<center>R E V I E W</center>

Drug desensitization in allergic children

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Summary. Drug allergy is an increasing problem worldwide, affecting all populations and races, children and adults, and for which diagnosis and treatment are not well standardized yet. Besides classical treatments, new drugs have been developed, especially for patients suffering from malignancies and chronic inflammatory diseases, that specifically target the cause of the disease. For those patients requiring such molecules, it is sometimes difficult to find an alternative drug when hypersensitivity reactions occur. Desensitization is therefore the best option whenever no alternative therapy is available but also when alternative treatments are considered therapeutically inferior and or more toxic. Despite its clinical success, little is known about the mechanisms and molecular targets of drug desensitization. Desensitization protocols use a gradual dose escalation to allow the safe administration of a treatment to which a patient previously presented a hypersensitivity reaction. The procedure requires special training and coordination of an allergy team, including physicians, nurses, and pharmacists, working together to safely and successfully implement desensitization protocols when appropriate. There is no difference in desensitization protocol between adults and children, except for the final cumulative dose of the administered drug. (www.actabiomedica.it)

Key words: children, drug allergy, drug desensitization, hypersensitivity reactions, premedication

Background

Drug hypersensitivity reactions may occur after intake of any kind of drug. Antibiotics are among the most common molecules associated to such reactions. Drug hypersensitivity may affect any organ or system, and manifestations range widely in clinical severity from mild pruritus or urticaria (1) to anaphylaxis (2, 3). In most cases, the suspected drug is subsequently avoided. The decision to desensitize should not be taken lightly since it is an expensive and time-consuming procedure, possibly associated to severe reactions. Potential indications to undergo a desensitization protocol should include the lack of a viable alternative, or the lower efficacy and/or a greater toxicity of available alternative. This seems to be particularly important when dealing with patients suffering from chronic conditions, for which few effective drugs have been approved (4). When treating patients presenting with an infectious disease, physicians may usually select a safe antibiotic alternative. Nonetheless, in some cases, no alternative treatment exists for optimal therapy,

such as in multi-resistant patients with cystic fibrosis or tuberculosis, or in patients needing chemotherapic agents, monoclonal antibodies, anti-epileptic drugs, or vaccines. Indeed, in patients with multi-resistant infections or with a history of multiple drug allergy a desensitization protocol may outweigh the risks (5). Desensitization protocols have been developed only for therapeutic purposes to safely administer a drug to which the patient has a proven or highly suspected hypersensitivity reactions.

They consist of administration of increasing doses of the drug with a pre-determined time schedule. When tolerance to the required dose of the drug is reached, such molecule will be accepted by the patient's immune system, for the whole course of the therapy. On the other hand, if the treatment is stopped, patients will require to undergo a new desensitization before starting any further course of treatment using the same drug (6,7). Such approach allows to protect patients from experiencing unexpected anaphylactic reactions, and to optimize the clinical outcomes.

The aim of the present paper is to focus on possible drug desensitization protocols in children. An evidence-based review is currently not feasible, because there is a lack of controlled studies in children.

Drug desensitization

The drug desensitization is a process through which a patient's immune response to a drug is modified to generate impermanent tolerance, taking advantage of well characterized inhibitory pathways (8).

In contrast to desensitization through allergen immunotherapy to aeroallergens or hymenoptera venoms (9), drug desensitization only provides a temporary state of tolerance, being sustained only for the time the drug remains in the patient's system (3-4 half-lives).

Rosa et al. (10) reported a 11 years-old girl, who had previously experienced a hypersensitivity reaction to recombinant human erythropoietin, and failed a 2-days desensitization protocol with epoetin alfa, while tolerating the drug after a 17-days protocol. Two months later, the patient developed a systemic reaction after intravenous injection of the molecule, but she had actually been missing several doses of epoetin alfa. In

fact, desensitization protocols require that the drug is regularly administered (usually at least once a day). In case of treatment discontinuation, drug reactions may occur again if the molecule is re-administered at standard dose. Therefore, patients should undergo a desensitization protocol for each course of drug. Desensitization has been used to induce tolerance not only in patients with a proven (or a strongly suspected) IgE-mediated allergy, but also in those presenting with non IgE-mediated reactions. Most protocols require a one-day hospitalization to be effective, but some patients need slower protocol, over a few days, to reach tolerance to a drug. Such consideration strengthens the fact that desensitization should be tailored to the patient's reaction and that a single protocol may not fit all possible occasions.

