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REVIEW

Clinical practice

Drug desensitization in children

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Abstract Immediate type allergic reactions to medication are potentially life threatening and can hamper drug therapy of several medical conditions. Exact incidence and prevalence data for these reactions in children are lacking. If no alternative drug treatment is available, a desensitization procedure may secure the continuation of necessary therapy. Desensitization is only appropriate in case of a strong suspicion of an IgE-mediated allergic reaction. It should be performed by trained clinicians (allergy specialists) in a hospital setting where treatment of a potential anaphylactic reaction can be done without any delay. In this article, literature describing desensitization procedures for several antibiotics, antineoplastic agents, and vaccines in children is reviewed. In general, desensitization schemes for children differ only in final dose from schemes for adults. Contradictory data were found regarding the protective effects of premedication with antihistamines and glucocorticoids.

Keywords Children · Drug allergy · Prevalence · Desensitization · Protocol

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Introduction and definitions

A drug allergy is an adverse drug reaction that results from a specific immunologic response to a medication. Allergic drug reactions account for about 6–10% of all adverse drug reactions, but up to 10% of fatal reactions in the adult population [17]. There are no prevalence data or incidence data for children regarding these allergic drug reactions.

The World Allergy Organization (WAO) has recommended dividing immunologic drug reactions into immediate type I reactions (onset within 1 h of exposure) and delayed reactions (onset after 1 h), based upon the timing of the appearance of symptoms [10]. The signs and symptoms of type I reactions are directly attributable to the vasoactive mediators released by mast cells and basophils. The most common signs and symptoms are urticaria, pruritus, flushing, angioedema (sometimes leading to throat tightness with stridor), wheezing, gastrointestinal symptoms, and hypotension. Anaphylaxis is the most severe presentation of an IgE-mediated drug reaction.

The drugs most commonly implicated in type I reactions in children are beta-lactam drugs, i.e., penicillins and cephalosporins.

Diagnostic procedures in drug allergy are confined to a detailed clinical history and confirmation of an IgE-mediated reaction. The ENDA (European Network for Drug Allergy, an interest group of the EAACI) has set up guidelines on how to perform these tests [4]. In drug allergy, skin tests and in vitro laboratory tests are cumbersome, because the test reagents are not standardized and may even be harmful for a patient with a severe drug reaction. For this reason, the guidelines provide practical skin test methods, test concentrations, and selection of patients. The drug provocation test, the controlled administration of the suspected drug is considered to be the gold

Table 1 Summary of published desensitization protocols in children

Reference	Children (sexe, age, disease)	Drug(s)	Drug allergic symptoms	Result of skin tests	Desensitization protocol	Successful
Brown [6]	♂, 11, CF	Ticarcillin	Burning throat, periorbital edema, pruritus	Positive (penicilline)	IV Start 1:10E6 of dose, in 50 ml/45 min. Tenfold increases	Yes
Stark [22]	♀, 15, CF	Phenoxymethyl-penicillin	Anaphylaxis	PPL positive	Oral	No (procedure stopped due to bronchospasm)
	♂, 8, hyper IgE syndrome		Urticaria	Penicillin G and penicilloic acid positive	Start at dose positive skin test. Doubling every 15 min	Yes
Turvey [23]	8 children, 13 adults (1–44) (15 ♀, 6 ♂; 19 CF)	Multiple antibiotics (51/59 beta-lactam anti-biotics)	IgE-mediated reactions	31/59 with positive skin test	IV Starting dose 2 micrograms or 1/10E6 of full therapeutic dose infused in 30 min. Followed by tenfold increases	75% of desensitizations successful. No individual data. No differences between adults and children reported
De Maria [8]	♀, 16, CF	Aztreonam, ceftazidime	NR	Positive	IV	Yes
	♂, 10, chondritis	Meropenem	NR	Positive	Starting dose 1/10E5 of full therapeutic dose infused in 20 min. Doubling every 20 min	Yes
Soffritti [20]	♂, 7, allogenic haematopoietic stem cell transplantation after refractory anemia	Co-trimoxazole	Itching rash	Negative	NR (probably oral) Starting dose 0.000004 mg/0.0002 mg bid, 10-fold increases up to 0.04 mg/0.2 mg, followed by dose doubling	Yes
Kletzel [12]	♂, 7, 3 ♂, 15, 3 adults, All hemophiliac, HIV+	Co-trimoxazole	Rash, dyspnea, swelling	NR	Oral Starting dose 1/10,000 of full dose tid, followed by 1/5,000, 1/1,000, 1/500, 1/100, 1/50, 1/10. Then therapeutic dose bid	Yes (except in one child (♂, 15) due to noncompliance)
Kreuz [13]	3 children (3–4y), HIV+	Co-trimoxazole	Exanthema, fever	NR	Oral 0.2–0.4–1.6–3.2–4.8–9.2–20–40–80 mg. Dose increased every 3 days, 40 mg/day for 1 week	Yes
Erdem [9]	♀, 2.5, chronic osteomyelitis	Ciprofloxacine	Trembling, tachycardia, flushing, fever, vomiting, headache at first dose	Positive	IV Starting dose 0.00001 mg in 15 min, tenfold increases. From 0.01 mg twofold increases every 15 min	Yes
Kim [11]	♀, 7, tuberculosis	Rifampicin and isoniazide	Dyspnea, rash, pruritus	Positive	Oral Starting dose 0.1 mg, twofold increase every 15 min	Yes
Morgan [18]	♀, 4, astrocytoma	Carboplatin	Flushing, urticaria, facial edema, cough	ND	IV 1–2.5–5–7.5–10–10–25–50-remaining mg. Dose repeated if symptoms occurred	Yes
Broome [5]	♂, 3, astrocytoma	Carboplatin	Cough, congestion, flushing,	Negative	IV	Yes
	♂, 7, astrocytoma		Abdominal pain, erythema	Negative	1–2.5–5–10–25 mg iv push q15 min followed by	

