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ALLERGIC AND NON-ALLERGIC DRUG HYPERSENSITIVITY REACTIONS IN CHILDREN

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Adverse drug reactions (ADR) are an important medical problem. The aim of this study is to investigate the clinical characteristics of children with ADR and to assess the tolerability of alternative drugs in children (under 16 yrs of age) with a history of ADR. We studied 278 children (132 males and 146 females). Patients were studied by recording personal history and performing *in vivo* skin testing, *in vitro* laboratory tests and challenge tests. Patients who had experienced mild adverse reactions underwent challenge tests without any premedication; patients with a clinical history of moderate reactions, received a premedication with sodium cromolyn 30 min before the oral challenge; patients with a clinical history of severe reactions or undergoing parenteral challenges, were given an antihistamine 30 minutes before. A total of 660 adverse events were reported with 126 different drugs involved. Antimicrobial agents were the most involved drugs (51.7%). Non-steroidal anti-inflammatory drugs were involved in 22.7% of episodes. The most reported symptoms were cutaneous. Allergy testing was negative in 272 patients. A diagnosis of drug allergy was reported for 6 patients. A total of 669 challenge tests were performed. 639 were negative at first attempt while 22 were positive. Eight were repeated using a different premedication and resulted negative. Hypersensitivity drug reactions in children are mainly non-allergic. A premedication with sodium cromolyn or with oral H_1-antihistamines may be useful in preventing ADR.

All drugs, even if properly used, may be responsible for unwanted effects, which represent a matter of concern for the patient and a challenge for the attending physician. The majority (about three-quarters) of these events are due to the chemical and pharmacological properties of the drugs themselves and so they are usually predictable and avoidable; they include side effects, drug interactions and overdosing.

Unexpected adverse drug reactions, which are not related to the mechanism of action of drugs, may also occur; these include idiosyncrasy and hypersensitivity reactions (1-4). Adverse drug reactions (ADR) are a frequent cause of hospital admission (3 to 8%) and the incidence among the US hospitalized patients is 15.1% (1).

Prevalence may vary in the pediatric population, depending on the groups of patients and the methods

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used to detect the reactions. Some authors found that 1.91% of pediatric hospital admissions because by ADR (2) and that ADR are responsible for 1.51% of visits to private pediatricians (3).

Hypersensitivity drug reactions can be divided into allergic and non-allergic reactions (drug intolerance) (Table I) (5). Hypersensitivity drug reactions affect 10-20% of hospitalized patients and up to 7% of outpatients (6). Of these, only a small number are caused by an immune-allergic mechanism (usually type I and IV) while in most cases allergy testing is negative. The pathogenic mechanism of non-allergic reactions is still poorly understood. Several pathogenic hypotheses have been suggested: 1) direct release of inflammatory mediators from mast cells and basophils; 2) activation of the classical and/or alternative pathway of complement with the formation of anaphylotoxins (C3a, C4a, C5a); 3) inbalance of cycloxygenase/lipoxygenase system [the mechanism of non-steroidal anti-inflammatory drug (NSAID) hypersensitivity].

Several years ago we identified the "multiple drug intolerance syndrome" (MDIS) which included all patients who had presented with many drug hypersensitivity reactions ($\geq$ 3) with negative allergy testing (7). The drugs, taken on 3 different occasions, were chemically, pharmacologically and immunogenically unrelated. We recently reported the clinical findings and the results of tolerance challenge tests in 480 adult patients affected by MDIS (8).

The aim of this paper is to investigate the clinical characteristics of children with a clinical history of hypersensitivity drug reactions and to assess tolerability of alternative drugs in these patients.

MATERIALS AND METHODS

Outpatients, aged under 18 years presenting with a clinical history of one or more hypersensitivity reactions at the Allergy Unit of Policlinico Gemelli in Rome were studied in the 2003-2005 period.

Only patients with a convincing history of drug hypersensitivity were included in the study. All patients underwent the following procedures: recording of clinical history, *in vivo* skin testing, *in vitro* laboratory tests and tolerance tests.

Personal history

Parents were asked about patient characteristics (age, medical history, underlying diseases, etc.), drug treatment (suspected drug, dosage, route of administration, indication, date of beginning and stopping therapy, concomitant medications, etc.) and clinical characteristics of the adverse event (onset, clinical manifestations, remission, etc.).