Mechanisms

Since the first case of drug desensitization was published by Peck et al. (11), many Authors have been trying to have a better understanding of the immunological basis of drug desensitization. Nevertheless, the exact mechanisms remain poorly understood. Rapid drug desensitization is a process through which mast cells and possibly basophils become hypo-responsive to a drug allergen, providing therefore temporary tolerance in drug hypersensitive patients (12). In sensitized patients, drug exposure causes the quick release of inflammatory mediators from activated mast cells, leading to the systemic allergic reaction. In the early phase of mast cells activation, the release of mediators is quickly followed by an increased synthesis of prostaglandins (PGD2) and leukotrienes (LTC/D4 and LTB4) that play an additional role in the clinical expression of the allergic reaction (13). During the late phase of mast cell activation, cytokines such as TNFα and IL-6 are released along with chemokines and other factors. Mast cells are key effector cells in IgE-dependent immediate hypersensitivity because they express large amounts of a high-affinity tetrameric receptor (FceRI) for the Fc region of IgE. Multivalent allergen activates mast cells through binding to IgE and aggregating IgE–FceRI complexes. FceRI-mediated signaling induces the activation of Src family

tyrosine kinases Lyn and Fyn followed by the recruitment and activation of tyrosine kinase Syk. Phosphorylation of LAT by Syk induces the recruitment and activation of PLCc, leading to calcium mobilization and mast cell degranulation (14).

In desensitization, a central role is played by the downregulation of the expression of mast cells and basophils. Three non-mutually exclusive hypotheses explaining how RDD could impair mast cell activation have been suggested: (1) depletion of activating signal transduction components such as syk kinase; (2) sub-threshold depletion of mediators; and (3) internalization of FcɛRI through progressive cross-linking at a low antigen concentration. On the other hand, basophils downregulation causes the activation of SHIP; the processing of syk by ubiquination; the degradation and loss of FcɛR1 receptors; and the resorting of receptors in the cell membrane. The desensitization process also seems to be related to the inhibition of the release of mediators such as β-hexosaminidase, prostaglandins and leukotrienes (15).

The precise mechanism of desensitization in cell-mediated reactions is only supposed in studies focusing on phenytoin. In these cases, the process seems to be mediated by the activation of T regulatory cells, demonstrated by the simultaneous reduction in skin lesions and skin recruitment of Foxp3+ regulatory T cells (16,17). Other studies on desensitization to allopurinol, showed similar results (18).

Indication and contraindication

The general rules for drug desensitization in adults are also applied to children. Drug desensitization is indicated when no alternative drug is available; when the prescribed drug is more effective than other possible alternatives; if there are no comorbidities putting the patient at increased risk during the procedure; and when the reported drug reaction was not a severe, life-threatening immune-toxic reaction, vasculitis or bullous skin disease such a Stevens-Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN) or drug induced hypersensitivity syndrome (DIHS). Desensitization in type II and type III hypersensitivity reactions is contraindicated, because the interaction between the antigen and the antibody may possibly lead to the activation and consumption of the complement system (19).

In patients with history of severe hypersensitivity reaction, an alternative may not be available, which makes it difficult to decide to rule out the possibility of a desensitization. In 2018, Saripassorn et al. (20) showed a success rate of 62% of drug desensitization in adults with previous history of severe allergic reactions, such as SJS, TEN, DRESS. Corrado-Chagoya et al. (21) reported that a 6 years-old boy experienced a SJS/TEN overlap syndrome to the anti-tuberculosis (TB) drugs, and he tolerated the anti-TB drugs after undergoing a desensitization protocol with premedication. Witcher et al. showed that a 5 years-old boy was successfully desensitized to phenobarbital, after having presented a DRESS syndrome (22). Other cases of successful desensitization protocols in adults with history of severe hypersensitivity reactions are reported in Table 1 (23, 24).

An individual risk/benefit evaluation should be assessed, before performing any procedures (25). Physicians and patients (and their caregivers) should be aware that desensitization may be associated with a possible risk of acute hypersensitivity reaction during the procedure.

