2020 Volume 5, Issue 1

Journal of Medicines Development Sciences

ISSN: 2382-6371(Online) ISSN: 2382-6363(Print)

Desensitization for the Prevention of Drug Hypersensitivity

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Abstract

Drug desensitization is a treatment strategy for patients with hypersensitivity to essential drugs without alternatives. The gradual increase in the drug dosage from low doses to therapeutic levels induces a transient immune tolerance to the culprit drug. Although desensitization has traditionally been recommended for IgE-mediated immediate hypersensitivity, this indication has recently been expanded to include non-IgE-mediated immediate responses, nonimmunological responses, and T-cell-mediated delayed hypersensitivity reactions. Although the exact mechanism behind desensitization remains unclear, the process is thought to attenuate various intracellular signals in target cells through the high-affinity IgE receptor (FcεRI) internalization, alteration in signaling pathways in mast cells and basophils, reduction in Ca^{2+} influx, and production of anti-drug IgG4 blocking antibody. Desensitization can be used for the safe administration of anti-neoplastic agents, antibiotics, aspirin, and nonsteroidal anti-inflammatory drugs. Various desensitization protocols have been proposed for each drug. The optimization of drug concentration, target dosage, administration interval, and route of administration is key to successful desensitization. In addition, the desensitization protocol should be individualized for each patient with consideration of the severity of the initial hypersensitivity response, the characteristics of the culprit drug, and the nature of the breakthrough reactions.

Keywords

Drug hypersensitivity
Desensitization
Antineoplastic agent
Antibiotics
Antitubercular agents

1. Introduction

A drug hypersensitivity reaction is an excessive immunological or non-immunological inflammatory response to a drug in the body that is independent of the drug's intrinsic pharmacological action and can occur in small doses. Depending on the time of onset

after administration, it can be classified into immediate or delayed reactions, each of which has a characteristic clinical presentation.

In order to properly diagnose drug hypersensitivity reactions, it is most important to understand the patient's condition through a detailed questionnaire and examination and to properly evaluate the relevance of the drug based on accurate medication history. In addition, allergy tests such as blood tests, skin tests, and provocation tests should be performed to identify the causative drug and take measures to prevent future recurrence.

Once a drug hypersensitivity reaction has occurred, it is most important to immediately stop using the offending drug and switch to an alternative drug. However, suboptimal pharmacotherapy may result in delayed or prolonged treatment of the underlying disease, increased incidence of comorbidities and complications, and increased socioeconomic burden. In some cases, the reintroduction of the drug that caused the hypersensitivity reaction may be unavoidable, especially if no alternative drug is available or if the treatment is significantly less effective. In this case, desensitization can be applied to minimize the risk of recurrence of hypersensitivity reactions and has been increasingly applied in recent years in Korea and abroad.

However, the literature on drug desensitization published in Korea is mostly case reports, and there are no clinical guidelines for desensitization. Therefore, we would like to share the concepts, mechanisms, and clinical applications of drug desensitization through our experience and the latest domestic and international literature review.

2. Summary

2.1. Historical background

An antigen is an organism or substance that can be recognized by the immune system or interact with the immune system when it enters the body from the outside. Although the immune system recognizes foreign antigens, it does not produce an immune response to all of them, and even if an immunogen induces an immune response, the immune system will not respond if it is present in very small amounts. Therefore, drug desensitization is a method of temporarily inducing tolerance by gradually raising the threshold of the immune response, starting with an extremely low dose below the threshold, allowing time for adaptation, and then resetting the threshold by gradually raising the threshold above which no response occurs, until a therapeutic dose is reached [1]. The first desensitization concept reported in the literature to date was Bezredka's animal model in 1907 [2], and in 1922, Widal *et al.* first attempted oral aspirin desensitization in patients with respiratory hypersensitivity to aspirin [3]. The first documented success of desensitization was in the 1940s when rapid drug desensitization was used to reintroduce penicillin to soldiers who had experienced penicillin anaphylaxis during World War II in the absence of other alternative antibiotics [4]. In the last decade, desensitization has been actively applied worldwide in a variety of drug hypersensitivity reactions.

