Original Article

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Hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) – a retrospective study

Flavia Angeletti*, Franziska Meier*, Nadja Zöller, Markus Meissner, Roland Kaufmann, Eva Maria Valesky

Department of Dermatology, Venereology and Allergology, University Hospital Frankfurt, Frankfurt am Main, Germany

* The first two authors contributed equally to the present article.

Summary

Background: The aim of this study was to verify the validity of clinical history and oral provocation challenges of patients with NSAID hypersensitivity and to identify safe alternatives. The COX-2 inhibitor etoricoxib, in particular, was studied.

Patients and methods: In all, 104 patients with confirmed diagnoses of NSAID hypersensitivity treated at the Department of Dermatology, Frankfurt University Hospital, Germany between 2004 and 2012 were retrospectively studied.

Results: The medical history and hypersensitivity symptoms during oral provocation testing (OPT) largely coincided and were mostly mild to moderate. Acetylsalicylic acid (ASA) was the most frequent trigger both anamnestically (27.9 %) and during OPT (47.8 %). Etoricoxib caused the fewest reactions during OPT (4.2 %). Acetaminophen led to reactions in only 6.7 % of the cases studied although it was named more often in clinical histories (14 %).

Conclusions: OPT should be the aim whenever possible as most symptoms are mild to moderate. To distinguish between selective and cross-hypersensitivity reactions, ASA should be part of the test protocol. Furthermore, the findings of this study indicate that etoricoxib and acetaminophen are safe treatment alternatives in case of NSAID hypersensitivity. However, these drugs should not be administered without prior OPT in an inpatient setting, as severe symptoms can occur.

Introduction

Hypersensitivity reactions (HR) to non-steroidal anti-inflammatory drugs (NSAIDs) are very common and range from minor symptoms to severe and potentially life-threatening anaphylactic reactions. Once hypersensitivity is suspected, analgesic and antipyretic treatment options are limited. The fact that NSAIDs are among the most commonly prescribed pharmaceuticals worldwide underscores the significance of the topic [1]. The underlying causes of HR to NSAIDs are not fully understood. Anaphylactic reactions can be caused by immunologic as well as non-immunologic mechanisms [2]. The former are classified as allergic or selective reactions (SRs), such as IgE-mediated allergies of the immediate type (type I). The latter non-immunologic reactions, however, can result from G-protein-mediated pathways, activation of the complement system, or interactions in the arachidonic acid cascade and are referred to as cross-hypersensitivity reactions (CRs) [3, 4]. NSAIDs take effect *via* cyclooxygenase (COX) inhibition leading, in turn, to a decrease of prostaglandins in favor of leukotrienes. Consequently, increased levels of leukotrienes promote anaphylactic reactions manifested as bronchoconstriction, urticaria and pruritus in patients with hypersensitivity. There are at least three isoforms of COX, of which COX-1 and COX-2 have the highest clinical relevance [5]. Adverse side effects via inhibition of the cytoprotective prostaglandin E2 are caused mostly by COX-1, whereas COX-2, which is synthesized mainly in inflammatory tissue, is the actual target for analgesic effects [6]. Coxibs that specifically inhibit COX-2 were developed to prevent side effects [7]. Whether COX-2 inhibitors also cause fewer hypersensitivity reactions is an obvious question. Symptoms caused by allergy and cross-hypersensitivity do not differ clinically. However, there is no sensitization in cross-hypersensitivity reactions, so anaphylaxis can occur at first drug contact. Furthermore, dose-dependency is a factor. Selective reactions can appear after the intake of NSAIDs of all compounds of COX-1 inhibition, whereas CRs are mostly observed in relation to strong COX-1

