

H₁-Antihistamine Premedication in NSAID-Associated Urticaria



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What is already known about this topic? A total of 10% to 30% of patients with chronic spontaneous urticaria experience exacerbations after intake of strong cyclooxygenase (COX)-I inhibiting nonsteroidal anti-inflammatory drugs (NSAID).

What does this article add to our knowledge? The study demonstrates the prophylactic effect of an oral H₁-antihistamine medication given 30 minutes before administration of a strong COX-I inhibiting NSAID in patients with NSAID-associated urticaria.

How does this study impact current management guidelines? In the majority of patients with NSAID-associated urticaria concurrently suffering from intermittent pain, a premedication regimen with an oral H₁-antihistamine before intake of a strong COX-I inhibitor seems to be effective and practicable.

BACKGROUND: Therapeutic options for pain management are restricted in patients with nonsteroidal anti-inflammatory drug (NSAID)-induced or NSAID-exacerbated urticaria because strong cyclooxygenase (COX)-I inhibiting NSAID cannot be used. Alternative NSAID such as weak COX-I inhibitors or selective COX-II inhibitors are sometimes not sufficiently effective or have potentially troublesome adverse effects.

OBJECTIVE: To date, prophylactic premedication with H₁-antihistamines is rarely practiced in patients concurrently suffering from recurrent pain and NSAID-associated urticaria. Our data analysis aims to clarify whether prophylactic premedication before the intake of NSAID is effective, safe, and practicable.

METHODS: Data of 21 patients with NSAID-induced or NSAID-exacerbated urticaria who underwent single dose NSAID provocation 30 minutes after premedication with 5 mg desloratadine were retrospectively evaluated.

RESULTS: After H₁-antihistamine premedication, 17 patients tolerated 16 single dose provocation tests with strong COX-I inhibitors and 2 tests with weak COX-I inhibitors. Despite H₁-antihistamine premedication, 2 patients developed acute urticaria after intake of 400 mg ibuprofen. Another 2 patients with acute urticaria after intake of 800 mg ibuprofen tolerated 400 mg ibuprofen and 1000 mg paracetamol, respectively.

CONCLUSIONS AND CLINICAL RELEVANCE: In the majority of patients with NSAID-induced or NSAID-exacerbated urticaria concurrently suffering from intermittent pain, a premedication regimen with 5 mg desloratadine 30 minutes before intake of a strong COX-I inhibitor seems to be effective, safe, and practicable. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:1205-12)

Key words: Nonallergic drug hypersensitivity; Nonsteroidal anti-inflammatory drug-exacerbated urticaria; Nonsteroidal anti-inflammatory drug hypersensitivity; Nonsteroidal anti-inflammatory drug-induced urticaria; Provocation test

A total of 10% to 30% of patients with chronic spontaneous urticaria (with or without angioedema) experience exacerbations after the intake of strong cyclooxygenase (COX)-I inhibiting nonsteroidal anti-inflammatory drugs (NSAID). The intensity of these urticaria boosts depends on the COX-I inhibition capacity of the triggering NSAID, its dose, and the overall activity of spontaneous urticaria.¹ Different synonyms and acronyms have been proposed for this clinical entity, namely NSAID-exacerbated cutaneous disease (NECD) or aspirin-exacerbated urticaria.² Another subgroup of patients without underlying spontaneous urticaria suffers from episodes of acute urticaria (with or without angioedema) exclusively after taking COX-I inhibiting NSAID. According to an international consensus, NSAID-induced urticaria/angioedema (NIUA) is diagnosed in these patients.² Contradictory results were published whether NIUA may precede the appearance of chronic spontaneous urticaria by years.^{3,4}

Inhibition of COX, the pharmacological principle of NSAID action, seems to be responsible for nonallergic drug hypersensitivity reactions occurring after NSAID intake.⁵ Affected patients develop symptoms after intake of strong COX-I inhibiting NSAID irrespective of their chemical structure, whereas selective COX-II inhibitors (INH) or weak COX-I INH are well tolerated at least up to a certain dose.⁶⁻⁹