Severity of reactions was arbitrarily classified into 3 categories:

- "severe" reactions, such as generalized urticaria/angioedema, bronchial asthma, anaphylaxis, requiring parenteral antihistamines and steroids and/or epinephrine;
- "moderate" reactions, such as mild urticaria, generalized itching requiring oral antihistamines and/or steroids;
- "mild" reactions, such as mild itching and/or erythema (plus malaise, heartburn) which remitted spontaneously.

Skin test

Skin tests were carried out according to the criteria of the European Network for Drug Allergy (ENDA) and the European Academy of Allergology and Clinical Immunology (EAACI) interest group on drug hypersensitivity (9). Prick and, if negative, intradermal tests (by injecting 0.02 mL of the testing material) were performed on the volar surface of the forearm. Drugs unavailable on the market for parenteral use, could not be tested intradermally and were "prick by prick" tested only, using the powdered tablet dissolved in saline. Concentration of drugs are indicated elsewhere (8, 10).

Immediate-type skin tests were read after 20 minutes, and 48 hours in case any delayed reaction occurred, and were considered positive for a wheal diameter larger than 3 mm for prick tests and 5 mm for intradermal tests. Negative (with saline) and positive (with 10 mg/mL histamine) controls were also performed.

Patch test

Patch tests were carried out using the same drugs as for skin tests. All drugs were mixed in petrolatum at 25% w/w for ampicillin and amoxicillin and at 20% w/w for other drugs. Patches were applied on the interscapular region and evaluated after 72 hours. Patch results were scored according to ENDA indications (9): faint erythema was considered as a doubtful reaction; erythema, induration and discrete papules – a weak positive reaction (+); erythema, induration, papules and vesicles – a strong positive reaction (++); intense erythema, induration and coalescing vesicles – an extremely positive reaction (+++). Negative controls were performed with petrolatum (9).

Laboratory test

Assay of serum specific IgE was performed for penicillins G and V, amoxicillin, ampicillin, cefaclor, insulin and succinylcholine (UniCAP Pharmacia, Uppsala, Sweden). Values above 0.35 kU/L were considered positive. Total IgE (UniCAP, Pharmacia) (normal values <100 kU/L for children under 10 years and <200 for children up to 10 years) were detected.

Challenge test

Challenge tests were performed with alternative drugs which were chosen: 1) on the basis of the patient's medical history, 2) on the basis of allergy testing results (avoiding those belonging to the same families which had provoked symptoms or sharing the same action); 3) among the most tolerated ones on the basis of medical literature (12-13) and our clinical experience (8).

The protocol was carried out in accordance with good clinical practice after being approved by our hospital's ethics Review Board. The patients' parents gave their fully informed written consent.

The single-blinded challenges were performed in a day-hospital regimen. Resuscitative equipment and trained personnel were available. Expiratory peak flow, pulse rate and blood pressure monitoring were performed during challenges. A preliminary oral challenge was performed with placebo.

The drug challenge test consisted of ingesting (or injecting) increasing doses of the drug every 30 minutes until the usual daily dose was administered or symptoms occurred. All challenge tests were performed starting from 1/10 of the therapeutic dose followed by 2/10, 3/10 and 4/10 every 30 minutes until the therapeutic dose was reached (14-15).

Patients with adverse reactions to local anesthetics underwent a subcutaneous test with increasing doses of a different local anesthetic (0.1 ml of the drug diluted 1: 100 and 1:10; 0.1, 0.6, 1.1 ml of the undiluted drug) until the cumulative dose of 1.8 ml (progressive challenge test) (16).

Patients with a history of reactions to ophthalmic products underwent a conjunctival challenge test with an alternative drug by instilling a drop of each solution (diluted 1:100, 1:10, and pure) into the lower conjunctival fornix (first in the right eye, then in the left and finally in the right again).

Patients who had previously experienced only "mild" ADR, underwent tolerance challenge tests without any premedication.

In patients with "moderate" or "severe" reactions, according to our previous experience (8) and because we did not consider it ethical to put our young patients at risk (even if theoretically) of other ADRs, challenge tests were performed as follows:

- "moderate" ADR: in case of oral challenges, patients received a premedication with sodium cromolyn: 250 mg (in children < 30 kg), 500 mg (in children ≥ 30 kg) 30 min before. This drug was chosen on the basis of published reports on food allergy (17) and our previous personal experiences with multiple drug allergy syndrome (8). In case of a parenteral challenge patients received an antihistamine (cetirizine or loratadine according to patient's age and weight) 30 minutes before;
- "severe" ADR: patients were given an antihistamine (cetirizine or loratadine according to patient's age and weight) 30 minutes before the oral or the parenteral challenge.