					25–50 mg infusion q15 min, followed by 331 mg 200 mg/hr continuous infusion		
Ogle [19]	♀, 3, neurofibromatosis	Carboplatin	Abdominal discomfort, flushing, increased respiratory effort	NR	IV 0.01–0.1–0.5–1.0–2.5–5–10–22.5 mg push q15 min followed by 66 mg over 44 min.	Yes	
Soyer [21]	8, ALL	*E. coli* L-asparaginase	Anaphylaxis	NR	IV Starting dose 1 IU, dose doubling every 10 min dose	Yes in 3 cases	Five uneventful (3 due to anaphylactic reaction during desensitization)
Bouchireb [3]	♀, 9, astrocytoma	Methotrexate	Urticaria	ND	IV 1/1,000 of full dose in 1.5 h followed by 1/100 in 1.5 h, 1/10 in 6 h and the remaining dose in 24 h	Yes	
Caldeira [7]	♂, 9, ALL	Methotrexate	Urticaria	ND	IV 1/1,000 of full dose in 1.5 h followed by 1/100 in 1.5 h, 1/10 in 6 h and the remaining dose in 24 h	Yes	

CF cystic fibrosis, *ALL* acute lymphatic leukemia, *PPL* penicilloyl-poly-L-lysine, *NR* not reported, *ND* not done

standard in order to confirm the diagnosis drug allergy [ENDA, 1].

Desensitization can be considered in patients who are proven (by positive skin testing or in vitro tests) or are strongly suspected to have an IgE-mediated drug allergy and for whom there are no acceptable alternate drugs (see "Practical proposal"). In patients with (multi)resistant bacteria or patients with multiple drug allergies the effect of a desensitization procedure (successful treatment) may outweigh the risks. Desensitization is a procedure which alters the immune response to the drug and results in temporary tolerance, allowing the patient with IgE-mediated allergy to receive a subsequent course of the medication safely. Desensitization should not be attempted in patients with histories of non-IgE-mediated reactions such as Stevens–Johnson syndrome or toxic epidermal necrolysis because even small doses of the drug may induce severe progressive reactions. Desensitization is also not appropriate for patients with type III (IgG-mediated) hypersensitivity drug reactions like hemolytic anemia or nephritis.

Drug desensitization should only be performed by clinicians trained in the technique (usually allergy specialists), in a hospital setting (or outpatient setting under close observation), with intravenous access and necessary medications and equipment to treat anaphylaxis. Pharmacy staff may be consulted prior to the procedure to assist with preparation of the required drug dilutions. Articles concerning protocols are scarce and involve primarily adult patients. In this review, we summarize the known literature concerning pediatric patients who underwent a desensitization procedure.

Review of the literature

For studies describing desensitization procedures in children, PubMed was searched using the combination of keywords "desensitization", "drug hypersensitivity or drug allergy", and "child". The articles found were reviewed for relevance and references were searched where appropriate. Most articles are case reports. Some studies describe case series of adult patients and include one or more children. Very few studies confined to children only were found. This review is limited to desensitization procedures with antibiotics, beta-lactam drugs [8, 22, 23], co-trimoxazole [12, 13, 20], ciprofloxacin [2, 9, 15], cytostatics, carboplatin [5, 14, 18, 19], L-asparaginase [21], and MMR-vaccine [16] in children only.

Procedures

In general, protocols for children differ from those for adults only in the final dose, which should be the daily dose used for adequate therapy.

General principles of desensitization in adult protocols are:

- Starting doses range from 10% to 0.00001% of the therapeutic dose (mean 0.001%)
- Administration route orally or intravenously
- Time interval between two gifts range from 15 to 120 min (mean 30 min)
- Total duration of desensitization range from 2 h to 21 days (mean 6 h)
- Increment step range from two times to ten times (mean three times)

Whether premedication with corticosteroids and antihistamines reduces the risk of a desensitization procedure is not known.

Antibiotics

Desensitization procedures are reported to be successful in children with symptoms of an IgE-mediated hypersensitivity reaction like urticaria, angioedema, itch, or anaphylaxis. If reliable skin test procedures are available, such as for beta-lactam antibiotics, these should be performed first. Negative results to intradermal tests with penicilloyl-poly-L-lysine and minor determinant mixture reduce the risk of hypersensitivity symptoms upon re-exposure to less than 5%. In these patients, incremental dosing may be chosen, however, studies comparing this strategy to desensitization with regard to safety and efficacy have not been published.