inhibitors, including acetylsalicylic acid (ASA) [3]. Proposed risk factors for NSAID-induced HR are associated primarily with atopy, including allergic rhinoconjunctivitis, polyposis nasi, allergic asthma, atopic dermatitis and urticaria. Once NSAID-induced hypersensitivity is suspected, oral provocation challenge is the gold standard with a negative predictive value of 97.8 % [3]. By means of exposition to the culprit drug, potential triggers can be identified. Evasive testing, by contrast, secures safe alternative treatment options and may reveal cross-reactions. In 2013, the European Network for Drug Allergy (ENDA) revised a consensus document including definitions and classifications of hypersensitivity reactions to NSAIDs as well as practical algorithms for diagnosis and management [3, 8]. Table 1 shows a classification system for NSAID-induced hypersensitivity according to timing and type of reaction, clinical manifestation, underlying conditions, and cross-reactivity to other drugs. The type of hypersensitivity reaction is expected to facilitate proper management. The aim of this study was to verify the validity of clinical history and oral provocation challenges of patients with NSAID-hypersensitivity and to identify safe alternative analgesics. The COX-2 inhibitor etoricoxib, which was approved in 2004, was particularly studied.

Patients and Methods

Patient data

We retrospectively evaluated oral provocation tests (OPT) of 104 patients with diagnosis of NSAID hypersensitivity who were referred to the Department of Dermatology, Venereology and Allergology, Frankfurt University Hospital, Germany between 2004 and 2012. All patients studied belonged to the NIUA (NSAID-induced urticarial/angioedema) group of possible hypersensitivity reactions (Table 1). Written

Table 1 Classification of NSAID hypersensitivity reactions (modified after [8, 38]).

Type of reaction	Symptoms	Latency	Underlying condition	Cross-reactivity	Suspected mechanism
NERD (NSAIDs-exacerbated respiratory disease)	Rhinitis/ asthma	30–120 min	asthma/ rhinosinusitis/ polyposis nasi	Yes	COX1-Inhibition
NECD (NSAIDs-exacerbated cutaneous disease)	Urticaria/ angioedema	1–4 h (15 min–24h)	chronic urticaria	Yes	COX1-Inhibition
NIUA (NSAIDs-induced urticaria/ angioedema)	Urticaria and/or angioedema	1–6 h (–24 h)	None	Yes	Suspected COX1-Inhibition
SNIUAA (single NSAID-induced urticaria/ angioedema or anaphylaxis)	Cutaneous/anaphylaxis	Min–1 h	None	No	IgE mediated (type I)
SNIDR (single NSAID-induced delayed hypersensitivity reactions)	Various cutaneous and organ-specific symptoms i.e. drug related exanthema (TEN, SJS), AGEP, DRESS, contact dermatitis, photoallergic dermatitis, pneumonitis, aseptic meningitis, nephritis	Delayed	None	No	T-cell mediated (type IV) Cytotoxic T-cells, NK-cells

Abbr.: TEN, toxic epidermal necrolysis; SJS, Stevens-Johnson syndrome; AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms.

informed consent was obtained from all patients for allergological work-up. The study protocol was approved by the Ethical Board of the Goethe University of Frankfurt, Germany (No. 327/14).

Inclusion and exclusion criteria

Patients were included when medical history and/or OPT were compatible with HR and patients belonged to the NIUA (NSAID-induced urticarial/angioedema) group of possible hypersensitivity reactions. Furthermore, the allergological work-up had to be within one year of the suspected drug reaction. The name of the culprit drug had to be recallable, the reaction had to have occurred within five hours of exposure and the skin prick test (SPT) had to be negative. Exclusion criteria were suspicion or evidence of a delayed-type hypersensitivity such as fixed drug eruption, erythema multiforme or acute generalized exanthematous pustulosis (AGEP). Patients either suffering from chronic urticaria or presenting a history of moderate to severe asthma, a combination of nasal polyposis, sinusitis and ASA-induced asthma were excluded from the study. Beta-blockers or ACE inhibitors were stopped before performing the oral provocation test. Patients with placebo reactions were withdrawn from the study.