Patients who needed a premedication underwent an oral test dosing with cetirizine, loratadine or sodium cromolyn to rule out the possibility of an ADR to any of these drugs.

Patients remained under medical control for 6 hours after the last dose and were asked for any delayed reaction occurring within 48 hours. If symptoms occurred (erythema, local or generalized cutaneous itching, urticaria, angioedema, rhinitis, conjunctivitis, cough, dyspnoea, asthma, etc) the test was considered positive and immediately interrupted and, if necessary, rescue therapy was administered. Our patients did not undergo provocation tests with the culprit drug to avoid the risk of severe adverse reactions. In fact, the negative predictive value of allergy testing is low but does not rule out the possibility of non-allergic hypersensitivity drug reactions. For these reasons we did not consider it ethical to submit children to such a procedure.

RESULTS

General characteristics of the study population

Two hundred and seventy-eight patients were studied: 146 females and 132 males. Patients had experienced their first adverse drug reaction at a mean age of 5.2 ± 4.1 years. One hundred and sixty-seven patients (60%) had a familial history of atopy; 78 of them (28%) had a personal history of atopy; 64 (23%) of them had a familial history for adverse drug reactions. One hundred and seven (38%) subjects suffered from allergic diseases, mostly allergic asthma and rhinitis.

Responsible drugs

Six hundred and sixty adverse events were reported (mean 2.37 for patients). We identified 126

Table I. *Classification of hypersensitivity drug reactions.*

	Drug Allergy	Non-allergic drug hypersensitivity (drug intolerance)
Immuno-allergological tests	Positive	Negative
Prevailing sex	Females	Females
Incidence	Low (1-20%)	High (80-99%)
Dose-dependence	No	Yes
Possibility of desensitization	Yes	Yes (clinical tolerance)
Prevailing drugs	Penicillins	NSAIDs

different culprit drugs. Some ADR were caused by more than one drug and so 790 drugs were identified [responsible drugs (790) are higher than ADR (660) because some ADR were caused by more than one drug]. Antimicrobial agents were involved in 51.7% of cases while NSAIDs were involved in 22.7% (Table II).

Reported symptoms

Based on the clinical history, the majority of reactions were cutaneous, mainly urticaria/ angioedema, but also maculopapular exanthems (Fig. 1).

Symptoms occurred within 6 hours after the administration in 13.6% patients, within 6-24 hours in 32.7% and after 24 hours in 53.6%. In 57.6% of cases reactions were mild, in 35.2% were moderate, in 7.2% were severe.

Allergy testing

Skin tests, patch test and specific IgE were negative in 272 (97.8%) patients, therefore these patients were affected by non-allergic drug hypersensitivity. Sixty-four patients out of 272 (23.5%) had adverse reactions to almost 3 drugs and were therefore considered as affected by MDIS.

Thirty patients out of 272 (11%) were affected by "NSAIDs intolerance" because the drugs involved belonged only to this class of drugs.

A diagnosis of drug allergy was reported for just 6 patients (2.2%):

- 2 patients had an IgE-mediated allergy to penicillins [1 had positive immediate skin tests to penicilloylpolilysine (PPL), penicillin G, penicillin V and ampicillin and positive specific IgE to penicillin G and penicillin V and the other had positive specific IgE to penicillin V and cefaclor];
- 4 patients had a cell-mediated allergy (positive patch tests) respectively to acetaminophen (1 patient), carbamazepine (1 patient), penicillin G (1 patient) and V (1 patient).

Laboratory tests

Specific IgE

Specific IgE were detected in 153 patients. Of these, one patient had positive IgE to penicillin G (1.94 kU/L) and to penicillin V (5.58 kU/L) and another had positive IgE to penicillin V (2.06 kU/L) and to cefaclor (0.88 kU/L).