Table 1. Case reports of patients experiencing severe allergic reactions, but tolerating desensitization protocols

Author	Year	Number of patients	Age	Reaction	Drug
Corrado-Chagoya (21)	2018	1	Pediatric	SJS	Anti-TB
Witcher (22)	2018	1	Pediatric	DRESS	Phenobarbital
Thong (24)	2014	2	Adult	SJS	Anti-TB
Thong (24)	2014	5	Adult	DIHS	Anti-TB
Minor (23)	2012	1	Adult	SJS	Veramufanib

Legend - SJS: Stevens-Johnson syndrome; DRESS: drug reaction with eosinophilia and systemic symptoms; DIHS: drug induced hypersensitivity syndrome; Anti-TB: anti-tuberculosis drugs

Desensitization protocols

Choosing a specific desensitization protocol depend on the patient's medical disease requiring the specific drug, the presence of atopy and other comorbidities, and the type of adverse hypersensitivity reaction presented in the clinical history (26). Generally, it should be advisable to use protocols previously published and validated on few patients. However, many times and for specific reasons, protocols may have to be tailored on single patient. A few studies on drug desensitization in children have been performed. So, it has been suggested that protocols applied for adults should be adapted in children (26, 27). In general, protocols in children differ from those in adults only in the cumulative dose, which should be the daily dose used for adequate therapy (5).

At baseline, patients should be in a stable clinical condition and any concomitant medication used for treating underlying diseases must be continued, with the only exception of beta-blockers, that should be discontinued, if the cardiologist allows it, since they may interfere with the treatment of a severe hypersensitivity reaction. Caution and surveillance by well-trained specialists and nurses are mandatory in all cases, with continuous monitoring of the child (28). Caregivers should be taught to recognize early signs and to notify the nurse or doctor. Desensitization for more severe reactions, like anaphylaxis, should be carried out in the intensive care unit (25). An informed and signed consent, by parents and/or tutors, is required (25).

It is still debated the role of premedication with corticosteroids and antihistamines. Premedication is supposed to reduce the risks for a hypersensitivity reaction occurring during desensitization. Premedication regimens vary from one center to the other and aim to prevent or minimize the severity of any allergic reactions. In some studies, authors advise to administer, 20 minutes before starting desensitization, diphenhydramine (1 mg/kg), famotidine (20 mg iv in patients of at least 12 years of age) and/or ranitidine (1,5 mg/kg). Others include a dose of dexamethasone (10 mg/m², maximum 20 mg) that should be taken the night before the protocol and the same morning, especially when desensitizing patients to chemotherapeutic agents. In patients who previously failed a desensitization protocol, or in those having experienced flushing reactions, montelukast (10 mg orally for children > 14 years old, 5 mg for children 6-14 years old; 4 mg for children 2-5 years old) and/or acetylsalicilic acid (10-15 mg/kg) 1 hour before desensitization may be considered as additional premedication. In patients requiring desensitization to monoclonal antibodies, a premedication with paracetamol/acetaminophen (15 mg/kg) and antihistamines is advised, to reduce reactions due to possible cytokine release (4). Nevertheless, the European Network of Drug Allergy (ENDA) and the European Academy for Allergy and Clinical Immunology (EAACI) interest group on drug hypersensitivity claim that premedication with systemic corticosteroids and antihistamines is not necessary and may mask early signs of a hypersensitivity reaction (27). Such consideration may be relevant in research settings, but it is probably less important when the target is to achieve the possibility to administer a drug to a needing patient.

Route of administration and dosing scheme

The drug should be administered though the same route required for therapeutic purposes. Both oral and parenteral routes may be used in the procedure and they both seem equally effective. Regarding drugs that may be administered both orally and parenterally, the oral route seems to be safer, easier and less expensive. In some protocols both routes may be combined for the same patient (27). Specific protocols for parental routes have been developed and have been widely used for many drugs, including beta-lactams, insulins, chemotherapeutic agents and monoclonal antibodies.