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Abbreviations used

AERD- Aspirin-exacerbated respiratory disease
 ASA- Acetylsalicylic acid
 COX- Cyclooxygenase
 INH- Inhibitor
 NIUA- NSAID-induced urticaria/angioedema
 NECD- NSAID-exacerbated cutaneous disease
 NSAID- Nonsteroidal anti-inflammatory drug

Episodes of urticaria/angioedema due to NECD or NIUA can be treated successfully with H₁-antihistamines (including the option of using higher than licensed doses) as well as leukotriene receptor antagonists.^{10,11}

For patients with NECD or NIUA with recurrent pain problems, the question of analgesic treatment alternatives arises inevitably. Besides selective COX-II INH and opioids, these patients may tolerate weak COX-I inhibiting NSAID such as paracetamol, meloxicam, nabumetone, or nimesulide up to an individual threshold dose.^{6,12,13} Depending on the cause and character of pain, these alternative analgesics, however, are sometimes not sufficiently effective. Furthermore, their use is restricted by a variety of contraindications and significant adverse effects, for example, COX-II INH-related cardiovascular morbidity or paracetamol- and nimesulide-induced hepatotoxicity. In the literature, we found 2 small case series describing premedication with leukotriene antagonists or H₁-antihistamines in patients with NECD and NIUA based on pathogenic assumptions of COX-I inhibition and histamine mediation. Patients in these studies tolerated COX-I inhibiting NSAID under the respective premedication regimen.^{14,15} In treatment of acute pain, the appropriate time interval between antihistamine premedication and the intake of COX-I inhibiting NSAID is of particular interest as the required waiting time until the onset of antihistamine activity delays the relief of pain.

In this data evaluation, we have examined whether patients with NECD or NIUA tolerated strong COX-I inhibiting NSAID after pretreatment with an H₁-antihistamine. Oral premedication was scheduled 30 minutes before the NSAID intake to ensure both the antihistamine's onset of action, and rapid pain relief.

PATIENTS AND METHODS

Patients

Data of patients with NECD or NIUA who received an NSAID provocation test preceded by H₁-antihistamine premedication at our allergy center from 2012 to 2015 were retrospectively evaluated. Patients with NSAID-exacerbated respiratory disease (also denominated as aspirin-exacerbated respiratory disease [AERD]) were excluded from this evaluation based on their NSAID-induced symptoms such as rhinorrhea, nasal congestion, and bronchial obstruction, which are quite different from generalized urticaria. In addition to the diagnosis of NECD or NIUA, the clinical history of the triggering NSAID and reactions to previous NSAID provocation tests was documented. All patient-related procedures were part of routine diagnostic practice; written informed consent was obtained for provocation testing. The institutional review board of the University Hospital Würzburg consented to the retrospective review and publication of anonymized clinical data.

Provocation testing

There were 3 indications for NSAID provocation testing: (1) diagnostic NSAID provocation using strong COX-I INH in patients with an uncertain clinical history of NECD or NIUA; (2) provocation testing with alternative analgesics, that is, weak COX-I INH and selective COX-II INH; (3) NSAID provocation tests preceded by H₁-antihistamine premedication. In our single-blinded approach, patients did not know which NSAID was given during diagnostic provocation testing and in tests with alternative analgesics. Placebo testing was not deemed necessary because we evaluated objective clinical signs of generalized urticaria with or without angioedema. In the provocation tests after premedication, and also in the tests with alternative analgesics, both the selection and dosing of the NSAID were adjusted to therapeutic needs (as defined by the treating physician) and to the patient's preferences. Patients preferred specific NSAID and certain dosages because of optimal analgesic efficacy and good tolerability with regard to, for example, gastrointestinal side effects.