Clinical history and allergological testing

Clinical histories were obtained according to the S2K-Guideline for the diagnosis of drug hypersensitivity reactions of the German Society for Allergology and Clinical Immunology (DGAKI) and the German Dermatological Society (DDG) [9]. In addition to basic patient data and comorbidities, circumstances, amount of time to reaction, and grade of severity were recorded. OPT was performed at our inpatient clinic with anaphylaxis surveillance, single-blinded and placebo-controlled. Briefly, escalating doses of different NSAIDs were orally administered at intervals of 90 minutes. Table 2 shows the detailed dosing scheme of different drugs used in challenges. Not every patient received all agents. Patients were discharged after a 24-hour monitoring phase after intake of the last dose.

Statistics

Statistical analyses were calculated using IBM SPSS Statistics for Windows version 22 (SPSS Inc., Chicago, Illinois, USA). The chi-square four-field test was used to test the independence of two features. A *P*-value of < 0.05 % was considered statistically significant. If applicable, Fisher's exact test was conducted for verification purposes.

Results

Patient characteristics

A total of 104 patients, 31 males (29.8 %) and 73 females (70.2 %), were included. The average age for males was 46.3 years (range 14–74 years) and 48.47 years for female patients (range 17–78 years). With respect to secondary diagnoses of atopic diseases, 20 patients had rhinoconjunctivitis allergica with concomitant type I allergies (19.2 %), and eight patients suffered from mild seasonal bronchial asthma (7.7 %). Moreover, 21 patients had concomitant cardiovascular diseases (20.2 %).

Clinical history

Anamnestically, a total of 222 hypersensitivity reactions were reported. ASA was the most frequent trigger (27.9 %), but ibuprofen (22.5 %) and diclofenac (17.1 %) were also likely to cause hypersensitivity reactions according to clinical

Table 2 Dosing scheme of different drugs used in OPT.

	Oral provocation testing	
Tested substance	**Single doses (mg)**	**Cumulative dose (mg)**
Acetylsalicylic acid	50 – 100 – 250 – 500 – 1000	1900
Acetaminophen	125 – 250 – 500 – 1000	1875
Ibuprofen	100 – 200 – 400 – 800	1500
Metamizole	125 – 375 – 750	1250
Diclofenac	6.25 – 12.5 – 25 – 50	93.75
Indomethacin	12.5 – 25 – 50 – 100	187.5
Etoricoxib	30 – 90	120

histories. Acetaminophen (14.0 %) and metamizole (12.6 %) were reported to be less-frequent triggers. Reactions to other analgesics were very rare and accounted for less than 6.0 % of all reactions. In all, 63 patients (60.6 %) reported to respond to more than one drug. The medical history most frequently revealed that patients who developed symptoms to more than one substance showed reactions to ibuprofen in addition to ASA. Most reported clinical symptoms were mild to moderate, according to *Ring and Messmer's* classification [10] (Table 3). There were no grade IV events. Urticaria and angioedema were the most frequently reported symptoms in 71 reactions (32.0 %). Anamnestically collected data on the time interval between drug intake and onset of symptoms were available for 94 individuals; 67 reactions occurred within two hours (71.3 %). In addition, 41 patients were able to name other NSAIDs that had been well tolerated after the index reaction. Among them, 26 patients stated that acetaminophen was a safe alternative, eleven patients named ASA, and four patients reported that ibuprofen had been tolerated. Diclofenac was taken safely by three individuals, and metamizole as evasive drug did not lead to any anaphylactic reactions in two patients.

Oral provocation testing (OPT)

A total of 340 OPTs were conducted; 81 of these were challenges to the culprit drug and 259 were evasive tests. A total of 7 drugs were tested. Not every patient received all agents. Etoricoxib was tested 72 times, ASA 67, metamizole 49, acetaminophen 45, indometacin 41, ibuprofen 35 and diclofenac 31 times. OPT-protocols were adapted to the medical needs of our patients. In all, 104 hypersensitivity reactions were registered, which accounted for 30.6 % of all OPTs. Almost one-third of the patients showed symptoms related to two or three test substances. However, no drug combination was identified that caused statistically more reactions than others. According to *Ring and Messmer*, 71.2 % of the reactions classified as grade I, 24 % were grade II, and 4.8 % were referred to as grade III (Figure 1). All grade III incidences presented as severe dyspnea. Severe or lethal adverse events did not occur in our study population. The anamnestically reported severity of the reactions largely coincided with the symptoms during OPT. All patients developing symptoms could be sufficiently treated with antihistamines, intravenous prednisolone, inhalative budesonide, or salbutamol. The results for the individual substances are presented below.