The starting dose should be determined considering the severity of the reported reaction: in patient with severe anaphylaxis the initial dose should be between 1/1.000.000 and 1/10.000 of the full therapeutic dose. In patients with a positive skin test to a non-irritating concentration of a drug, the starting dose may be determined based on the endpoint titration. This concept is applicable only in patients with positive skin prick test performed according to available guidelines (29, 30) and using recommended concentrations (30). In patient with a very low endpoint titration value and/or with previous severe reactions, the protocol should

be accordingly modified, by either reducing the initial dose, or decreasing the rate of infusion, or increasing the time interval between doses, or increasing the total number of doses. Most protocols increase doses by doubling, others by tripling the dose, compared with the previously administered one. Incremental step ranges from two-times to ten-times the previous dose (2) and the total amount of steps goes from 12 to 20. Time interval between two steps ranges from 15 minutes to 120 minutes and total duration of desensitization from 2 hours (rapid desensitization protocol) to a few weeks (slow desensitization schemes).

The protocol by Demoly et al., starts at a 1/1.000.000 of the therapeutic dose, and, through a total of 13 steps, they triple each time the previous dose, to reach the final cumulative dose (31,32). In protocols developed by Castells et al. for chemotherapeutics and monoclonal antibodies, the final step entails both a much larger dose (around 17-30 times greater than the previous one), and a much longer time of administration (5, 17). It is probably for such reason that the same Authors showed a greater rate of adverse reactions occurring during the administration of the last dose.

The Brigham and Women's Hospital Rapid Drug Desensitization Program (BWH) assessed a 12- to 20-step standard protocol based on an in vitro mouse mast cell model, in which unresponsiveness to a triggering antigen dose was achieved by delivering doubling doses of antigen at fixed time intervals starting at 1/1000 the final dose (33). The most commonly used protocol has 12 steps, using three solutions at escalating rates. Patients who have had severe anaphylactic reactions to the agent of choice or who have reacted early in the standard 12-step desensitization may experience fewer symptoms if desensitized using a 16-step protocol, which adds another bag containing 1/1000th of the full dose. The use of a 16-step (four bags) or a 20-step (five bags) protocol is reserved for high-risk patients. It was also observed that 70% of reactions during desensitization occurred during the 12th and the final step using standard 12-step protocol (34).

In conclusion, when doses are too high and delivered too fast, the state of unresponsiveness may be delayed; this can explain breakthrough reactions during desensitization. Also, a certain time interval between doses of the drug antigen is needed to achieve maximum tolerance of the therapeutic dose (12).

Desensitization to antibiotics

Desensitization protocols to antibiotics seem to be very successful especially in some patients, such as HIV-positive patients with a sulfonamide hypersensitivity or cystic fibrosis patients with any antibiotic hypersensitivity, showing efficacy rates of above 80%. However, in most published cases, a pre-existent sensitization and allergy have not been proven by positive skin tests and/or drug challenge. Therefore, in some reported cohorts, successful re-administration may be achieved in non-allergic patients (19). On the other hand, adverse reactions to cotrimoxazole in HIV-positive patients are rarely IgE mediated. Therefore, while skin tests may be useful for diagnosing IgE-mediated reactions, allergy to cotrimoxazole is usually diagnosed on medical history. Once an adverse reaction to cotrimoxazole occurs, a desensitization protocol is the management strategy of choice as it has proven to be more beneficial and less risky than a drug challenge to prescribe the drug for prophylaxis purposes (35). In most cases of cotrimoxazole allergy, the same symptoms occur on several administrations of the drug. So, the causative link between drug administration and hypersensitivity symptoms makes the challenge an unnecessary step to reach a diagnosis of drug allergy (36). Nagarajan et al. (37) successfully performed a 7-h desensitization protocol to cotrimoxazole in 4 of 5 HIV-positive children. After a 10-month follow-up, all patients continued to tolerate cotrimoxazole. Based on a paper by Moreno-Ancillo et al. (36), Gomez-Traseira (38) performed a successful 28-days desensitization protocol on a 5 years-old girl, after she had presented mild reactions during a faster desensitization procedure. A variety of cotrimoxazole desensitization protocols have been performed in HIV patients in adulthood, but there is still a lack of validated protocols for such drug in children (38).