Total IgE

Total IgE (normal value: <100 kU/L for children under 10 years of age and <200 kU/L for children above 10 years) were measured in all patients. Seventy-two (25.9%) patients under 10 years of age had total IgE values higher than 100 kU/l (mean 370.5 ± 212.83), while 94 (33.8%) patients had total IgE values lower than 100 kU/l (mean 40.4 ± 18.24). Thirty-six (13%) patients over 10 years of age had

Table II. *Drugs (126) responsible for ADRs in children.*

DRUGS	EPISODES (%)	
ANTIMICROBIAL AGENTS		
BETA-LACTAMS (62.5%)		
cephalosporins (33.9%)		
• cefaclor	62 (44.6)	
• cefixime	22 (15.8)	
• ceftriaxone	19 (13.7)	
• others	36 (25.9)	
penicillins (28.6%)		
• aminopenicillins	105 (89.7)	51.7
• others (natural penicicillins, ureido-penicillins)	12 (10.3)	
MACROLIDES (27.7%)		
• erythromycin	39 (34.5)	
• clarithromicyn	30 (26.5)	
• azithromycin	19 (16.8)	
• others	25 (22.2)	
OTHER ANTIBIOTICS (9.8%)	40	
NSAIDs		
• acetaminophen	66 (36.9)	
• acetylsalicilylic acid*	28 (15.7)	
• metamizole	23 (12.8)	
• niflumic acid	20 (11.2)	22.7
• ketoprofen	12 (6.7)	
• nimesulide	8 (4.5)	
• Others	22 (12.2)	
OTHER classes of drugs (antiemetics, local and general anaesthetics, antiseizure)	180	22.8
UNKNOWN	22	2.8

** acetylsalicilylic acid is not recommended in pediatric patients, but it was prescribed by their attending physicians, especially in children aged over 12.*

total IgE values higher than 200 kU/l (mean 472.5 ± 352.85), while 76 (27.3%) patients had total IgE values lower than 200 kU/l (mean 80.6 ± 28.28).

Results of tolerance challenge tests

Twenty-eight (10.1%) of the 278 patients reported reactions after the placebo. Symptoms, such as itching, nausea and malaise were subjective. Two hundred and forty-four out of 278 patients underwent 669 tolerance challenge tests with alternative drugs (2.74 tests per patient): 613 oral, 50 intramuscular, 4 subcutaneous (progressive challenge test) and 2 conjunctival tests.

In patients with "mild" ADR, tolerance tests were performed without any premedication for a total of 436 tests. Of these, 425 were negative (97.5%)

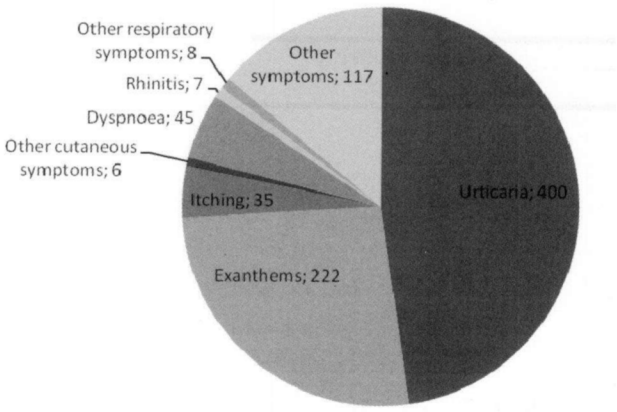

Fig. 1. *Symptoms which occurred in the pediatric population (840).*

and 11 were positive (2.5%). Ten patients did not need any therapy and one was treated with oral antihistamines.

In patients with "moderate" ADR, tolerance challenge tests were performed with previous administration of sodium cromolyn for a total of 173 tests. Of these, 165 (95.4%) were negative and 8 (4.6%) were positive. Reactions were mild and nobody needed therapy.

In patients with "severe" ADR or who had to undergo intramuscular tests, challenge tests were performed with an oral anti-H_1 antihistamine premedication (cetirizine or loratadine according to the patient's age and weight) for a total of 52 tests. Forth-nine tests were negative (94.2%) and 3 were shown to be positive (5.8%). Reactions were mild and nobody needed therapy. In all, 22 positive tests patients showed mainly cutaneous symptoms, particularly erythema (40.6%). No patients needed hospitalization.

In 8 patients with positive tolerance tests, these were repeated with a different premedication:

- 5 positive tolerance tests without any premedication were repeated with sodium cromolyn and the drug was tolerated in all cases;
- 1 positive tolerance test without any premedication was repeated with an antihistamine because patients showed an important reaction and we thought sodium cromolyn was ineffective; the drug was tolerated;
- 2 positive tolerance tests with previous sodium cromolyn administration were repeated with an antihistamine and the drug was tolerated.

Among antimicrobial agents, the most tolerated drugs were ceftibuten (97.4%) followed by cotrimoxazole (96.1%) (Table IV). Among NSAIDs, nimesulide was tolerated in 96.8% of cases and acetaminophen in 97.3% of cases (Table III).