Diagnostic provocation tests (single-blinded oral NSAID provocation)

Patients with an uncertain diagnosis of NECD or NIUA underwent single-blinded diagnostic provocation testing with strong COX-I inhibiting NSAID including acetylsalicylic acid (ASA). General principles of our provocation protocol follow existing guidelines and consensus panels.^{1,2,16} (1) Urticaria was in remission. (2) Patients had not taken any H₁-antihistamines for at least 1 week before NSAID provocation. (3) Oral NSAID provocation was carried out by experienced personnel capable of treating adverse reactions. (4) During the entire procedure, patients had intravenous catheters in place, they were observed continuously, and equipment for immediate treatment was available. (5) Only 1 NSAID was administered per day; intervals of 1 hour were kept between the individual doses. (6) Doses were incrementally increased up to the total dose, as indicated in Table I.

Provocation tests with alternative analgesics (single-blinded oral NSAID provocation)

Provocation tests with alternative analgesics were carried out to assess the individual tolerability of selective COX-II INH and/or weak COX-I INH such as paracetamol, meloxicam, nabumetone, and nimesulide. General prerequisites and precautions were the same as defined above, and doses were incrementally increased as depicted in Table I.

Provocation tests preceded by H₁-antihistamine premedication (open oral NSAID provocation)

The indication for NSAID provocation after H₁-antihistamine premedication was based on 2 prerequisites: (1) a therapeutic necessity to administer NSAID due to a history of recurrent pain, for example, back pain, arthralgia, or headache; (2) history of an optimal analgesic effect of a specific COX-I INH before the onset of NECD or NIUA. Prerequisites and safety measures were the same as defined above. Patients received the specific COX-I inhibiting NSAID as a single dose 30 minutes after pretreatment with desloratadine 5 mg as an orodispersible tablet.

RESULTS

Patients

Age and gender of the 21 evaluated patients are listed in Table II. Diagnosis of NECD or NIUA, offending NSAID, and

TABLE I. Single-blinded NSAID provocation tests: sequence of increasing doses

Nonsteroidal anti-inflammatory drugs	Single doses (mg)	Total dose (mg)
Strong COX-I inhibitors	Administered in diagnostic provocation tests	
ASA	50; 100; 250; 500; 1000	1900
Ibuprofen	100; 200; 400; 600	1300
Diclofenac	25; 50; 75	150
Metamizol	125; 250; 500; 1000	1875
Weak COX-I inhibitors	Administered in provocation tests with alternative analgesics	
Paracetamol (acetaminophen)	125; 250; 500; 1000	1875
Nabumetone	125; 250; 500; 750	1625
Meloxicam	1,875; 1,875; 3,75; 7,5	15
Nimesulide	25; 50; 100	175
Selective COX-II inhibitors	Administered in provocation tests with alternative analgesics	
Celecoxib	100; 200	300
Etoricoxib	15; 30; 60	105

ASA, Acetylsalicylic acid; COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug.

detailed results of provocation testing are listed in Table II and are summarized in Figure 1. Because of an uncertain history, diagnostic provocation testing with ASA was required in 2 patients to establish a definite diagnosis of NECD. Seventeen patients received provocation testing with alternative NSAID, that is, weak COX-I INH and/or selective COX-II INH. To extend therapeutic options for pain treatment, all 21 patients were subjected to provocation tests preceded by premedication with desloratadine. Strong COX-I INH were tested on 21 occasions, whereas the weak COX-I INH paracetamol was given on 3 occasions because the corresponding patients 2, 3, and 7 developed urticaria flares after previous paracetamol provocation testing (Table II).

Diagnostic provocation tests

In 2 patients with chronic urticaria (patients 5 and 6), the history did not unequivocally clarify whether NSAID really triggered urticaria flare-ups. Thus, a diagnostic provocation to demonstrate NECD was required. Both patients developed acute urticaria after administration of ASA.