Several specific protocols for penicillin desensitization have been widely published, but the one described by Sullivan et al. (39) seems to be the most applied in clinical practice. For penicillin-derived antibiotics, the oral route seems to be safer, because it is

less prone to expose patients to multivalent penicillin conjugates, which play a key role in IgE- mediated reactions. It is the preferable route in children too (Table 2). Protocol for oral and intravenous desensitization to penicillin usually starts with 1/10.000 to 1/1.000 of the target dose, and doses have a two-folds increase at each step. Doses are administrated every 15-20 min, over the course of several hours, until the therapeutic dose is reached. Intravenous protocols and protocols with mixed routes are also available. In patients with severe anaphylaxis, the initial dose should be 1/1.000.000 to 1/10.000 of the full therapeutic dose (17).

There are some cases in the literature of successful desensitization to other non-penicillin beta-lactams such as meropenem, cefotaxime, ceftriaxone and ceftazidime. Most of the reactions reported with these molecules are IgE mediated. Most studies on desensitization to such agents are reported in patients suffering from cystic fibrosis. Protocols differ in initial doses, dose increments, number of steps (6-12 steps), use of premedication, and success rates, that range from 75% to 100% (25).

Hypersensitivity reaction to anti-TB drugs ranging from maculopapular or urticarial rush to severe reactions, have been reported in 4% to 5% of patients (21). If an adverse drug reaction occurs in a child taking multiple drugs simultaneously, a careful clinical assessment should be performed to determine a possible allergic mechanism causing the adverse event. After

stopping all drugs, they should be re-administered one at the time, with a 4-5 days-interval to detect the responsible drug (25). Thereafter, patients may be desensitized to the culprit drug. There are only some pediatric case reports with rapid desensitization in suspected IgE mediated allergy and with slow desensitization in T- cell mediated allergy.

Desensitization to vaccines

Immunization with DTP vaccine (diphtheria, tetanus and pertussis) is a part of the vaccination calendar for children. Adverse allergic reactions vary from minimal urticarial reactions to life-threatening anaphylaxis. In infancy, these reactions usually interrupt the vaccination calendar, but immunization with tetanus-vaccine in these children should still be assured. Desensitization to tetanus-vaccine is performed using a 9-step graded dosing schedule with the tetanus toxoid vaccine (40) (Table 3).

Desensitization to MMR-vaccine is performed by subsequent subcutaneous administration of 0.05 ml of a 1/100 dilution, 0,05 ml of a 1/10 dilution, and 0,05 ml of the non-diluted vaccine up to the 0,5 ml dose (41,42).

Desensitization to chemotherapeutics and monoclonal agents

Chemotherapeutics and monoclonal antibodies are expensive, and they often are the best treatment option for those patients requiring such treatment. So, over the last 15 years, attention has been focused on desensitization to chemotherapeutics and monoclonal antibodies. In most cases desensitization has

Table 2. Oral Penicillin desensitization protocol. The time between doses is every 15-20 minutes (39)

Step	Penicillin mg/ml	Amount (ml)	Dose (mg)	Cumulative dose
1	0.5	0.1	0.05	0.05
2	0.5	0.2	0.1	0.15
3	0.5	0.4	0.2	0.35
4	0.5	0.8	0.4	0.75
5	0.5	1.6	0.8	1.55
6	0.5	3.2	1.6	3.15
7	0.5	6.4	3.2	6.35
8	5.0	1.2	6.0	12.35
9	5.0	2.4	12.0	24.35
10	5.0	5.0	25.0	49.35
11	50.0	1.0	50.0	100.0
12	50.0	2.0	100.0	200.0
13	50.0	4.0	200.0	400.0
14	50.0	8.0	400.0	800.0

Table 3. Desensitization protocol to tetanus vaccine; injections should be performed every 20 minutes (40)

Dose number	Volume (ml)	Dilution	Route
1	0.2	1:1000	Intradermal
2	0.2	1:100	Intradermal
3	0.2	1:100	Intradermal
4	0.2	1:10	Subcutaneous
5	0.10	1:10	Subcutaneous
6	0.05	Non-diluted	Subcutaneous
7	0.10	Non-diluted	Subcutaneous
8	0.15	Non-diluted	Subcutaneous
9	0.20	Non-diluted	Subcutaneous

been shown to be effective and safe (6). As chemotherapeutics are usually dosed per meter squared, the full therapeutic dose differs for each child. Intravenous desensitization with carboplatin starts at dose of 0.01-1 mg, infused over 1 min. Dose increments are made every 15 minutes, by prolonging the infusion time, while holding the infusion rate constant. When a dose of 15-22.5 mg administered over 15-22.5 minutes is well tolerate, the infusion rate may be increased to 100 mg/h for 1 h and then to 200 mg/h for the remaining dose (5).