2.2. Immunological mechanisms

The exact molecular biological and immunological mechanisms of drug desensitization are still not fully understood. After desensitization, the concentration of specific IgE in the offending drug decreases, but the concentration of specific IgE in other allergens remains constant, suggesting that desensitization acts in an antigen-specific manner [5]. Recent studies have proposed hypotheses such as abnormalities in the internalization of the high-affinity IgE receptor (FcεR1), changes in proteins in the signaling pathways of mast cells/inflammatory cells, and the production of drug-specific IgG4 blocking antibodies as immunological mechanisms of desensitization [6-10].

Firstly, activation of mast cells and basophils is impaired when subtherapeutic doses of the drug are

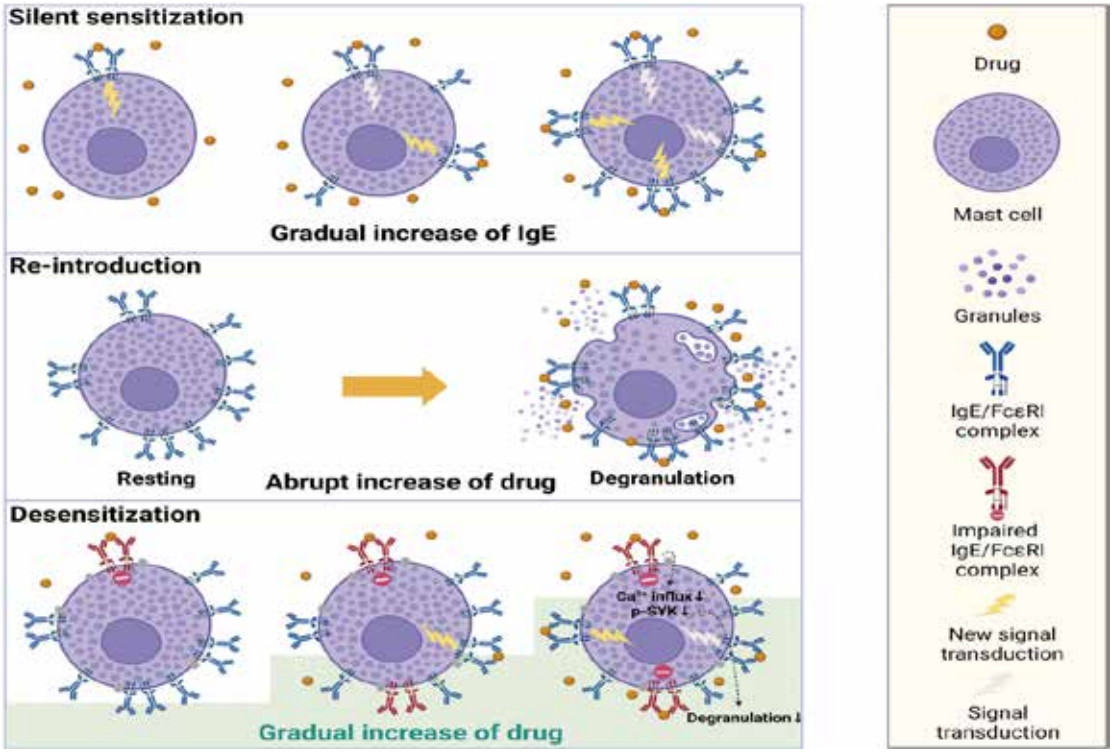

Figure 1. The mechanism of mast cell unresponsiveness and desensitization. (A) During sensitization, the production and binding of drug-specific IgE antibodies to Fcε receptor 1 (FcεRI) occur gradually without activating the mast cell; (B) Re-exposure to the same drug at a high dose activates sensitized mast cells resulting in degranulation; (C) During desensitization, the culprit drug is administered from an extremely low dose and gradually increased. At low drug concentration, the number of drug/IgE/FcεRI complexes are low and functionally impaired. A slow formation of drug/IgE/FcεRI complexes may contribute to mast cell unresponsiveness and a decrease in Ca^{2+} influx, which may inhibit signal transduction. The figure was created with BioRender.com.

administered, even at therapeutic doses, due to impaired calcium influx beyond internalization of the antigen/IgE/FcεRI complex [11,12]. In addition, various proteins in the signal transduction pathways of mast cells and basophils may be altered during desensitization, leading to blocked activation and degranulation. For example, spleen tyrosine kinase (SYK), which signals activation of mast cells and basophils, is reduced in expression after desensitization [13], resulting in reduced FcεRI activation signaling, even when drug and IgE are bound. FcγRII, which possesses an immunoreceptor tyrosine-based inhibitory motif, competitively inhibits FcεRI upon desensitization, and, through Src homology 2 domain-containing inositol phosphatase 1, dephosphorylates early signaling molecules such as SYK, blocking downstream signaling involved in mast cell activation [8,14,15]. Reduction of intracellular calcium ions and impaired calcium ion influx by actin filament remodeling can also inhibit mast cell degranulation (Figure 1) [6,7,11,16].