In conclusion, 639 tolerance tests scored to be negative at the first attempt (with or without a premedication) while 22 were positive; therefore, 8 of these were repeated using a different premedication and they all became negative. Considering that each patient on average underwent 2.74 tolerance tests, we can say that we were always able to identify an alternative antibiotic or NSAID tolerated by the patient (with or without premedication).

DISCUSSION

The aim of this paper is to study hypersensitivity drug reactions in children from a clinical, diagnostic and therapeutical point of view. Our results highlight that females (52.5%) are slightly more involved than males. This finding is similar to what happens in an adult population (8, 18) in which females are prevalent.

Familial history was positive for atopy in 60% of cases and for adverse drug reactions in 23%. A personal history of atopy was positive in 28% of patients. These data do not agree with other studies regarding a general population: in fact, we have already observed that a personal history of atopy was present in about 10.8-11.8% (19). Thus, children with a personal history of atopy seem to be at higher risk of experiencing hypersensitivity drug reactions.

According to other studies (20-21), the drugs mainly involved were antibiotics (first of all cephalosporins and aminopenicillins), followed by NSAIDs (acetaminophen and acetylsalicylic acid). Cutaneous symptoms such as urticaria and/or angioedema are prevalent, as already observed in literature (22-23).

It is interesting to underline that the placebo challenge was positive in just 10.1% of patients. This result is different from the findings of Passalacqua et al. who found 21% of adults reacting to placebo (4). This may be explained by the fact that children are less influenced than adults by psychological

Table III. *Results of tolerance tests with alternative chemioantibiotics and NSAIDs.*

Drugs (doses according to patient's age and weight)	No premedication		Premedication with cromolyn sodium		Premedication with anti-histamines	
	Negative	Positive	Negative	Positive	Negative	Positive
Ceftibuten	76	1	32	2	5	-
Cotrimoxazole	45	-	27	1	3	2
Clarithromycin	40	3	12	4	4	-
Rokitamycin	26	2	22	1	2	1
Josamycin	34	2	9	1	3	-
Imipenem	19	2	-	-	6	-
Fosfomycin	11	-	1	1	1	1
Azithromycin	11	-	3	1	3	-
Nimesulide (> 12 years)	43	1	17	-	1	-
Acetaminophen	23	1	11	-	2	-
Total	328	12	134	11	27	4

influences. Mainly, children with anxious parents had a positive placebo challenge.

Detection of serum total IgE is not particularly useful since total IgE were within normal ranges in most patients.

Only 6 (2.2%) patients had an allergic drug hypersensitivity. Only two patients were finally considered as having an IgE-mediated allergy to beta-lactams; in fact, it has been shown that part of the reactions during beta-lactam treatments are more a consequence of the infectious disease for whom beta-lactams have been prescribed than a result of beta-lactam hypersensitivity (24). Some authors found that ADRs are frequently reported in children and that, after a complete evaluation, 94% of patients could tolerate the initially suspected drug (25), but 6% of children had some kind of reaction. The majority of our patients had experienced more than one ADR and so they were considered at higher risk of new reactions. For these reasons we decided not to perform drug provocation tests. We think that: 1) drug provocation tests in such patients, who have the tendency to react to more than one drug, should be avoided; 2) avoidance of the responsible drugs is mandatory; 3) drug tolerance tests with alternative drugs, with or without a prophylactic premedication, should be preferred. However, it is important to underline that non-allergic drug reactions are less serious than allergic ones. In our study no life-threatening reactions (such as Stevens-Johnson/ Lyell syndrome, anaphylactic shock, drug rush with eosinophilia and systemic symptoms) were observed.

The main problem for these patients who are thought to be allergic to every drug, is the identification of alternative drugs that can be safely administered. The first approach is to record a detailed medical history to identify the drugs involved and the patient's symptoms. These drugs should be avoided and replaced, if possible, by alternative drugs choosing them among the most tolerated on the basis of medical literature (12-13) and the allergist's clinical experience (8).

Nimesulide and acetaminophen were the most tolerated drugs among NSAIDs because of their mechanism of action; while NSAIDs such as aspirin and pyrazolones are inhibitors of both COX-1 and COX-2, acetaminophen and nimesulide are poor inhibitors of COX (nimesulide is partially selective for COX-2). It should be underlined that these drugs can also be responsible for adverse reactions (26).