Provocation tests with alternative analgesics

The majority of patients tolerated weak COX-I INH and selective COX-II INH. A total of 29 provocation tests with weak COX-I INH and 13 with selective COX-II INH were performed. Four patients developed urticaria because of provocation with weak COX-I INH (Figure 1, Table II), whereas no reactions to selective COX-II INH were observed. In patients 2, 3, and 7, paracetamol provocation was positive. Patient 3 alternatively tolerated nabumetone and meloxicam, and patient 7 celecoxib and meloxicam. In patient 11, meloxicam provocation was positive, whereas celecoxib and paracetamol were tolerated (Table II). Thirteen patients tolerated all individual provocation tests with alternative analgesics. Provocation tests with alternative analgesics were not performed in 4 patients (patients 9, 12, 16, and 21).

Provocation tests preceded by H₁-antihistamine premedication

Of a total of 24 provocation tests with COX-I inhibiting NSAID after H₁-antihistamine premedication (21× strong COX-I INH, 3× weak COX-I INH), 20 were tolerated. In 2 patients (patient 7 with NECD, patient 16 with NIUA), provocation tests with 800 mg ibuprofen were positive, but subsequent tests with 1000 mg paracetamol and 400 mg ibuprofen, respectively, were tolerated. In another 2 patients (patients 19 and 20), acute urticaria was observed after intake of 400 mg ibuprofen despite antihistamine premedication. In most patients, however, a strong COX-I inhibiting NSAID could be identified that can be taken safely after pretreatment with desloratadine. Tolerated provocations included 17 strong COX-I INH, namely ibuprofen (13×), metamizol (2×), ASA (1×), and diclofenac (1×). In 3 patients who had previously reacted to paracetamol, tolerability of this weak COX-I INH after H₁-antihistamine premedication could be demonstrated. Of 5 provocation tests with 800 mg ibuprofen, 3 were tolerated, but 2 patients developed a burst of urticaria despite H₁-antihistamine premedication. Of 12 tests using single doses of 400 mg ibuprofen, 10 were tolerated well.

DISCUSSION

We herein present the hitherto largest series of patients with NECD or NIUA undergoing NSAID provocation tests after pretreatment with H₁-antihistamines. In contrast to the previous study by Asero,¹⁵ a significant proportion of patients were exposed to strong COX-I inhibiting NSAID. Our findings demonstrate the prophylactic effect of H₁-antihistamine premedication in this patient group. We, therefore, consider antihistamine pretreatment an effective tool to improve the tolerability of NSAID in patients with NECD and NIUA suffering concurrently from recurrent pain, such as back pain, arthralgia, menstrual cramps, or headaches of different origin.

The criteria for the diagnosis and classification of nonallergic hypersensitivity reactions to NSAID proposed in recent years are internationally accepted.^{1,2,16,17} Accurate differentiation of the 2 major forms of NSAID-related urticaria or angioedema, NECD and NIUA, from NSAID-exacerbated respiratory disease (also denominated as AERD) or single NSAID-induced anaphylaxis is important¹⁸ as the latter 2 entities are considered nonresponsive to antihistamine treatment and may take a severe course. It is still discussed controversially, whether NECD or NIUA can be diagnosed by history alone without provocation testing.¹⁹⁻²² Although Kowalski et al² recommend that NIUA can be diagnosed in patients suffering from urticaria/angioedema to at least 2 different NSAID by history alone, this is not possible in patients with NECD because other triggers might exacerbate chronic urticaria. In 2 of our patients (patients 5 and 6), diagnostic provocation testing was necessary to demonstrate NECD, because history did not unequivocally clarify whether NSAID really triggered urticaria flare-ups. In the other patients with NECD, the close temporal relationship between intake of a strong COX-I INH and the onset of urticaria exacerbation was reproducible, that is, several similar episodes had occurred. Patients with NECD had a history of at least 4 hypersensitivity reactions induced by 2 different analgesics (patients 9, 12, 14, 21), whereas others had reacted to 3, 4, or 5 different COX-I inhibiting NSAID (patients 1, 2, 3, 7, 13). All our patients