Secondly, the increased concentration of drug-specific IgG during desensitization raises the possibility that IgG4 may play a major role in desensitization [17]. However, although the role of antigen-specific IgG4 in blocking the interaction between antigen and IgE in allergen immunotherapy is well established [18], IgG4 cannot fully explain the immediate acquisition of drug tolerance and the sustained effect of desensitization.

More recently, the role of T cells in desensitization has been emphasized. Some studies have reported a reduction in the severity of hypersensitivity reactions and the incidence of breakthrough reactions following desensitization, suggesting that desensitization may attenuate immunological memory [19]. Several cases

of successful desensitization for T-cell-mediated delayed hypersensitivity reactions have been reported in the literature. When desensitization was applied to allopurinol-induced immobilization, $CD4^+CD25^+$ T cell expression, presumably regulatory T cells, was significantly increased at the lesion site, whereas $CD8^+$ T cell expression was decreased, suggesting that delayed-type hypersensitivity reactions could be suppressed [20]. Increased expression of interleukin-10 (IL-10), IL-35, $CD4^+CD25^+$, and $CD4^+CD25^+FoxP3^+$ after desensitization also suggested the importance of regulatory T cells in delayed-type reactions [19,21,22]. Successful desensitization has also been reported in delayed-type hypersensitivity reactions to antituberculosis drugs and trimethoprim-sulfamethoxazole and fluconazole [23-25].

By reducing various intracellular signals, desensitization therapy inhibits the activation of the immune response in the target cells, thereby inducing a temporary tolerance to the immunological memory of the drug, allowing safe re-dosing.

2.3. Clinical application of desensitization therapy

2.3.1. Overview of desensitization therapy

2.3.1.1. Application and protocol selection

In order to perform desensitization therapy, a clear diagnosis through thorough history taking and examination is essential. Desensitization can be considered when a drug hypersensitivity reaction occurs and there is no alternative to the drug, when the efficacy of the causative drug is so superior to the alternative drug that reuse is inevitable, and when the benefits of using the causative drug outweigh the risks. However, it should be used with caution in patients with a history of severe hypersensitivity reactions such as anaphylaxis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, in patients with risk factors for fatal extrapulmonary reactions, in patients with cardiovascular or respiratory disease, or in patients whose usual use of beta-blockers is expected to result in a poor response to emergency measures in the event of anaphylaxis.

Drug desensitization is most effective in IgE-mediated immediate-type anaphylaxis and may be indicated in non-IgE-mediated reactions, such as infusion-related reactions in which the agent directly causes mast cell degranulation or cytokine release [26].

There are two modalities of desensitization: rapid drug desensitization and slow drug desensitization. Rapid desensitization is recommended for immediate allergic and non-allergic reactions, and the most widely used protocol is to double the dose every 15 minutes to reach the target dose [27]. Slow desensitization is indicated for T-cell-mediated type IV delayed hypersensitivity reactions. However, for slow desensitization, there is currently no established protocol for the initial dose, the rate of dose escalation between phases, and the time interval between phases. Therefore, more clinical experience and research are needed to establish the role and efficacy of desensitization for delayed-type hypersensitivity reactions.

To design an appropriate desensitization protocol, the concentration, dose, dosing interval, and route of administration (oral, intravenous, intramuscular, or subcutaneous injection) of the offending drug should be considered. For example, oral and intravenous protocols are preferred in clinical practice because intramuscular and subcutaneous injection protocols are associated with significant patient discomfort due to repeated injections [28]. Routes of administration are interchangeable without compromising the efficacy of the drug, and although intravenous protocols are often used for careful dose titration, they can be administered by a variety of routes and can be switched during the study.

