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Short communication

Benzydamine: an alternative nonsteroidal anti-inflammatory drug in patients with nimesulide-induced urticaria

Background: Cutaneous adverse reactions to nonsteroidal anti-inflammatory drugs (NSAIDs), in particular urticaria/angiedema syndrome, represent a frequent problem in clinical practice. To date laboratory tests for the diagnosis of these adverse reactions are not available. A patient with an adverse drug reaction to NSAIDs needs an alternative drug to assume if necessary. Nimesulide is a highly prescribed nonsteroidal anti-inflammatory drug (NSAID) world-wide. It is also described as one of the most tolerated NSAID. In this paper we present data on the tolerability of benzydamine in nimesulide-sensitive patients.
Patients and methods: One hundred and thirty-seven patients with nimesulide-induced urticaria were submitted to a single-blind, placebo-controlled peroral challenge with increasing doses of benzydamine.
Results: One hundred and thirty-four out of 137 (98%) patients tolerated benzydamine without adverse effects, only three (2%) experienced immediate systemic urticaria (1 at the first dose and 2 at the second dose).
Conclusion: Benzydamine is a well tolerated drug in patients with nimesulide-induced urticaria and it may represent a valid alternative NSAID in nimesulide-sensitive patients.

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Key words: benzydamine; nimesulide; adverse reactions; urticaria.

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Nonsteroidal anti-inflammatory drugs (NSAIDs), together with antimicrobials, are the drug categories with the highest number of cutaneous reactions (1). In particular, NSAIDs may elicit adverse reactions such as urticaria/angiedema, bronchial asthma, rhinithis, and anaphylaxis. Pathogenic mechanisms are still obscure. The inhibition of prostaglandin endoperoxide H synthase (PGHS) 1 and/or 2 enzymes, which is a pharmacological effect of these drugs, has been proposed in the case of bronchial asthma. The inhibition of these enzymes may create an imbalance between PGHS (1 and/or 2) and 5-lipoxygenase (5-LO) in the arachidonic acid cascade with a lower production of the bronchodilator prostaglandin (PG) E_2, (2, 3) and with a relatively higher production of the bronchoconstrictors leukotrienes (LT) C_4 and D_4.

The other clinical manifestations are classified as drug allergy or nonallergic drug hypersensitivity (position paper). In the drug allergy immunological mechanisms have been shown to be either antibidy or cell mediated. In the literature the documented NSAIDs allergy refer mostly to pyrazolone derivatives, (4–6) aspirin,(7, 8) anthranilic-acid derivatives,(9) and diclofenac (10).

In the majority of cases it is not possible to demonstrate an immunological mechanism. These are nonallergic drug hypersensitivity reactions and, to date, little or nothing is known about the pathogenetic mechanisms (11).

It is a frequent problem in clinical practice, to find an alternative NSAID in subjects who refer an adverse drug reaction to NSAIDs. The choice is usually focused on classes of NSAIDs other than those responsible for the adverse reaction and that offer the least amount of adverse reactions.

At the moment there are no NSAIDs absolutely void of adverse reactions.

Acetaminophen and nimesulide are NSAIDs that appear to have fewer side-effects than most members of the class of NSAIDs (12–14).

Benzydamine is a nonsteroidal anti-inflammatory drug that acts partly through an inhibitory effect on the phospholipase A2 by diminishing the liberation of arachidonic acid from phospholipids, and partly as a weak inhibitor of PGHS 1 and/or 2 by reducing the production of PGs (15, 16).

In this paper we present data on a single-blind, placebo-controlled peroral challenge with benzydamine in patients with nimesulide-induced urticaria.

Material and Methods

Study groups

Patients The study was carried out with 137 patients (51 males and 86 females; aged 14–79, mean age (SD) 35.1 years old (6.16)) seen at

this allergy center between January 1991 and January 2000. The study population was divided into the following two groups of patients:

Group A: 83 patients with a history of urticaria/angiedema following administration of nimesulide (26 males and 57 females aged 14–71 years old, mean age (SD) 35.4 years old (16.3)).

Group B: 54 subjects who had positive reactions to oral challenge with nimesulide (25 males and 29 females aged 14–79 years old, mean age (SD) 34.8 years old (17.1)).

All adverse drug reactions were well documented and diagnosed by a specialist.

Personal history data of allergic diseases were obtained by the investigators: self-reported allergy history, including rhinitis, rhinoconjunctivitis, asthma, atopic dermatitis, chronic urticaria and food allergy; self-reported medical history including any current or previous medication allergies apart from NSAID sensitivity. An allergic rhinoconjunctivitis or asthma was assessed by a careful clinical history, and skin-prick test (SPT) with common inhalant allergens (Bayropharm DHS, Milan, Italy): *Dermatophagoides pteronyssinus and farinae*, parietaria pollen, grass pollen, olive pollen, cypress pollen, *Artemisia vulgaris, Alternaria tenuis, Aspergillus,* dog and cat dander.