TABLE II. Patients with NSAID-exacerbated cutaneous disease (NECD) or NSAID-induced urticaria/angioedema (NIUA): offending NSAID and results of provocation testing

Patient no., age (y), sex	Offending NSAID	Diagnosis	Time interval (mo)*	Provocation tests with alternative analgesics	Reaction	Provocation tests after H ₁ -antihistamine premedication	Reaction
1, 38, f	ASA Ibuprofen Metamizol	NECD	1	Celecoxib Nimesulide Nabumetone	— — —	800 mg ibuprofen	—
2, 57, m	ASA Ibuprofen Metamizol	NECD	<1	Paracetamol	+	500 mg paracetamol	—
3, 62, f	ASA Diclofenac Metamizol Paracetamol	NECD	1	Nabumetone Meloxicam Paracetamol	— — +	500 mg paracetamol	—
4, 27, m	ASA Ibuprofen Metamizol Paracetamol	NIUA	10	Celecoxib Paracetamol	— —	800 mg ibuprofen	—
5, 60, m	ASA	NECD	3	Paracetamol Meloxicam	— —	500 mg ASA	—
6, 59, m	ASA Ibuprofen	NECD	2	Celecoxib Paracetamol Peloxicam Nabumetone	— — — —	800 mg ibuprofen	—
7, 45, m	ASA Diclofenac Ibuprofen Metamizol Paracetamol	NECD	<1	Celecoxib Meloxicam Paracetamol	— — +	800 mg ibuprofen 1000 mg paracetamol	+ —
8, 54, m	ASA Diclofenac Metamizol Ibuprofen	NIUA	<1	Etoricoxib Paracetamol Meloxicam	— — —	400 mg ibuprofen	—
9, 46, f	ASA Metamizol	NECD	2	n.d.	n.a.	400 mg ibuprofen 750 mg metamizol	— —
10, 67, m	ASA Diclofenac	NIUA	4	Paracetamol Meloxicam	— —	50 mg diclofenac	—
11, 38, f	ASA Diclofenac Metamizol Ibuprofen	NIUA	9	Celecoxib Paracetamol Meloxicam	— — +	400 mg ibuprofen	—
12, 18, f	ASA Ibuprofen	NECD	2	n.d.	n.a.	400 mg ibuprofen	—
13, 42, f	ASA Metamizol Ibuprofen	NECD	1	Celecoxib Paracetamol Meloxicam	— — —	400 mg ibuprofen	—

14, 41, f	ASA Ibuprofen	NECD	<1	Etoricoxib Meloxicam	— —	500 mg metamizol	—
15, 47, f	ASA Metamizol Ibuprofen	NIUA	2	Etoricoxib Paracetamol	— —	400 mg ibuprofen	—
16, 31, f	ASA Ibuprofen Metamizol Paracetamol	NIUA	2	n.d.	n.a.	800 mg ibuprofen 400 mg ibuprofen	+ —
17, 29, m	ASA Ibuprofen	NIUA	3	Celecoxib Paracetamol	— —	400 mg ibuprofen	—
18, 21, f	ASA Metamizol Ibuprofen	NIUA	2	Celecoxib Meloxicam	— —	400 mg ibuprofen	—
19, 58, m	ASA Diclofenac Ibuprofen Metamizol	NIUA	9	Etoricoxib Paracetamol Meloxicam	— — —	400 mg ibuprofen	+
20, 42, m	Diclofenac Ibuprofen Metamizol	NIUA	3	Celecoxib Meloxicam	— —	400 mg ibuprofen	+
21, 38, f	ASS Ibuprofen	NECD	3	n.d.	n.a.	400 mg ibuprofen	—

ASA, Acetylsalicylic acid; *n.a.*, not applicable; *n.d.*, not done; *NSAID*, nonsteroidal anti-inflammatory drug.