The starting dose for intravenous procedures is generally 1/1,000,000–1/1,000 of full therapeutic dose, but may be higher (1/100) in oral desensitization [2, 8, 9, 12, 13, 15, 20, 22, 23]. During intravenous desensitization the doses are infused continuously over 15–30 min intervals, followed by intravenous administration of the full therapeutic doses. In the oral procedure, dose intervals described range from 15 min (for ciprofloxacin [15]) to 12 h (for cotrimoxazole [12]). Slow or incomplete absorption from the gastrointestinal tract should be taken into account when choosing this dose interval.

Cytostatics

As cytostatics are usually dosed per square meter, the full therapeutic dose is different for every child. Intravenous desensitization with carboplatin starts at a dose of 0.01–1 mg, infused over 1 min (0.01–1 mg/min). Dose increments are made every 15 min by prolonging the infusion time holding the infusion rate constant. When 15–22.5 mg in 15–22.5 min is well tolerated, the infusion rate is increased to 100 mg/h for 1 h followed by 200 mg/h for the remainder of the dose [5, 18, 19].

L-Asparaginase is administered intramuscularly, but intravenous desensitization had been described starting at a 1 IU dose, doubled every 10 min [21].

Intravenous desensitization for methrotrexate is started at 1/1,000 of the full dose in 1.5 h followed by 1/100 in 1.5 h, 1/10 in 6 h and the remaining dose in 24 h every therapeutic cycle [3, 7]. This procedure may necessitate a dose reduction due to increased toxicity as a result of prolonged exposure to methotrexate [3].

Vaccines

Desensitization to MMR-vaccine is performed by subsequent sc administration of 0.05 ml of a 1/100 dilution, 0.05 ml of a 1/10 dilution, and 0.05 ml of the full strength vaccine up to the 0.5-ml dose [16].

Premedication

Premedication can be done with (methyl)prednisolone, antihistamine, and ranitidine with or without montelukast 13, 7, and 1 h, respectively, before start of the desensitization procedure [18, 19, 21] but the protective effects have not been systematically studied. Administration of a full therapeutic dose in combination with premedication, as an alternative to desensitization, resulted in severe hypersensitivity reactions in three of eight patients reacting to *E. coli* asparaginase [21]. A recent study in children with carboplatin hypersensitivity reactions suggests that administrating a full dose in combination with premedication may be as effective as desensitization without premedication [14]. However, due to its retrospective nature, it cannot be ruled out that desensitization was preferably initiated in children with more severe hypersensitivity reactions.

Symptoms

In almost 50% of the procedures reviewed in this article, symptoms did occur during the procedure. In general, the symptoms could be treated by antihistamines and dose reduction or postponing dose increase [5, 12, 22, 23].

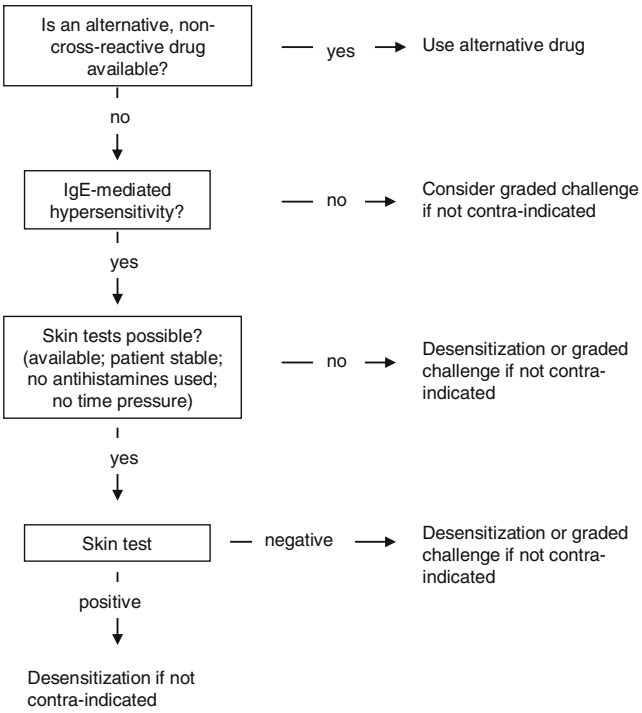
Effectivity

Success rates in the reports described (mostly IgE-mediated allergy) range from 50% to 100% (see Table 1 for details). However, due to the low number of cases reported and lack of comparative prospective studies, success rate may be either lower or higher in reality. Larger case series in adult patients report a success rate of more than 90% in both allergy to antibiotics and to cytostatics.

Setting

Desensitization in a child with drug allergy should be done by experienced staff with all facilities to treat medical emergencies.

Practical proposal



This flowchart is used to decide if desensitization or graded challenge (adapted from Turvey et al. [23]) should be employed.

Conflict of interest The authors declare that they have no financial relationship with a pharmaceutical company or organization that sponsored the research.

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