Acetylsalicylic acid

Acetylsalicylic acid was tested 67 times and caused 32 hypersensitivity reactions (47.8 %) (Table 4). As reported in

Table 3 Medical history: Reported drugs and symptoms (according to Ring and Messmer [10]).

Symptom / Substance	I					II			III		
	Pruritus	Flush	Urticaria	Angioedema	Rhinorrhea	Moderate dyspnea	Nausea	Tachycardia	Hypotension	Vomiting/ defecation	Severe dyspnea	Shock
Ibuprofen	19	2	30	35	4	18	1	0	1	2	4	1
Diclofenac	14	5	12	23	1	15	2	1	10	1	2	1
Acetylsalicylic acid	10	3	21	41	4	15	0	2	1	0	3	0
Metamizole	8	1	17	17	1	11	1	2	1	0	2	0
Acetaminophen	7	0	15	13	0	8	0	1	0	0	1	0
Etoricoxib	0	0	0	1	0	0	0	0	0	0	0	0

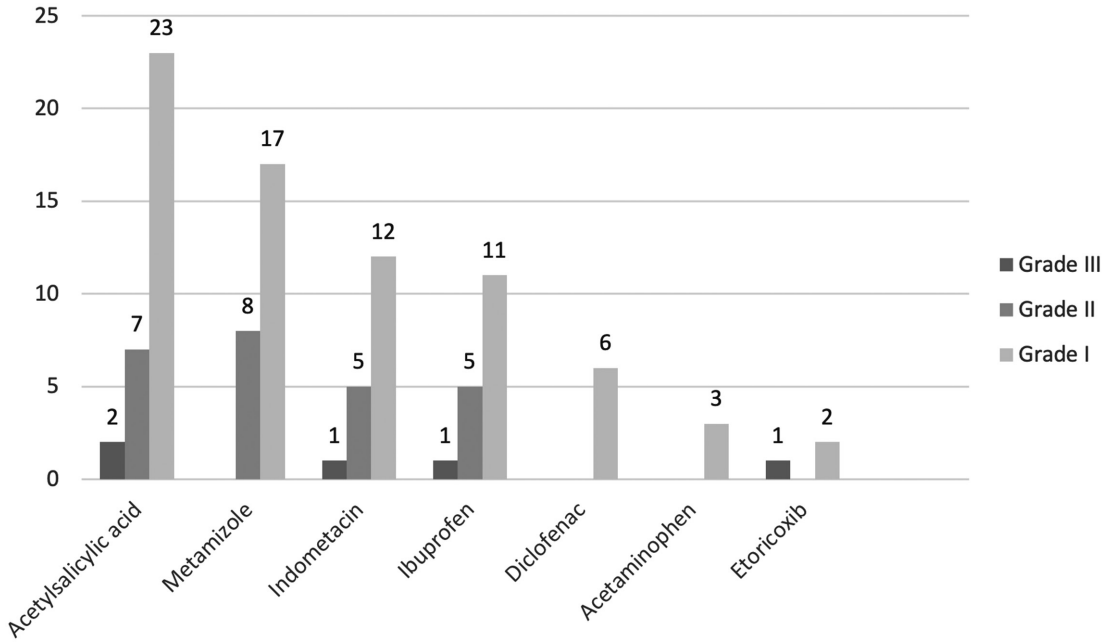

Figure 1 Severity grade of HR during OPT (according to Ring and Messmer [*10*]).

the medical histories, as well as during OPT, most reactions were mild according to *Ring and Messmer's* classification (n = 23). Only seven grade II and two grade III reactions occurred (Figure 1). ASA was the most tested substance during challenges to the culprit drug (n = 40). Twenty-six HR (65.0 %) occurred during these challenges to the culprit drug. In evasive testing six positive OPTs were recorded out of 27 tests (22.2 %). Patients reacted significantly more often when exposed to ASA as the culprit drug compared to evasive testing (p = 0.001) (Figure 2).