*Time interval between last NSAID-induced urticaria episode and controlled provocation testing.

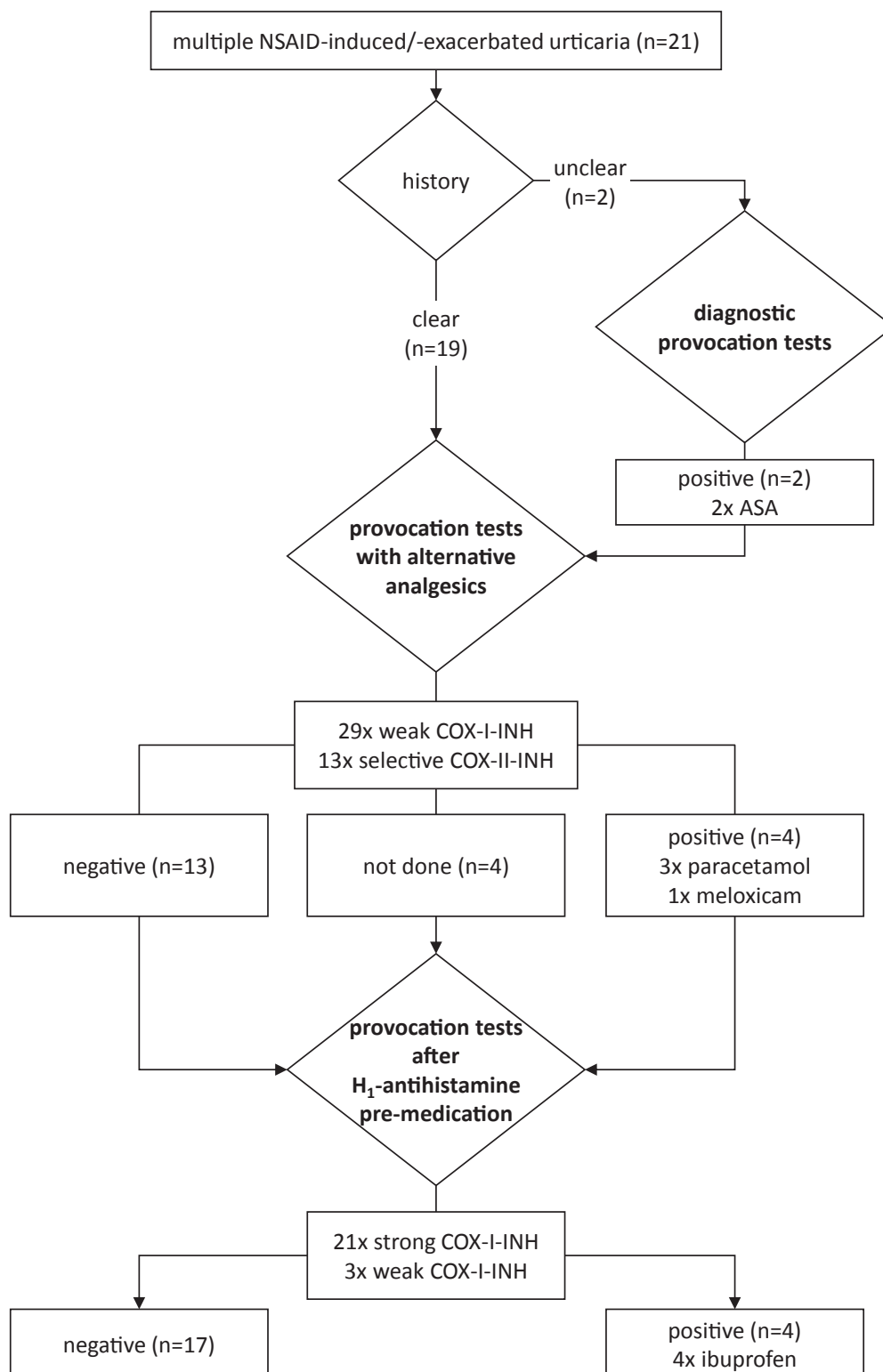


FIGURE 1. NSAID provocation tests in patients with NSAID-exacerbated cutaneous disease (NECD) or NSAID-induced urticaria/angioedema (NIUA): results of diagnostic provocation, provocation with alternative analgesics, and provocation tests preceded by antihistamine premedication. ASA, Acetylsalicylic acid; COX, cyclooxygenase; INH, inhibitor; NSAID, nonsteroidal anti-inflammatory drug.

had exclusively taken NSAID to treat recurrent pain. Other potential nonallergic or allergic causes of acute urticaria, such as febrile infectious diseases or antibiotics, were excluded based on a meticulous history. It is possible that NSAID reactivity in NECD is dependent on the activity of the underlying urticaria. However, all our patients with NECD developed last NSAID-induced urticaria flares within 3 months before controlled testing (Table II).

Our present observations concerning the tolerability of weak COX-I inhibiting NSAID in patients with NECD or NIUA are in agreement with data from the literature stating that 75% to 90% of these patients tolerate weak COX-I INH in controlled provocation tests.^{6,7,23} Considering the relatively low, but significant remaining risk of hypersensitivity reactions, our findings underline that weak COX-I INH should not be generally released for intake in an established diagnosis of NECD or NIUA. There is to date no formal international consensus on how to perform oral NSAID provocation testing. Most authors recommend to start with a low initial dose that is followed by 3 to 4 incremental steps until a normal therapeutic dose is reached. The recent article by Asero et al¹ reviews different provocation protocols and provides a table summarizing the respective first and last provocative doses. Compared with these previous protocols, we consciously used higher NSAID doses for provocation testing because nonallergic NSAID hypersensitivity reactions are characterized or even defined by a pronounced dose dependency.²⁴

