region, this still translates to significant absolute numbers of patients [47]. As such, rapid oral desensitization regimes have been described for streptomycin [57], isoniazid [58], rifampicin [58-60], ethambutol [60], and para-aminosalicylic acid [61]. These regimes often involve reintroducing the anti-tuberculous drugs as soon as the allergic reaction has settled. In addition, more than one drug often needs to be reintroduced, reaching target

dose within 3 days, with at most a 3-5 day interval apart, because leaving patients on anti-tuberculous monotherapy increases the risk of emergence of drug-resistant tuberculosis. If the initial allergic reaction was SJS/TEN, the risks of desensitization versus the benefits would need to be considered very carefully in consultation with the patient, the attending infectious diseases physician or pulmonologist. Most of the published literature on oral desensitization to TB drug therapies in the Asia-Pacific region originates from Japan [61, 62] and Korea [63]. In a series which followed desensitization guidelines of the Japanese Society of Tuberculosis [62], adverse reactions among 19 patients aged 23-88 years old, included drug eruption (42.1%), drug fever (36.8%), drug fever with drug eruption (15.8%), and drug fever with cervical lymphadenopathy (15.8%). The clinical effect of desensitization therapy for these antituberculous drugs was good in 14/17 (82%) cases for rifampicin, and 6/8 (75%) cases for isoniazid. In another case report from Korea, a child with tuberculous osteomyelitis of the ankle who developed fever, pruritis and hepatitis 3 days after isoniazid, rifampin, kanamycin and pyrazinamide, was successfully desensitized to rifampin, isoniazid and ethambutol with oral steroid and cetirizine after recurrence of skin rash, facial flushing, chest discomfort during the initial desensitization process. She successfully completed the standard isoniazid (10 mg/kg) and rifampin (12 mg/kg) regimens for 18 months without adverse reactions [63].

### Desensitization in human immunodeficiency virus infection

Around 4.87 million people are living with HIV in South, East and South-east Asia. The frequency of drug allergy/hypersensitivity among patients with HIV infection ranges from 3-20% [64]. Before the development of highly active anti-retroviral therapies (HAART), the majority of drug allergies/hypersensitivity were from antimicrobials used for the treatment or prophylaxis of opportunistic infections. These included TMP-SMX, sulfadiazine, dapsone, clindamycin, thiacetazine, aminopenicillins and atovaquone. Adverse reactions ranged from urticaria, maculopapular exanthems to fever, neutropenia, thrombocytopenia, nephritis, elevated liver enzymes, DiHS, SJS and TEN [65].

TMP-SMX is used in the treatment and prophylaxis of *Pneumocystis jiroveci* pneumonia and toxoplasmosis. Desensitization protocols have been shown to be useful in Cochrane metaanalyses [66], and protocols have been developed for use in both adults and children with TMP-SMX allergy. Oral

TMP-SMX is usually used, with target doses initially attained within 7 days in the earlier studies [67], subsequently reduced to 3-days [68] and 2-days [69] among adults, then to a 4-hour protocol in infants and children [70]. Where the initial reaction was SJS/TEN, desensitization has to be carefully discussed with the patient/family as the risks of desensitization may outweigh the benefits [71]. SMX haptentation, but not SMX-specific antibodies, appear to be important in the development of clinical sensitivity (i.e. failure of desensitization) in patients with AIDS who have undergone SMX desensitization [14].

With the introduction of HAART in the 1990s, reports of hypersensitivity reactions to antiretroviral agents have increased. HAART drugs are classified as reverse transcriptase inhibitors (nucleoside [NRTI] and non-nucleoside reverse transcriptase inhibitors [NNRTI]), protease inhibitors (PI), fusion inhibitors, integrase inhibitors and entry inhibitors (CCR5 co-receptor antagonist). Single and various combination (fixed dose) drug therapies are currently available. While most of the anti-retroviral therapies have been associated with drug hypersensitivity/allergy, abacavir (NRTI) and nevirapine (NNRTI) are particularly important as they are associated with potentially serious adverse reactions.