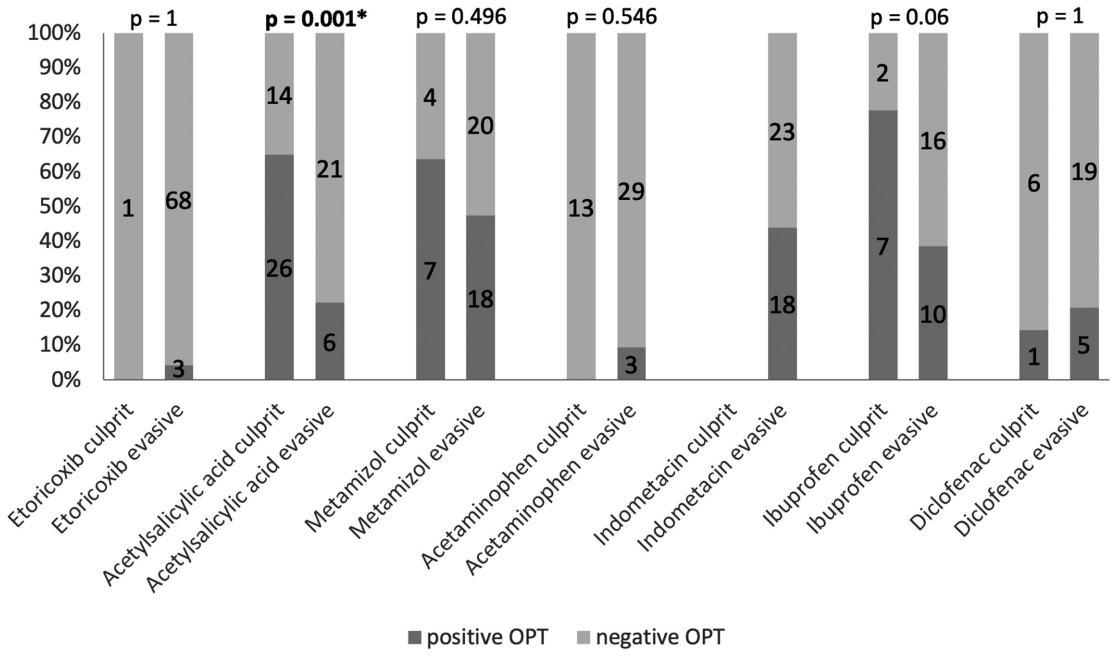

Figure 2 OPT: Hypersensitivity reactions to culprit versus evasive drugs. A *P*-value of < 0.05 % was considered statistically significant.

Table 4 OPT: Frequency of administered drugs and number of hypersensitivity reactions. Percentages indicate the fraction of positive reactions for the tested substance. HR to one drug was compared to all other tested substances.

Tested substance	n (340)	Hypersensitivity reactions (104)	Percentage	*P*-value
Etoricoxib	72	3	4.2 %	0.00000041
Acetylsalicylic acid	67	32	47.8 %	0.000094
Metamizole	49	25	51.0 %	0.00015
Acetaminophen	45	3	6.7 %	0.00059
Indomethacin	41	18	43.9 %	0.01871
Ibuprofen	35	17	48.6 %	0.00515
Diclofenac	31	6	19.4 %	0.24802

Acetaminophen

Acetaminophen was given 45 times and only three reactions occurred (6.7 %) (Table 4). There were neither grade II nor grade III adverse events. None of the OPTs regarding Acetaminophen as the accused drug showed any reactions. During evasive testing, three out of 32 tests were positive. No statistically significant difference was found between evasive testing and exposition to Acetaminophen as the culprit drug (Figure 2).