Confino-Cohen et al. (43) published a protocol, including patients' premedication, that starts with the administration of 1/1.000 of the total dose over 90 minutes, followed by 1%, 10%, and 89% of the total therapeutic dose, each perfused over 90 minutes.

Several large case series describing desensitization regimens have been published in adults with hypersensitivity to carboplatin (5, 37-40). Most of them include a premedication with 10 to 20 mg of dexamethasone, associated with an antihistamine. Leukotriene receptor antagonists such as zileuton or Montelukast have also been used. Desensitization protocols start with 1/1.000 or 1/100 of the total dose and increase to full dose over 6 to16 hours. Success rates range from 79% to 99% (8, 43-46).

Small case series in children reported that desensitization was largely unsuccessful (47, 48). The reason for the difference between children and adults is not clear yet, as the mechanism determining hypersensitivity reactions to carboplatin (49). Hypersensitivity reactions have been reported to all platinum-containing chemotherapeutics. The Canadian Pediatric Brain Tumor Consortium reported a 42% rate carboplatin hypersensitivity in children and very different outcomes after re-challenge (50). Other platinum compounds may act as haptens to stimulate the development of specific IgE antibodies which, in subsequent infusions, generate a type I hypersensitivity. In support of a type I IgE mediated hypersensitivity are the rising incidence of hypersensitivity reactions after repeated injections of these drugs and the occurrence of positive skin prick tests to platinum compounds. A possible non-IgE mediated mechanism may be due to a direct complement activation on the mast cell membrane causing histamine release (49).

L-Asparaginase is an immunogenic compound in humans and is often associated to allergic reactions. Even if the pathogenesis of hypersensitivity to L-Asparaginase has not been fully explained, some studies showed that the immunological mechanism may be either IgE mediated or related to complement activation mediated by IgG or IgM complexes with L- Asparaginase (51).

L-Asparaginase is administrated intramuscularly, but intravenous desensitization had been described starting at a 1 IU dose, that is then doubled every 10 minutes (52).

Intravenous desensitization to methotrexate is started at 1/1000 of the full dose over 1.5 hour, followed by 1/10 over 6 hours and by the remaining dose over 24 hours, for every therapeutic cycle (53,54). This procedure may necessitate a dose reduction due to increased toxicity secondary to a prolonged exposure to the agent (53).

Several protocols have been successfully applied to monoclonal agents, such as infliximab, trasduzumab, rituximab, omalizumab, natalizumab, basiliximab, abciximab and cetuximab (14, 55). An important feature of these protocols is that premedication with diphenhydramine and famotidine, aspirin, montelukast or glucocorticoids is usually included to considerably reduce adverse reactions.

Rapid desensitization protocols were reported in pediatric patients for rituximab (56), infliximab (31, 57), and alemtuzumab (58).

Conclusions

Drug desensitization induces a temporary tolerance to the drug that previously caused a hypersensitivity reaction, allowing the administration of the same drug, when there are no alternative treatments, or only fewer effective ones. Drug desensitization protects against anaphylaxis and activates inhibitory mechanisms which need further research and comprehension. Desensitization is dose and drug dependent, and therefore patient dependent. Unfortunately, it is not persistent, and when drug intake is discontinued, tolerance is lost over hours or days. Therefore, for patients needing several courses of the same treatment,

desensitization protocols must be performed before the beginning of every single course. Probiotics induce a Th1 response instead of Th1 which is associated with allergy (59, 60). Probiotics have been successfully used as adjuvants in desensitization to peanuts (61) and aeroallergen (62), and they may be a a promising means of enhancing unresponsiveness induced by drug desensitization. Desensitization is a high-risk procedure and should be performed only by well- trained allergy teams in selected patients, after assessing a personalized risk/ benefit profile. The literature lacks cohort studies on drug desensitization in children and the availability of validated protocols is crucial for the success of this procedure. Both successful and unsuccessful outcomes should be published to establish the most efficient and safer protocols.

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