Abacavir hypersensitivity syndrome is usually multi-organ, potentially life-threatening reaction that occurs in both adults and children and approximately 5% to 8% of HIV-infected treated patients [72]. HLA-B5701 has been found to be associated with abacavir hypersensitivity among Caucasians [73] but not in non-Caucasian populations [74]. Thus, the use of genetic screening prior to prescription of abacavir in Caucasians was the first clinical application of screening of at-risk individuals prior to drug prescription. This originated in Perth, Western Australia which was one of the study sites for the PREDICT-1 study [75].

Nevirapine hypersensitivity occurs in 13% [76], most commonly MPE, with severe cutaneous adverse reactions (SCAR) (including SJS/TEN) occurring in 0.5-1% [77, 78]. The various types of hypersensitivity/allergy reaction with other anti-retroviral therapies has been comprehensively reviewed elsewhere [64].

Single case reports of successful desensitization protocols have been described for amprenavir [79], darunavir [79, 80], efavirenz [81], enfuvirtide [82, 83], nelfinavir [84] and zidovudine [85]. As is the case for TB drug allergy, one of the main challenges in HAART drug allergy is the identification of the putative drug: especially since standard therapy often involves 2 NRTIs plus a PI/NNRTI/integrase inhibitor often in addition to antimicrobials for prevention or treatment of opportunistic infections.

### Allopurinol desensitization

Gout is known to be prevalent in the Asia-Pacific region, ranging from 0.2% in Thailand and Vietnam, to 4% among Australian aboriginals [86]. Severe tophaceous gout has been described among the Malayo-Polynesian and Malayo-Mongoloid communities in urban and rural North Sulawesi, Indonesia [87] and Maoris in New Zealand [88]. Gout is also associated with the metabolic syndrome among Koreans [89] and Japanese [90], and an important cause of all-cause and cardiovascular mortality among Taiwanese [91].

Allopurinol is a xanthine oxidase inhibitor which is commonly used in the treatment of gout and as prophylaxis against tumor lysis syndrome in the treatment of haematological malignancies. Although 2% of patients administered allopurinol may develop a mild MPE [92], SJS and TEN are not uncommon [77]. In Asia, HLA B\*5801 has been found to be associated with allopurinol induced SJS/TEN in Han Chinese from studies in Taiwan [93], Thais [94], Japanese [95], and DiHS, SJS/TEN among Koreans [96, 97]. However, HLA-A\*0201 was not found among Korean patients with SCAR despite relatively high frequency among tolerant controls, suggesting a negative association [97].

Allopurinol desensitization was first described by Meyrier in a patient with chronic renal disease [98]. Subsequent protocols using intravenous [99] and oral [100] formulations have been shown to be generally safe and effective in the long-term [101]. Cutaneous eruptions are easily managed with temporary withdrawal and dose adjustment of allopurinol, even in individuals with renal impairment [101]. However, immediate hypersensitivity reactions can recur even after successful desensitization, hence the need for constant vigilance [102].

Febuxostat, a selective xanthine oxidase/ xanthine dehydrogenase inhibitor is an alternative treatment for patients who develop adverse reactions to allopurinol [103]. In the Asia Pacific region where this drug is presently not available, the alternatives for patients with allopurinol allergy who cannot undergo desensitization include [104, 105]:

- Probenecid, a uricosuric agent, provided renal function is not impaired and the patient does not have urate nephropathy,
- Benzbromarone, a uricosuric agent, which is only available in certain countries as it was withdrawn by its original manufacturer in 2003 after reports of serious hepatotoxicity,
- Rasburicase, a recombinant urate oxidase which is approved for the prevention and treatment of tumor lysis syndrome in patients receiving chemotherapy for hematologic cancers

such as leukemias and lymphomas. Its use in gout remains investigational [106].

### Desensitization to insulins for diabetes mellitus

The prevalence of diabetes mellitus in Asia Pacific countries ranges from 2.6% to 15.1%, with population attributable fractions ranging from 2% to 12% for coronary heart disease, 1% to 6% for haemorrhagic stroke, and 2% to 11% for ischaemic stroke [107]. Despite the high prevalence of diabetes mellitus, drug allergy to oral hypoglycemic agents is fortunately uncommon. Case reports of patients with psoriasiform [108, 109] or lichenoid drug eruptions [110] to sulfonylureas and biguanide, purpuric dermatoses [111] and hepatitis [112] from sulfonylureas, drug-induced hepatitis with thiazolidinediones [113], and angiotensin-converting enzyme inhibitor angioedema precipitated by dipeptidyl peptidase-IV inhibitors [114] have been reported.