Ibuprofen

Ibuprofen was tested 35 times. A total of 17 reactions were associated with ibuprofen (48.6 %) (Table 4). In total, eleven grade I reactions, five grade II and one grade III reaction were registered. Of nine patients with a clinical history of ibuprofen-triggered HR seven patients developed a positive drug-provocation test (77.8 %). A total of 26 evasive tests were performed and led to ten reactions (38.5 %). No statistically significant difference was found between evasive testing and exposition of ibuprofen as the culprit drug (Figure 2).

Metamizole

Following 49 OPTs of metamizole, 25 reactions occurred (51.0 %). Consequently, every second OPT for metamizole was positive (Table 4). Most of the reactions, however, were mild according to *Ring and Messmer* (n = 17). There were no severe events, and eight grade II reactions were recorded. Of eleven patients with a clinical history of metamizole-triggered symptoms, seven had a positive OPT (63.6 %). In 38 evasive tests, 18 patients showed symptoms of HR (47.4 %). No statistically significant difference was found between evasive testing and exposition of metamizole as the culprit drug (Figure 2).

Diclofenac

Following 31 exposures to diclofenac, 6 reactions (19.4 %) were registered (Table 4). All documented clinical reactions were mild. Of seven patients with a medical history of HR to diclofenac only one patient showed a reaction. During evasive tests (n = 24), five positive results were recorded (20.8 %). No statistically significant difference was found between evasive testing and exposition of diclofenac as the culprit drug (Figure 2).

Indomethacin

Indomethacin was given 41 times and 18 reactions were recorded (43.9 %). Indometacin caused significantly more HR compared to all other drugs (p = 0.02) (Table 4). Although most of the reactions to this drug were mild (n = 12), five grade II and one grade III reactions were noted. All reactions occurred during evasive testing.

Etoricoxib

Etoricoxib was specifically tested with regard to safe alternative treatments in case of NSAID hypersensitivity. A total of 72 oral provocation tests showed three HR (4.2 %) (Table 4).

Two patients reacted mildly, and one experienced grade III symptoms. All three patients had previously reported multiple NSAID-triggered HR in their clinical history. In addition to etoricoxib, these patients also reacted to at least one other drug during OPT. One patient who reported anaphylactic symptoms after intake of etoricoxib in the medical history was exposed to the culprit drug and showed no symptoms.

Dose dependence of HR

Table 5 shows detailed dose dependence of HR to each drug. Especially for ASA only eight of 32 patients developed

Table 5 OPT: Dose dependence of HR. Mean value, median, minimum and maximum are given for each substance.

Tested Drug	N	Median (mg)	SD min (mg)	SD max (mg)	CD min (mg)	CD max (mg)
ASA	32	900.0	50.0	1000.0	50	1900.0
Acetaminophen	3	375.0	250.0	250.0	375.0	375.0
Ibuprofen	17	700.0	100.0	800.0	100.0	1500.0
Metamizole	25	500.0	125.0	750.0	125.0	1250.0
Diclofenac	6	93.8	6.3	75.0	6.3	93.8
Indomethacin	18	37.5	25.0	100.0	37.5	187.5
Etoricoxib	3	120.0	90.0	90.0	120.0	120.0

a positive OPT after a cumulative dose of 150 mg or less. In eleven of 32 patients the threshold cumulative dose was 1900 mg ASA per day.

Discussion

Indications for the use of NSAIDs vary from mild pain or fever to more severe symptoms, for example, in the treatment of rheumatoid arthritis. One aim of this study was to identify safe alternative treatment options in patients where NSAID hypersensitivity is suspected. Several studies show that "NIUA" type of reaction, classified by the ENDA, is the most common clinical entity in the evaluation of NSAID- induced hypersensitivity [11, 12]. Due to the same mode of action via COX-1 inhibition, cross-reactions between different NSAIDs are suspected and explain the high proportion of HR to multiple NSAIDs [3].

Patient history

In our cohort, about 60 % of the patients reported symptoms in relation to more than one drug, which correlates with the findings of other authors [11, 12]. ASA was anamnestically mentioned to cause the largest number of anaphylactic symptoms (27.9 %). However, ibuprofen (22.5 %), diclofenac (17.1 %), acetaminophen (14 %), and metamizole (12.6 %) were also among the most frequently named drugs causing HRs. Other groups reported similar results with slight differences in the percentage distribution [3, 13, 14].

