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Original article

Discrepancies in the diagnosis and classification of nonsteroidal anti-inflammatory drug hypersensitivity reactions in children

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NSAID, Nonsteroidal anti-inflammatory drugs; CIs, cross-intolerants; SRs, selective responders; ENDA, European Network for drug Allergy; DPT, drug provocation test; NERD, NSAID-exacerbated respiratory disease; NECD, NSAID-exacerbated cutaneous disease; NIUA, NSAID-induced urticaria/angioedema; SNIUAA, single NSAID-induced urticaria/angioedema and/or anaphylaxis; SNIDR, single NSAID-induced delayed reactions; SPTs, skin prick tests; IDTs, intradermal tests; FEV1, forced expiratory volume in 1 s; aOR, adjusted odds ratio

ABSTRACT

Background: Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently encountered in daily clinical practice. The aim of this study was to determine the confirmation rates, risk factors of NSAID hypersensitivity in children and to try to classify them with a standardized diagnostic protocol.
Methods: All patients with a suspicion of NSAID-induced hypersensitivity were evaluated with European Network for drug Allergy (ENDA) recommendations. The children were classified as selective responders (SRs) or cross-intolerant (CI) depending on the drug provocation test (DPT) results.
Results: We evaluated 106 children with a suspicion of NSAID hypersensitivity. NSAID hypersensitivity was confirmed with tests in 31 patients; 4 (12.9%) were diagnosed by skin tests and 27 (87.1%) by DPTs and two patients with a history of anaphylaxis by medical records. Eleven patients (33.3%) were classified as SRs, whereas twenty-two (66.6%) children as CIs. SRs and CIs were further classified as NSAID-induced urticaria/angioedema (n = 8), NSAID-exacerbated cutaneous disease (n = 6) and NSAID-exacerbated respiratory disease (n = 1) and single NSAID-induced urticaria/angioedema and/or anaphylaxis (n = 11). Eight (24.2%) patients could not be categorized according to ENDA/GA^{2}LEN classification; one CI patient could not be classified based on pathomechanisms, seven CIs could not be categorized based on the underlying disease and clinical manifestations. A reaction within an hour of drug intake (aOR:3.0, 95% confidence interval: 1.18–7.67, $p = 0.021$), a history with multiple NSAIDs hypersensitivity (aOR:2.9, 95% confidence interval: 1.16–7.60, $p = 0.022$), and family history of atopy (aOR:4.0, 95% confidence interval: 1.50–10.82, $p = 0.006$) were found as the independent risk factors related to confirmed NSAID hypersensitivity.
Conclusions: This study suggests the presence of different phenotypes which do not fit into the current classifications in children with NSAID hypersensitivity.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are most commonly prescribed group of drugs in children. Hypersensitivity to NSAIDs are of great concern because they are frequently encountered in daily clinical practice.[1] Although the overall prevalence of NSAID hypersensitivity has been reported between 0.6 and 5.7% of the general population, the results vary significantly depending on the population studied and the method of assessment.[2,3] In children, the reported prevalence of NSAID hypersensitivity is 0.3%, and the aspirin sensitivity in children with asthma is 5%, as assessed by provocation tests.[4,5] Proposed risk factors for NSAID-induced hypersensitivity reactions are older age, the number of drugs taken, chronic urticaria, a previous history of anaphylaxis, immediate reactions, and the family history of NSAID hypersensitivity.[6–8] Among other conditions, atopy was reported as a risk factor for NSAID hypersensitivity.[9,10]

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The diagnosis of hypersensitivity reactions to NSAIDs is usually based on patient history. However it is mostly misleading, and a standardized diagnostic work-up is necessary for a definitive diagnosis.[11,12] A complete allergy work-up should include a detailed clinical history of the patient's reaction, associated risk factors and reaction interval. NSAID associated reactions are divided into two major categories according to the underlying mechanisms: reactions without previous immunological recognition (cross-hypersensitive type reactions) or through immunological mechanisms (allergic or selective reactions) involving specific IgE antibodies (immediate reactions) or T cells (delayed reactions).[13,14] Patients with immediate reactions (reactions <24 h after drug intake) to NSAIDs may be selective responders (SRs, hypersensitive to only one type of NSAID) or cross-intolerants (CIs, hypersensitive to more than one chemically unrelated NSAID).[15,16] Recently, European Network for drug Allergy (ENDA) has further classified CIs into three subgroups and SRs into two subgroups.[13] Kowalski *et al.*, classified NSAID hypersensitivity as NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease (NECD), NSAID-induced urticaria/angioedema (NIUA) and single NSAID-induced urticaria/angioedema and/or anaphylaxis (SNIUAA) and single NSAID-induced delayed reactions (SNIDR) in 2013.[13] Clinical observations and the data in the literature showed that some patients with confirmed NSAID hypersensitivity could not be categorized according to ENDA classification.[17] The proper evaluation and classification of children with NSAID hypersensitivity according to different phenotypes is essential due to the fact that it is a really important and complex issue in pediatric population.