To ensure both the antihistamine's onset of action and rapid pain relief, our patients received 5 mg desloratadine orally 30 minutes before NSAID administration. In our series, an orodispersible H₁-antihistamine tablet was used for premedication. Whether this special formulation accelerates the onset of pharmacological action is a matter of speculation, but might explain its efficiency within only 30 minutes.²⁵ However, in a pharmacokinetic study, the peak plasma desloratadine concentration after oral administration was reached not until 3 to 4 hours.²⁶ It is tempting to speculate whether an increased desloratadine dose of 10 mg may be even more effective. The characteristic dose dependency of nonallergic NSAID hypersensitivity reactions is corroborated by our evaluation. Despite H₁-antihistamine premedication, 2 of 5 provocation tests with 800 mg ibuprofen were positive, whereas 10 of 12 provocations with 400 mg ibuprofen were tolerated.

Main limitations of this evaluation

This is a retrospective data analysis of a relatively small number of patients. The diagnosis of NECD or NIUA was not based on a positive provocation test in the majority of patients. The types and doses of NSAID used in provocation tests were not standardized, but were adjusted to individual needs and preferences. Other than diagnostic provocation and provocation with alternative analgesics, provocation after H₁-antihistamine premedication was carried out in an open setting. Furthermore, as any data derived from in-hospital provocation tests, our findings might not be entirely generalizable to complex everyday situations with, for example, coincidence of infections, physical effort, activity of spontaneous urticaria, alcohol intake, or necessity for prolonged pain treatment.

CONCLUSIONS

Our study demonstrates the prophylactic effect of an H₁-antihistamine orodispersible tablet given 30 minutes before administration of a strong COX-I inhibiting NSAID in patients with NECD or NIUA. Adequate pain management may be facilitated in these patients by the option to take specific COX-I inhibiting NSAID in a defined dose preceded by antihistamine premedication.

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