Insulin allergy, in the form of localized or systemic reactions which may be immediate, delayed or serum sickness like, occurs in less than 1% of diabetic patients on insulin. It may be due to the insulin itself or its additives (zinc, protamine, cresol, phenol, glycerol). The causative agent can be determined by skin prick and intradermal tests to the insulin preparation, insulin additives; and in specialized centres, measurement of specific IgE or IgG levels to insulin. Insulin allergy is less common these days in view of the use of recombinant insulins [115]. Nonetheless, diagnostic skin testing and effective desensitization regimes have been well described [116]. From the Asia-Pacific region, successful desensitization using insulin glargine [117, 118], crystalline zinc insulin [119] and continuous insulin infusion [120] have been reported from Japan and various types of recombinant insulin from Korea [121-123]. Human insulin-specific antibody measured 4, 8 and 12 weeks after successful desensitization in a 68-year-old Korean man showed gradual decrease in human insulin specific IgE levels, and increase in IgG1, IgG2 and IgG4 over time [124]. Recurrence of systemic reaction following successful desensitization to human recombinant insulin has been described in a case report from Singapore [125].

### ASA desensitization for coronary artery disease

The incidence of ASA hypersensitivity in the general population ranges from 0.6-2.5% [126, 127], but that in adult asthmatics ranges from 4.3-11% [128]. In the Asia-Pacific region, studies from Korea have demonstrated specific genetic and ethnic risk factors in Korean populations for AERD, AIU and AICU [129].

The true prevalence for ASA hypersensitivity among individuals with coronary artery disease in the Asia-Pacific region is unknown. Nonetheless, low-dose (81-325 mg/day), rapid ASA desensitization-challenge regimes appear to be useful in patients with ASA/NSAID sensitivity with coronary artery disease, in particular those who have undergone percutaneous coronary intervention [26, 130]. ASA desensitization is not desensitization in the truest sense of the word as the majority of ASA reactions are largely idiosyncratic with no immune mechanisms involved. The mechanisms are likely to be similar to high-dose ASA desensitization. The published protocols so far have been effective in the majority of patients studied [131-133], with relatively low rates of desensitization failure up to 24 months from initiation [131]. For ASA desensitization failures, alternative types of stents [134] or other anti-platelet combinations may need to be considered.

### Chemotherapeutic and biologic agents

Cancer is a major cause of death in the Asia-Pacific with cancer frequencies and cancer types varying across different Asian countries. The incidence and prevalence of gastric cancer is high in East Asia and very low in the South East Asian countries. In contrast, hepatocellular carcinoma rates are high in the entire region in view of the endemicity of chronic hepatitis B infection [135]. Chemotherapeutic agents that are most commonly associated with hypersensitivity reactions include platinum-based drugs in the treatment of ovarian, small cell lung and germ cell cancer; taxanes and monoclonal antibodies (trastuzumab) used in the treatment of breast cancer; and rituximab in the treatment of non-Hodgkin's lymphoma. These drugs are often needed for refractory or recurrent disease. Standardized 12-step desensitization protocols given intravenously/intraperitoneally over 6 h have been found to be safe and effective in 94% of infusions (mild or no reactions), with no life-threatening adverse reactions reported [136]. Among patients who received standardized 12-step desensitization protocols for trastuzumab, rituximab and infliximab, hypersensitivity reactions occurred during 29% of desensitizations, including 27 mild reactions, 1 moderate reaction, and 2 severe reactions [137]. In these studies, the initial desensitizations were done in an intensive care setting, and subsequent infusions as outpatients. Breakthrough symptoms can be managed with anti-histamines and systemic glucocorticoids, and decelerating the dose escalation with intermediate infusion steps [5].

## CONCLUSION

The objectives, indications, contraindications, principles of drawing up drug desensitization regimes are similar. However, the mechanisms of desensitization for immediate versus non-immediate reactions are clearly distinct. Most current desensitization regimes are effective and can be safely carry out with careful patient selection and close monitoring under the supervision of trained allergists and nursing staff.

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