SPTs were performed using histamine (10 mg/ml) and normal saline as positive and negative controls, respectively. Wheals of 3 mm or more were regarded as positive in the absence of a reaction to normal saline.

Study protocol and test dose

Tolerance of benzydamine was assessed in both groups with peroral challenge. Included criteria for oral challenge with benzydamine and nimesulide were: a 60-day latency period from the last NSAIDs-induced urticaria, no assumption of antihistamines in the week prior to the oral challenge (4 weeks for Astemizole). No use of drugs for at least 48 h before the challenge, no respiratory problems and a Forced Expiratory Volume at the 1st second (FEV_1) $\geq 80\%$ of the predictive value. Patients with chronic urticaria were challenged during a period of clinical remission of the disease. Written consent was obtained from all patients. The peroral challenges were performed according to Stevenson (5). Benzydamine (Tantum drops, Angelini, Rome, Italy) and nimesulide (Aulin tablets, Boehringer Mannheim, Milan, Italy) were used. The doses of benzydamine administered were 4.8 mg, 8.4 mg, 15.6 mg, and 21.6 mg, respectively, with a total therapeutic dose being 50.4 mg. Doses of nimesulide were 10, 20, 30, and 40 mg, respectively, with the total therapeutic dose being 100 mg. Increased drug doses were given at 60 min intervals. Patients were kept for observation for 6 hours after the challenge, and returned the first and second days after the challenge for additional controls. Blood pressure and FEV_1 were monitored during and at the end of the challenge. In a preliminary session, at least 1 week apart, each patient received a placebo challenge in the same manner. In the peroral challenge with benzydamine the placebo administered was saccharose diluted in water. Placebo (talc) and nimesulide were administered with inert capsules as drug vehicle.

The challenge was considered positive if one of the following symptoms appeared: erythema, pruritus accompanied by erythema, urticaria/angiedema, rhinorrhea, nasal obstruction, sneezing, dispnoea and cough associated with a decrease of at least 20% in the FEV_1, and hypotension.

Results

Patients

Of the 137 nimesulide-intolerant subjects considered in this study, 115 (84%) had a positive history of urticaria/angiedema after assumption of NSAIDs apart from nimesulide (Tables 1 and 2): 62 (53.9%) patients belonged to Group A (Table 1) and 53 (46.1%) to Group B (Table 2).

Within the 137 patients with nimesulide-induced urticaria, the NSAID with the highest number of urticaria was aspirin with 53 episodes of urticaria (39%) followed by noramidopyrine with 24 episodes of urticaria (18%), and paracetamol with 15 episodes of urticaria (10%).

Out of the 137 patients considered, 67 (48.9%) had a personal history of allergies or allergic-like diseases apart from adverse drug reactions (Table 3).

Forty had a positive history of chronic idiopathic urticaria/angiedema, (20) 29 belonging to Group A and 11 belonging to Group B.

Furthermore, 21 participants (15.3%) in the study group had a positive history of urticaria/angiedema after the assumption of drugs not included in NSAIDs with 17 antimicrobials (13 β-lactams, 1 cotrimoxazole, 1 quinolones, 1 macrolides, 1 tetracyclines), 1 local anesthetics, 2 gastrointestinal drugs (metoclopramide and butylscopolamine), 1 diuretics (acetazolamide).

Table 1. NSAIDs reported as causes of adverse reactions in Group A patients (83 patients with a history of urticaria/angiedema after assumption of nimesulide)

Drug	No. of patients	Percentage of patients
Nimesulide	21	25.3
Nimesulide + Pyrazolone derivatives	11	13.3
Nimesulide + ASA	11	13.3
Nimesulide + others*	8	9.7
Nimesulide + Propionic acid derivatives	7	8.4
Nimesulide + Pyrazolone derivatives + ASA	7	8.4
Nimesulide + ASA + others	7	8.4
Nimesulide + Pyrazolone derivatives + others	4	4.8
Nimesulide + Pyrazolone derivatives + Propionic acid derivatives	3	3.6
Nimesulide + ASA + Propionic acid derivatives	2	2.4
Nimesulide + Propionic acid derivatives + others	1	1.2
Nimesulide + others	1	1.2
Total	83	100.0

*others: Diclofenac, indomethacin, ketorolac, morniflumate, paracetamol, piroxicam, tenoxicam

Table 2. NSAIDs reported as causes of adverse reactions in Group B patients (54 patients with positive oral challenge with nimesulide)

Drug	No. of patients	Percentage of patients
ASA	12	22.2
Pyrazolone derivatives	11	20.4
Pyrazolone derivatives + ASA	10	18.5
Others*	9	16.7
Pyrazolone derivatives + others	4	7.4
Propionic acid derivatives	3	5.5
ASA + others	3	5.5
ASA + Propionic acid derivatives	1	1.9
Nimesulide	1	1.9
Total	54	100.0