Interestingly, compared to the current literature, acetaminophen was cited much more frequently as a trigger for allergic symptoms [3, 13]. Conversely, about 50 % of our patients named acetaminophen as a tolerated pain medication. None of the patients with a positive medical history to acetaminophen however, showed any symptoms of hypersensitivity in OPT. The overall discrepancy between the culprit drug in the patients' history and OPT results might be explained by the intake of several drugs at the same time. Moreover, concomitant infections and other cofactors may influence tolerance and hypersensitivity reactions. However, the patients' history and OPT results were mostly consistent with respect to the severity grade of reported symptoms, though for second and higher degree reactions the information was less concordant. Nevertheless, compilation of a detailed anamnesis is the first step in every diagnosis. An exposition to the culprit drug should be avoided, in any case, if the patient reports severe symptoms in the sense of type I allergic reactions or other serious drug reactions such as toxic epidermal necrolysis. It must be noted that NSAIDs are largely freely marketable, and after food supplements, are considered the most common group of drugs for self-medication [15]. An accurate estimate about the type and frequency of NSAID use is therefore difficult. However, it is conceivable that the lower rate of reactions to prescription drugs is related to the frequency of use.

Patient selection and comorbid diseases

Approximately 70 % of our tested patients were females. This corresponds to the findings of other authors describing a higher prevalence of NSAID hypersensitivity in females [3]. This might be due to the fact that women tend to take more medication, including NSAIDs, which increases the risk of HR [15]. Although not statistically significant, in this study women were more likely to show symptoms during OPT than men (71 vs. 58 %).

Next to women, a higher prevalence of NSAID hypersensitivity is described for individuals with bronchial asthma and nasal polyposis [16]. Whether atopy is a significant risk factor for NSAID hypersensitivity has been discussed controversially [11, 17]. Unfortunately, due to the design of our study it was not possible to identify any predictors of NSAID hypersensitivity.

Etoricoxib and acetaminophen – safe alternative options

In this study, etoricoxib was well tolerated by 95.8 % of the patients during OPT, and these data align with the results of other studies [7, 18, 19]. As a strong selective COX-2 inhibitor, etoricoxib qualifies as a safe alternative. This is supported by the assumption that "NIUA" type of reaction is mediated by COX-1 inhibition and the imbalance between leukotrienes and prostaglandins. Yet, etoricoxib should not be prescribed without careful consideration, especially for patients with previous cardiovascular disease as it might increase the risk of cardiovascular events [20]. Next to etoricoxib, acetaminophen caused very few reactions in this patient group. This might be explained by the very low COX-1 inhibition. In their position paper, Kowalski et al. also recommended acetaminophen for patients with NSAID hypersensitivity [3]. OPT for acetaminophen and etoricoxib were positive in our study, albeit rarely. Therefore, these drugs can only be safely recommended after previous negative oral testing.

Acetylsalicylic acid and other NSAIDs

In order to distinguish between SRs and CRs, it is useful to administer ASA. Patients presenting SRs mostly tolerate ASA, while individuals with CRs react to all strong COX-1 inhibitors, including ASA [3, 21]. However, recent data have suggested temporary drug hypersensitivity in some patients should be considered. Dona et al. showed a regained drug tolerance of ASA after 72 months in about 63 % of the patients [22]. The dose of the substance at which anaphylactic reactions occur can also provide insight into whether an SR or CR is present. Patients with SRs react at lower doses, whereas higher doses indicate the presence of CRs [12, 23]. Unfortunately, due to the retrospective character of our study, not all patients were tested for ASA. Therefore, any conclusions concerning the type of reaction (SR vs. CR) cannot be drawn in our sample. ASA showed the highest potential to cause HR both anamnestically and during OPT; 65.0 % of the patients who were exposed to ASA as the culprit drug showed HR. However, symptoms were mild to moderate, and reactions during evasive testing were less frequent, supporting the recommendation to include ASA in any test protocol. As expected, HR showed dose dependence in our cohort. Hypersensitivity to acetylsalicylic acid (ASA) constitutes a serious problem for patients with vascular comorbidities. With a prevalence of 12.8 %, cardiovascular disease is a common illness in Germany [24]. On the one hand it is important to determine a patient's threshold dose for combating unnecessary avoidance, on the other hand it is necessary identifying patients with hypersensitivity reactions to ASA at low doses (< 100 mg) with medical need for ASA desensitization [25–27]. OPT with increasing doses under medical surveillance is a highly target-oriented tool to identify safe low-dose treatment options even in the case of suspected ASA hypersensitivity.