2.3.1.2. Pretreatment and treatment of adverse reactions

To date, there is no standardized pretreatment for desensitization, but the use of H1 and H2 blockers and

glucocorticoids can be considered pretreatment. Aspirin reduces the occurrence of flushing by inhibiting the production of prostaglandins via cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) [29], Montelukast blocks the end products of the arachidonic acid metabolic pathway and is thought to help reduce the incidence and severity of protrusive reactions, and nonsteroidal anti-inflammatory drugs (NSAIDs) may help reduce the symptoms of cytokine release syndrome. However, the use of glucocorticoids alone is not recommended because they do not prevent the initial degranulation of mast cells [30].

If a protrusion reaction occurs during desensitization therapy, it should be treated promptly and according to severity. If an extrusion reaction is suspected, even if it is mild, the infusion should be stopped immediately. Many mild reactions resolve with infusion discontinuation. For mild and moderate extrusion reactions that do not resolve with infusion alone, antihistamines and glucocorticoids may be tried, depending on the symptoms. Resumption of desensitization therapy at or before the onset of symptoms after the resolution of the reaction can be successful in many patients. However, in severe cases of anaphylaxis, intramuscular epinephrine, large amounts of fluids, and adequate oxygenation are essential, and desensitization should be discontinued until the patient is stable. In the event of anaphylaxis, desensitization can be resumed after complete resolution of symptoms, but due to the risk of recurrence of severe reactions, the protocol should be tailored to the patient in consultation with an allergist.

Tolerance achieved through desensitization is maintained as long as the drug is administered. However, in the case of intermittently administered medications such as anticancer drugs, tolerance may be lost during the washout period and desensitization may need to be repeated for each cycle of treatment. If desensitization does not result in anaphylaxis, the next step of desensitization can be progressively tapered [31]. However, this should be done carefully by an allergist, taking into account the severity of the initial hypersensitivity reaction, the inherent characteristics of the drug, and the frequency, pattern, and severity of anaphylaxis.

2.3.2. Key target agents

2.3.2.1. Anti-cancer drugs

Anticancer drugs are administered repeatedly at regular intervals and are prone to sensitization, and the incidence of hypersensitivity reactions varies from 1% to 80% depending on the type of drug [32]. In the case of anticancer drugs, hypersensitivity reactions to the drug as well as cytotoxicity caused by the drug itself are important causes of treatment discontinuation. Unlike conventional drugs, the use of alternative medications is limited, and continuation of chemotherapy with desensitization can have a significant impact on patient outcomes, including life expectancy. A large retrospective analysis by Sloane *et al.* reported that overall survival in patients with recurrent ovarian cancer who underwent rapid desensitization to carboplatin was non-inferior to that of the standard treatment group [33]. This suggests that the efficacy of chemotherapy is not reduced by desensitization.

Hypersensitivity reactions to anticancer drugs are usually caused by sensitization to drug-specific IgE [26], but non-IgE-mediated hypersensitivity reactions such as infusion-related or solvent-related reactions (e.g., CremophorEL, Polysorbate 80) have also been reported [34]. IgE-mediated reactions involving mast cells and basophils can present with symptoms such as urticaria, angioedema, dyspnoea, vomiting, and abdominal pain, and can also cause fatal reactions such as anaphylaxis. In general, hypersensitivity reactions due to IgE sensitization have a well-established correlation with positive skin prick tests [26,35]. Recently, there has been an increase in the number of cases of cytokine-mediated reactions associated with the increased use of monoclonal antibodies. These can occur even with the first dose of a drug and present with symptoms of generalized rash, chest discomfort,

dyspnoea, back pain, fever, chills, and myalgia without urticaria or angioedema [36]. Common anticancer drug hypersensitivity reactions in clinical practice include the platinum class (cisplatin, carboplatin, oxaliplatin, etc.), the taxane class (paclitaxel, docetaxel, etc.), and monoclonal antibodies (rituximab, infliximab, trastuzumab, bevacizumab) [37].

Hypersensitivity reactions to platinum-based drugs are reported in 1%–44% of patients receiving them [30]. Caused by progressive sensitization due to repeated drug exposure, the first hypersensitivity reaction usually occurs after 7–9 cycles of administration, especially when the drug is reused after a period of inactivity [32,37]. In addition, cross-reactions between platinum-based drugs can occur, so caution is advised when changing formulations within a platinum-based drug.