*others: Diclofenac, ketorolac, paracetamol, piroxicam

Table 3. History of allergies or allergic-like diseases apart drug adverse reactions

Clinical condition	Patients (%)	$n=67$
CIU* syndrome	32	(47.8)
CIU* + allergic rhinitis	3	(4.4)
CIU* + atopic dermatitis	2	(3)
CIU* +allergic rhinoconjunctivitis	2	(3)
CIU* + food allergy	1	(1.5)
Allergic rhinitis	12	(17.9)
Allergic rhinoconjunctivitis	4	(6)
Non allergic bronchial asthma	4	(6)
Atopic dermatitis	4	(6)
Non allergic perennial rhinitis	3	(4.4)
Skin test positivity	20	(29.9)

*CIU: chronic idiopatic urticaria/angiedema syndrome

Test dose

Out of the 137 patients, 134 (98%) tolerated benzydamine at the therapeutic dose well.

Three of the 137 peroral challenges with benzydamine (2%) were positive with generalized urticaria/angiedema.

In the first of the three cases, a 32-year-old woman belonging to Group A developed a reaction 30 min after the administration of the first dose of benzydamine. She had reportedly experienced episodes of urticaria/angiedema following the use of ASA and noramidopirine apart from nimesulide, and had a history of chronic urticaria.

The second reaction occurred in a 17-year-old man belonging to Group B 20 min after the assumption of the second dose of benzydamine. This subject had a history of facial angiedema following the administration of diclofenac.

The last reaction occurred in a 33-year-old man belonging to Group B with a history of urticaria caused by piroxicam. He developed urticaria/angiedema 25 min after ingestion of the second dose of benzydamine.

The three reactions disappeared completely within 2 hours after administration of clorfenamine (10 mg intravenously).

None of the patients suffered adverse reactions to the placebo challenge.

Thus, in this study it was necessary to stop the challenge in only three of the 137 total peroral challenges with benzydamine. This is a very low percentage and suggests a lack of cross reactivity of benzydamine with nimesulide. Moreover, all three patients had urticaria/angiedema and no one had subjective, functional, or objective bronchospasm signs, anaphylactic reactions or edema of glottis.

Discussion

NSAIDs are the most frequently consumed drugs world-wide. Adverse reactions to NSAIDs is a very important problem in clinical practice. Nimesulide is one of the most frequently prescribed NSAID, perhaps owing to its tolerability and efficacy. It is considered a tolerable NSAID and, along with acetaminophen, it seems to be responsible for the lowest number of adverse drug reactions among NSAIDs (12, 14). Nevertheless, in clinical practice, the number of patients who have adverse reactions to this drug is beginning to increase (13). Thus, finding of tolerable NSAID generally speaking is of great interest as well as a valid alternative to nimesulide because it is believed to be a tolerable NSAID.

The data reported here suggest that nimesulide is a tolerable NSAID. In fact 115 out of 137 patients (84%) had a positive history of urticaria to other NSAIDs apart from nimesulide, thus only 22 patients (16%) had an adverse reaction exclusively towards nimesulide. For this reason we can say that the patients in this study may be considered particularly reactive against NSAIDs.

Benzydamine is an NSAID with anti-inflammatory, antipyretic and anti edema activity. It is considered a weak inhibitor of PGHS 1–2 enzymes.

We have tested the hypotheses that benzydamine may be a tolerable NSAID and then it could be a valid alternative in NSAIDs-sensitive subjects, and, in particular, may represent a valid alternative in nimesulide-sensitive patients.

The results we have obtained are in favour of this hypotheses, in fact in this study population we have obtained only three (2%) positives out of 137 peroral challenges to benzydamine. This is a very low percentage, especially considering that the population of this study may be considered highly reactive against NSAIDs. These results clearly demonstrate that benzydamine is a tolerable NSAID and may represent a valid alternative in NSAIDs sensitive patients.

Moreover within the patients of group B (54 patients) who all had a positive peroral challenge with nimesulide only two (4%) had positive peroral challenge with benzydamine. This was probably the aim of this study because it suggests that benzydamine does not cross react with nimesulide.

As described by Stevenson and collegues, (21) the new

class of NSAIDs which selectively inhibits PGHS-2 enzyme, are better tolerated than other NSAIDs in aspirin-sensitive patients.

Our data allow us to conclude that benzydamine is a tolerable NSAID and together with other NSAIDs such as floctafenine (17) and meloxicam (18–19) whose tolerability has been demonstrated, it may be considered a valid alternative in patients with NSAIDs adverse reactions. Moreover, it may be considered a valid alternative in those patients highly reactive to NSAIDs and in those who react against nimesulide as well.

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