If the patient urgently needs a certain drug and it is impossible to carry out an accurate allergological evaluation, the responsible drug should be replaced by another one with a different chemical structure and/or with different pharmacodynamics. A premedication with sodium cromolyn, antihistamines or corticosteroids according to the severity of the

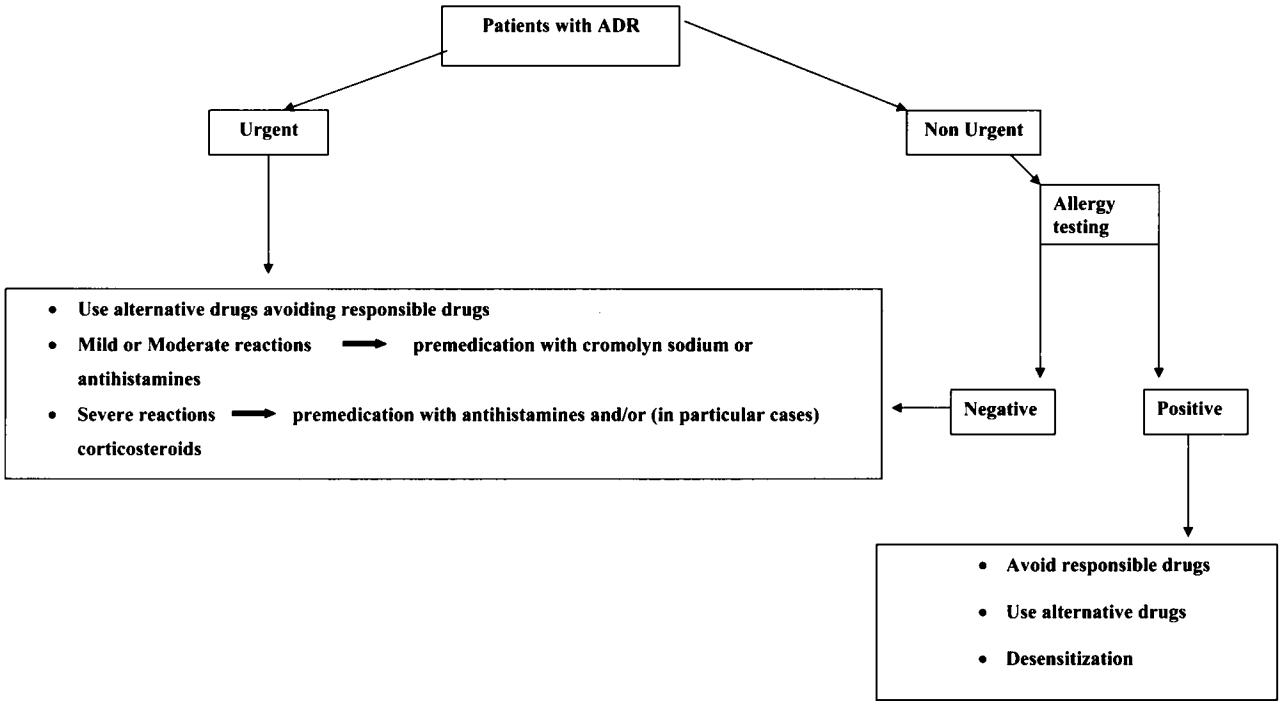

Fig. 2. *Guidelines for paediatric patients with adverse drug reactions.*

patients' reactions and to the route of administration of the drug itself should be administered. If the patient is free of symptoms and if it is possible to carry on the allergological work-up, the clinical management will be the following:

-negative allergy testing: alternative drugs will be chosen, using a premedication according to the severity of the reaction;

-positive allergy testing: the responsible drug will be avoided and alternative drugs will be used. A desensitization protocol could be taken into consideration if the responsible drug cannot be replaced by other ones (Fig. 2).

In 97.5% (425/436) of challenge tests without any premedication alternative drugs were tolerated. Successful results were achieved in 95.4% of cases (165/168 tolerance tests), using prophylactic oral sodium cromolyn. This suggests a possible role of sodium cromolyn in preventing non-allergic hypersensitivity reactions to drugs, according to a previous observation (8). With a prophylactic oral antihistamine therapy approximately 94.2% (49/52 tolerance tests) of successful results was achieved.

When the drug involved is necessary and irreplaceable two strategies may be carried out in a safe setting: a) the administration of the drug with a higher dose of premedication (sodium cromolyn, antihistamines, steroids, also combined); b) a desensitization protocol.

This approach may be useful for the management of hypersensitivity drug reactions, providing a solution for both the attending physicians and the patients.

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