Hypersensitivity reactions to the taxane class of drugs are reported in 5%–10% of patients receiving them. IgE-mediated reactions may also occur in some patients with specific IgE to *Taxus baccata* pollen, which is the source of the taxanes [38]. However, these are usually infusion-related reactions and tend to occur during the first 1–2 cycles of treatment [39]. Therefore, if anaphylactic reactions do not occur early in the desensitization regimen, step reduction in the protocol may be considered during repeated applications of desensitization.

Hypersensitivity reactions to monoclonal antibodies take many forms, including IgE-mediated hypersensitivity and infusion-related reactions, and cytokine-mediated reactions, and can occur at any point in the drug administration cycle. For monoclonal antibodies, hypersensitivity reactions are commonly reported with rituximab and cetuximab, but the incidence varies depending on the degree of humanization and glycosylation patterns of the drug. Rituximab is widely used to treat a variety of autoimmune diseases in addition to malignancies such as lymphoma and leukemia.40 Infusion-related reactions occur in 12.5% of patients receiving rituximab, most commonly during cycles 1–2. The risk of infusion-related reactions increases with higher patient stage and higher white blood cell/lymphocyte/absolute neutrophil counts, and the infusion rate of rituximab has also been reported to be a risk factor [41]. This may be related to the increased cytokine release induced by rituximab administration, which leads to increased recruitment of immune cells and complement, inducing a massive cytokine release [42]. For cetuximab, the association with anti-α1,3-galactose IgE produced by ingestion of certain tick-bitten animals is well known [30].

Currently, desensitization to anticancer drugs is widely used, with the Adverse Drug Reaction and Desensitization Programme protocol from Brigham and Women's Hospital, USA, being well-established and widely used (Table 1) [43]. In addition, various desensitization protocols have been proposed for different countries. The Brigham and Women's Hospital desensitization protocol involves sequentially diluting the offending drug in a solvent at 1:10, 1:100, and 1:1,000 and increasing the concentration and rate of administration at 15-minute intervals. This stepwise dilution protocol allows most patients to complete desensitization therapy without serious adverse reactions but has the disadvantage of requiring additional time and manpower for dilution and fluid replacement, which may increase the risk of anticancer drug exposure [27,33]. There is also concern that the stability of the drug may be compromised by the increased time required for dilution and administration.

To overcome these disadvantages, single-concentration protocols have been proposed that involve dilution to a single concentration followed by a stepwise increase in the dosing rate at regular intervals (Table 2) [44,45]. To date, desensitization therapy using single-concentration protocols has been successfully performed for a variety of agents, including platinum- and taxane-based anticancer drugs and monoclonal antibodies [32,46]. Compared to the step-dilution protocol, there was no statistically significant difference in the completion rate of desensitization and the incidence

Table 1. Example of a 3-bag, 12-step desensitization protocol for oxaliplatin 120 mg [43]

Solution	Volume (mL)	Concentration (mg/mL)	The total dose in each solution (mg)		
A	200	0.005357	1.2		
B	200	0.05357	12.0		
C	200	0.5357	120.0		
Step	**Concentration (mg/mL)**	**Rate (mL/hr)**	**Infusion time (min)**	**Administered dose (mg)**	**Cumulative dose (mg)**
1	0.005357	2	15	0.0027	0.0027
2	0.005357	5	15	0.0067	0.0094
3	0.005357	10	15	0.0134	0.0228
4	0.005357	20	15	0.0268	0.0496
5	0.05357	5	15	0.0670	0.1166
6	0.05357	10	15	0.1339	0.2505
7	0.05357	20	15	0.2679	0.5183
8	0.05357	40	15	0.5357	1.0543
9	0.5357	10	15	1.3393	2.3933
10	0.5357	20	15	2.6785	5.0718
11	0.5357	40	15	5.3570	10.4288
12	0.5357	75	164	109.5712	120.000

Table 2. Example of a 1-bag, 13-step desensitization protocol using oxaliplatin of 120 mg [44]