Despite recent developments in the area of drug allergy, current classification system may not be sufficient to categorize all the children with a diagnosis of NSAID hypersensitivity. The purposes of this study were to determine the confirmation rates of clinician or parent reported NSAID hypersensitivity reactions in Turkish children and to try to classify them with a standardized diagnostic protocol based on ENDA guideline[13] and also to search for risk factors related to confirmed NSAID hypersensitivity. As a secondary aim, an investigation was conducted to determine safe alternative drugs for children with actual NSAID hypersensitivity.

Methods

Study population

The children referred to the Pediatric Allergy Clinic of Mersin University with a suspicion of NSAID-induced hypersensitivity reaction were evaluated between January 2009 to April 2016. Patients with a history of acute reactions (reaction time; immediate to several hours) such as urticaria/angioedema, bronchospasm, laryngeal edema and systemic reactions were included in the study. Delayed reactions (reaction time; more than 24 h after exposure) were not included. The Mersin University Hospital ethics committee approved this study. Prior to this study, parents of all the children received information about the possible risks of skin and challenge tests, and written informed consent was obtained.

Data collection

A comprehensive ENDA questionnaire was applied to the children with a history of NSAID allergy suspicion by the clinician or patient perspective.[18] This questionnaire comprised questions about demographic data, culprit drugs, reaction interval, characteristics of index drug reaction, management procedures and family and personal histories of drug allergy and atopy. The questionnaire was performed by a clinician using information provided by the parents or referring physician.

Atopy was assessed by questionnaire, food and inhalant specific IgE levels, serum total IgE, peripheral eosinophil counts and skin prick tests (SPTs) with inhalant allergens. The following inhalant antigens were applied to the volar surface of the forearm in addition to histamine and saline controls: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cockroach, cat and dog dander, Alternaria, mixed grass and tree pollen. A test was considered positive if the mean diameter of the wheal was $\geq$3 mm compared with the negative control.

Diagnostic evaluation

According to ENDA recommendations, the patients who had a history of immediate reactions to a single NSAID were classified as SR and tested by skin prick and intradermal tests (İDTs) and, if negative tests, were challenged with the culprit drug. In case of positive challenge, additional drug provocation tests (DPTs) were performed with ibuprofen or acetylsalicylic acid to confirm or exclude cross-reactivity. The patients with a history of hypersensitivity reactions to more than one chemically unrelated NSAIDs were classified as CI group and directly challenged with culprit drugs based on ENDA recommendations. In those cases with a positive DPT to the culprit drug, another challenge with potent COX1 inhibitors, such as ibuprofen or acetylsalicylic acid was performed.[13] SRs and CIs were further categorized according to the ENDA/GA^{2}LEN classification; NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease (NECD), NSAID-induced urticaria/angioedema (NIUA) and single NSAID-induced urticaria/angioedema and/or anaphylaxis (SNIUAA).[13]

Skin tests

Antihistamine medications and drugs that could affect skin tests were stopped 1 week before testing. SPTs with undiluted injectable forms and IDTs with 1/10 dilutions (0.1 mg/ml concentration) were used according to maximum non-irritant concentrations as recommended by ENDA.[19] Skin prick tests with acetaminophen (Perfalgan, 10 mg/ml), metamizole sodium (Novalgin, 1 g/2 ml) and diclofenac (Voltaren 75 mg/3 ml) were performed at concentrations of 10 mg/ml, 0.4 mg/ml and 25 mg/ml, respectively. A SPT was considered as positive if the wheal was at least 3 mm larger than the negative control with surrounding erythema. If SPTs were negative, 0.02 ml of the relevant agent was injected intradermally on volar forearm skin, and the reaction was evaluated 20 min later. When the mean diameter of the bleb created by the injection increased by 3 mm or more with surrounding erythema, then the results were considered as positive. In SPTs and IDTs, histamine at 10 and 1 mg/ml were used for positive controls respectively, and normal saline was used as a negative control.[19,20]

Drug provocation tests

In all children, except those with severe reactions, or if performed, skin test positive patients, oral DPTs were performed. An initial dose of 1/10,000–1/100 of the therapeutic dose was administered depending on the severity of the reaction. Four or five escalating doses of the culprit drug were administered during DPT with the intervals of 30–60 min up to a cumulative dose of maximum daily dose. The challenge doses were based on the recommendations of ENDA and were modified according to the weight of the children.[21,22] The children were kept under strict medical observation for up to 2 h after completing the test. If no sign of drug hypersensitivity reaction occured, then challenges were continued for 2 days to diagnose delayed responses. The DPT test was considered positive if any objective symptoms or signs such as