A fairly high number of reactions were recorded for indomethacin and metamizole. For metamizole especially, the findings of this study correlate with those of other studies that postulated metamizole to be a frequent trigger of HR [11]. It seems to have a high potential to cause symptoms. Not only patients who reported metamizole in their patient history but also patients who had never taken the drug before showed symptoms. In addition, besides immediate type reactions [28, 29], metamizole has the potential to cause severe cutaneous reactions [30, 31], disqualifying metamizole as a standard evasive test substance. The results of this study indicate that neither metamizole nor indomethacin serve as safe alternative treatment options.

Exposition to the culprit drug

OPT is the gold standard when NSAID hypersensitivity is suspected. By exposure to the culprit drug, suspected hypersensitivity can be verified. On the other hand, cross-reactivity, as well as tolerated treatment alternatives, can be determined during evasive testing. Several studies have shown that reliable results can be achieved only by oral provocation [32]. Regardless of the type of test (culprit vs evasive drug), the most frequently reported symptoms were urticaria and angioedema (grade I) in addition to pruritus and dyspnea; this was also observed in other studies [14, 18, 19, 33]. However, due to the lack of validated tests, the uncertainty of causing a severe allergic reaction during OPT remains. The medical history and a negative skin prick test do not always provide reliable evidence on the severity of adverse events. Thus, even when attempting to resolve an issue with a potentially less dangerous NIUA, a possibly lethal reaction of a SNIUAA may occur [3, 29, 34].

Almost three-fourths (74.5 %) of the symptoms occurred within 120 minutes of exposure, with an average of 33 minutes. These times are consistent with those of other studies [3, 33]. Exposition to the culprit drug should be the aim whenever possible. This way, suspected hypersensitivity can be verified, and patient management simplified. Especially in the case of ASA, where some patients showed symptoms only at high doses, the OPT is valuable since prophylactic doses of 100 mg daily could be prescribed [35].

Conclusions

Oral provocation testing is the gold standard in the diagnosis of NSAID hypersensitivity. Whenever possible, exposition to the culprit drug should be performed, as most symptoms are

mild to moderate. Our data do not allow any conclusions concerning the discrimination between SRs and CRs. In order to better distinguish between the types, ASA should be implemented in any test protocol. Complicating pathophysiological understanding is that ASA tolerance can also be present in patients who react to more than one NSAID [21, 23, 36, 37]. Whether this reflects reliable ASA tolerance in these patients, with hypersensitivity to multiple other NSAIDs in the sense of a CR, or temporary drug hypersensitivity as described by Dona et al. requires further research before clinical conclusions can be drawn [22]. Furthermore, the findings of this study indicate that etoricoxib and acetaminophen are safe treatment alternatives in cases of "NIUA" type of hypersensitivity. CRs may be caused by strong COX-1 inhibition. The assumption that COX-2 inhibitors are tolerated in a majority of our patients was broadly confirmed. Nevertheless, in case of suspected hypersensitivity, these drugs should not be administered without prior oral provocation testing, emphasizing the importance of in-patient care in the field of allergology.

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Conflict of Interest

None.

Correspondence to

Eva Maria Valesky, MD
Department of Dermatology, Venereology and Allergology
University Hospital Frankfurt

Theodor-Stern-Kai 7
60590 Frankfurt am Main, Germany

E-mail: eva.valesky@kgu.de

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