Step	Concentration (mg/mL)	Rate (mL/hr)	Infusion time (min)	Administered dose (mg)	Cumulative dose (mg)
1	0.5357	0.1	15	0.0134	0.013
2	0.5357	0.2	15	0.0268	0.040
3	0.5357	0.4	15	0.0536	0.094
4	0.5357	0.8	15	0.1071	0.201
5	0.5357	1.6	15	0.2143	0.415
6	0.5357	3.2	15	0.4286	0.844
7	0.5357	6.4	15	0.8571	1.701
8	0.5357	12.8	15	1.7143	3.415
9	0.5357	25.6	15	3.4286	6.844
10	0.5357	50	15	6.6964	13.540
11	0.5357	85	15	11.3839	24.924
12	0.5357	140	15	18.7500	43.674
13	0.5357	220	38.9	76.3259	120.00

An oxaliplatin 120 mg was reconstituted with 200 mL of 5% dextrose water. The concentration of the solution was 0.5357 mg/mL. Administered dose (mg) = rate (mL/hr) × infusion time/60 (hr) × concentration (mg/mL).

of extrapolation reactions; rather, the time required for desensitization preparation was significantly reduced with the single-concentration protocol. The incidence of extrapolation reactions decreased with repeated desensitization regimens in the single-concentration protocol, as in the step-dilution protocol [46]. Thus, the single-concentration protocol may replace the step-dilution protocol in the future, not only because of the shorter administration time, but also because of the advantages of reduced labor consumption, reduced risk of exposure of healthcare personnel to anticancer drugs, avoidance of errors in the dilution process, and improved stability of the desensitizing drug.

2.3.2.2. Antibiotics

Antibiotics are widely used in clinical practice and are one of the most common causes of adverse drug reaction reports [47]. It has been reported that 7%–15%

of drug-induced anaphylaxis in tertiary care hospitals in Korea is due to penicillin or cephalosporin [48]. Both typical immediate hypersensitivity reactions, such as urticaria, angioedema, and anaphylaxis, and delayed hypersensitivity reactions, such as skin rash and severe dermatological reactions, can be induced, and some patients have a mixture of both reactions [47]. In patients with immediate-type hypersensitivity reactions, specific IgE to antigenic groups of antibiotics such as penicillin G, penicillin V, ampicillin, amoxicillin, and cefaclor can be measured in serum and can increase the sensitivity of the diagnosis when combined with skin-prick testing [49].

For antibiotic desensitization, the type of drug and route of administration varies but generally involves diluting the therapeutic dose to 1:1,000 and increasing the dose by a factor of 2–3 at regular time intervals [50]. Desensitization of penicillin and cephalosporin antibiotics is well established. Successful desensitization has also been reported with non-beta-lactam antibiotics, including vancomycin, teicoplanin, amikacin, gentamicin, erythromycin, ciprofloxacin, clarithromycin, clindamycin, and tetracycline [51].

Redman syndrome, caused by direct activation of mast cells and release of histamine in a rate-dependent manner, is an infusion-related reaction characteristic of vancomycin, teicoplanin, ciprofloxacin, and amphotericin B [52]. In most cases, reducing the rate of administration and adding antihistamines as premedication can prevent the development of symptoms, but in cases of moderate to severe severity, desensitization therapy may be indicated. Rapid desensitization can be used as a first line of treatment and can be switched to slow desensitization if adequate desensitization is not achieved [51].

More recently, successful desensitization has been reported in hypersensitivity reactions associated with antifungal agents (amphotericin B, fluconazole, itraconazole, voriconazole, micafungin) and antiviral agents (acyclovir, valganciclovir, ribavirin, nevirapine) [53-59].

2.3.2.3. Anti-TB drugs

Although *Mycobacterium tuberculosis* is a bacterium, it does not respond to common antibiotics and is difficult to treat because it multiplies very slowly. Therefore, successful treatment requires the continuous administration of several anti-TB drugs for at least six months. Anti-TB drugs are notorious for their side effects, with adverse reactions reported in 20%–57% of patients taking long-term anti-TB drugs, and treatment interruptions or modifications due to adverse drug reactions occurring in 4%–5% of patients [23]. However, adverse drug reactions to anti-TB drugs can lead to poor patient compliance and drug discontinuation, which can contribute to the acquisition of resistance, leading to treatment failure and prolonged treatment duration [60].

Hypersensitivity reactions to antituberculosis drugs are more common to two or more drugs simultaneously than to a single agent [61], and are more common in the early intensive treatment period when four-drug regimens are used. Delayed hypersensitivity reactions, such as urticaria, angioedema, and anaphylaxis, are more commonly observed than immediate reactions, such as urticarial rash and severe skin reactions [61].

Since 1990, several publications have reported the success of antituberculosis drug desensitization using oral and intravenous protocols. Desensitization has been shown to allow 70%–80% of patients with hypersensitivity reactions to first-line antituberculosis drugs to safely continue treatment with the first-line drugs [62], and in patients with hypersensitivity reactions to second-line drugs such as streptomycin, kanamycin, and cycloserine, desensitization has also been shown to allow safe continuation of treatment [63]. In a Korean multicentre study of patients with drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome due to first-line antituberculosis drugs, multidrug hypersensitivity reactions were reported in which all first-line antituberculosis drugs were replaced with second-line antituberculosis drugs, but hypersensitivity reactions were also induced to

new drugs. Such multidrug hypersensitivity reactions are often reported in DRESS syndrome, but they are observed more frequently than when the causative agent is an anti-TB drug. Therefore, switching to a second-line anti-TB drug with relatively low treatment success and high side effects may not be a solution. As an alternative, when desensitization therapy is applied to first-line antituberculosis drugs, it has been reported that 84.6% of patients can continue to use them without hypersensitivity reactions and that some of the reactions that do occur are mild or less severe [64].

Both rapid desensitization, in which the drug dose is increased at intervals of 15 minutes to 1 hour, and slow desensitization, in which the drug dose is increased more gradually at intervals of several hours to 1 day, have been reported (Table 3) [64,65]. Traditionally, slow desensitization has been recommended for delayed hypersensitivity reactions, but there have been several recent reports of successful rapid desensitization for delayed reactions [66].

2.3.2.4. Aspirin and NSAIDs

Aspirin and NSAIDs are commonly prescribed drugs in daily life and are known to be one of the common causes of hypersensitivity reactions due to their easy accessibility [67]. They are known to affect arachidonic acid metabolism through COX-1 inhibition, causing symptoms such as urticaria, angioedema, bronchoconstriction, and hypotension by non-immunological mechanisms [68]. Clinical manifestations vary depending on the organ involved and are responsive to both aspirin and NSAIDs with the same action [69,70]. Hypersensitivity to aspirin, particularly in patients with asthma and rhinosinusitis/nasal polyps, is known as Samter's triad and is referred to as NSAID-exacerbated respiratory disease. NSAIDs can also cause urticaria or angioedema, which is sometimes referred to as NSAID-exacerbated cutaneous disease or NSAID-induced cutaneous disease, depending on the presence or absence of underlying chronic urticaria. Desensitization therapy for these NSAID hypersensitivities reduces the production of cysteinyl leukotrienes and their receptors in arachidonic acid metabolism, thereby attenuating cutaneous and airway reactions [71]. Hypersensitivity reactions due to immunological mechanisms have been described as immediate hypersensitivity reactions caused by IgE specific to aspirin and certain NSAIDs

Table 3. Example of 4-day isoniazid desensitization protocol (target dose: 300 mg)

Day	Step	Concentration (mg/mL)	Administered volume (mL)	Time interval (hr)	Administered dose (mg)
1	1	0.2	0.1	3	0.02
	2	0.2	0.2	3	0.04
	3	0.2	0.5	3	0.10
	4	0.2	1	3	0.20
	5	0.2	2	3	0.40
	6	0.2	4	3	0.80
	7	0.2	0.8	3	1.60
	8	0.2	1.5	3	3
	9	2.0	3	3	6
	10	2.0	6	3	12
2	11	2.0	12	3	24
	12	100-mg Tab	0.5 Tab	3	50
	13	100-mg Tab	1 Tab	3	100
3	14	100-mg Tab	2 Tab	24	200
4	15	100-mg Tab	3 Tab	24	300

Isoniazid 100 mg was reconstituted with 500 mL of normal saline. The concentration of the solution was 0.20 mg/mL. Isoniazid 100 mg was reconstituted with 50 mL of normal saline. The concentration of the solution was 2.00 mg/mL.

and delayed hypersensitivity reactions, such as severe skin reactions, caused by CD4+ or CD8+ T cells [67,72]. However, these reactions are specific to a particular NSAID class and take the form of hypersensitivity to a single NSAID with no cross-reactivity to NSAIDs in other classes [73].

In cases of NSAID hypersensitivity due to non-immunological mechanisms, selective COX-1 inhibitors such as acetaminophen and meloxicam, which have mild COX-2 inhibition, and selective COX-2 inhibitors such as celecoxib can be used with relative safety. However, caution should be exercised with these drugs as they may also cause symptoms in some patients [74]. In single NSAID hypersensitivity reactions, alternatives to the culprit drug are readily available, but desensitization can be used cautiously if the use of a specific NSAID is essential [75]. However, there is currently no established protocol, and desensitization protocols should be tailored to the patient's clinical presentation and medication. Desensitization to aspirin and NSAIDs is considered in patients with cardiovascular and musculoskeletal conditions that require continuous aspirin or NSAID administration. In addition, improvements in overall symptoms and quality of life, and reductions in nasal polyps and sinus infections have been reported after desensitization to aspirin in patients with aspirin-sensitive respiratory disease [70].

Oral desensitization protocols for aspirin (Table 4 and 5) are well established and the final desensitization dose will depend on the target therapeutic dose. For cardiovascular or musculoskeletal disease, low doses of

Table 4. Example of aspirin desensitization protocol (target dose: 100 mg)

Step	Concentration (mg/mL)	Administered volume (mL)	Time interval (hr)	Administered dose (mg)
1	10	0.1	30	1
2	10	0.2	30	2
3	10	0.4	30	4
4	10	0.8	30	8
5	10	1.6	30	16
6	10	3.2	30	32
7	10	6.4	30	64
8	100-mg Tab	1 Tab	30	100

Aspirin 100 mg was reconstituted with 10 mL of 5% dextrose in water. The concentration of the solution was 10 mg/mL.

Table 5. Example of aspirin desensitization protocol (target dose: 300 mg)

Day	Step	Concentration (mg/mL)	Administered volume (mL)	Time interval (hr)	Administered dose (mg)
	1	1	0.1	1	0.1
	2	1	0.2	1	0.2
	3	1	0.5	1	0.5
	4	1	1	1	1
	5	1	2	1	2
1	6	1	5	1	5
	7	10	1	1	10
	8	10	2.5	1	25
	9	10	5	1	50
	10	100-mg Tab	1 Tab	2	100
	11	100-mg Tab	2 Tab	2	200
2	12	100-mg Tab	3 Tab	24	300

Aspirin 100 mg was reconstituted with 100 mL of 5% dextrose in water. The concentration of the solution was 1.00 mg/mL. Aspirin 100 mg was reconstituted with 10 mL of 5% dextrose in water. The concentration of the solution was 10.0 mg/mL.

aspirin (75–100 mg/day) are used, whereas in patients with NSAID hypersensitivity respiratory disease or chronic sinusitis, high doses of aspirin (up to 625 mg/day) are administered, and desensitization therapy should be adjusted according to the target therapeutic dose [70].

Tolerance to aspirin and NSAIDs acquired through desensitization therapy persists for 48–72 hours after the end of desensitization therapy, but caution should be exercised because hypersensitivity reactions may recur if the drugs are discontinued for more than 2–5 days [76,77].

3. Conclusion

The development of hypersensitivity reactions due to repeated drug administration during treatment is a major impediment to therapeutic outcomes. Desensitization is the process of inducing temporary tolerance to a drug by gradually increasing the concentration of the drug from a very small amount in order to reach a therapeutic dose without hypersensitivity reactions. It can be used when alternative medications are not available, when the offending drug that caused the hypersensitivity reaction has a much higher efficacy than the alternative, or when the benefits of the offending drug outweigh the risk of developing an adverse reaction. The severity of anaphylactic reactions that occur during desensitization therapy can vary from mild to severe and are usually resolved with immediate discontinuation of the offending drug. However, it should be used with caution in patients with a history of severe hypersensitivity reactions or in patients with risk factors for developing a life-threatening reaction. In the future, optimized desensitization protocols should be developed for a wider range of drugs, taking into account patient and drug characteristics and the severity of the reaction.

Disclosure statement

The authors declare no conflict of interest.

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