

Floctafenine: a valid alternative in patients with adverse reactions to nonsteroidal anti-inflammatory drugs

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Background: Choosing an alternative anti-inflammatory agent for a patient who has suffered adverse reactions to nonsteroidal anti-inflammatory drugs is a common problem in clinical practice, and it is complicated by the possibility of non-immunologic cross reactivity among the various members of this drug class.

Objective: We performed a retrospective study based on oral challenge results in 150 patients with histories of adverse reactions to one or more nonsteroidal anti-inflammatory drugs. The alternative drugs tested included floctafenine, an analgesic of the fenamic acid group, nimesulide, or paracetamol (acetaminophen).

Patients and Methods: One hundred fifty patients with histories of adverse reactions to nonsteroidal anti-inflammatory drugs received oral challenges with floctafenine; 101 were also challenged with nimesulide and paracetamol. The oral challenges were administered under single-blinded conditions. One-fourth of the therapeutic dose (floctafenine, 200 mg; nimesulide, 100 mg; and paracetamol, 500 mg) was administered initially; the remaining 3/4 was given one hour later if no symptoms had developed with the initial administration. In patients with histories of rhinitis and/or bronchial asthma unrelated to drug use and those whose adverse reactions had included bronchospastic or rhinitic symptoms, the FEV₁ was measured. The response to the challenge was considered positive if any of the following symptoms developed: erythema, pruritus accompanied by erythema, urticaria/angioedema, rhinorrhea, nasal obstruction, sneezing, dyspnea or cough associated with a decrease of at least 20% in the FEV₁, hypotension.

Results: Floctafenine challenges were positive in 13/150 patients (8.7%). Nimesulide and paracetamol provoked reactions in 9/101 patients (8.9%). All positive reactions occurred within 24 hours of the challenge. None of the patients reacted to more than one of the drugs tested.

Conclusions: Our findings confirm those of other investigators regarding the use of nimesulide and paracetamol in patients who do not tolerate aspirin or other nonsteroidal anti-inflammatory drugs, although the percentage of reactions to nimesulide observed in the present study is somewhat higher than that reported by some other groups. The study also indicates that floctafenine, a relatively weak cyclooxygenase inhibitor, can be a valid alternative for many patients who react adversely to other nonsteroidal anti-inflammatory drugs.

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs have been known to provoke or exacer-

berate bronchial asthma, rhinitis and urticaria/angioedema and, in a few cases, they have triggered anaphylactic reactions.¹⁻³ The pathogenesis of intolerance of these drugs is often unclear, and convincing evidence of the involvement of allergic mechanisms is available only for a few of the cases reported in the literature. Immunologically mediated reactions have been re-

ported following the use of pyrazolone derivatives^{2,4} and, less commonly aspirin,^{5,6} anthranilic-acid derivatives,⁷ and diclofenac.⁸

Choosing an alternative anti-inflammatory agent for a patient who has suffered an adverse reaction to a nonsteroidal anti-inflammatory agent is a common problem in clinical practice, and it is complicated by the possibility of nonimmunologic cross reactivity among the various members of this drug class.^{1,9-13} In selected cases, aspirin-desensitization (based on the existence of a refractory period following positive reactions to aspirin challenges) can be used to render patients unresponsive to the adverse effects of this drug and other nonsteroidal anti-inflammatory drugs as well.¹⁴

The most common approach, however, is to prescribe a drug whose molecular structure is different from that of the product associated with the adverse reaction, after its tolerability has been verified with an oral provocation test. The alternative drug most commonly proposed several years ago was paracetamol (known in the United States as acetaminophen)^{2,9,15,16} but more recent reports have focused on the safety of nimesulide.¹⁷⁻²⁰ Nevertheless, adverse reactions have been reported to these drugs as well^{17,19-26} and the search for a well tolerated nonsteroidal anti-inflammatory agent thus continues.

The present paper describes the results of a retrospective analysis of oral challenge results in 150 patients with histories of adverse reactions to one or more nonsteroidal anti-inflammatory drugs. The drugs tested included floctafenine, an analgesic of the fe-

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namic acid group, nimesulide, and paracetamol.

PATIENTS AND METHODS

Over the last three years, 150 patients (42 males, 108 females aged 13 to 83 years; mean age 34.8 years) were seen in our department for adverse reactions to nonsteroidal anti-inflammatory drugs. All had experienced one or more episodes characterized by cutaneous and/or respiratory symptoms following the use of one of these agents. In 58% of the cases, the reactive episode had occurred 1 to 2 years prior to our study; 24% had experienced reactions 6 months to 1 year before the study, and in the remaining 18% 2 to 6 months had elapsed since the last reaction. On the basis of history alone, these patients were divided into two subgroups: those who had experienced reactions to only one nonsteroidal anti-inflammatory agent or to more than one member of a single class of these drugs (single-intolerance group (SI): 76 patients) and those who had reacted to two or more agents belonging to different classes (multiple intolerance group (MI): 74 patients). The patients of the former subgroup had all used nonsteroidal anti-inflammatory agents other than those associated with reactions and had not suffered any disturbances whatsoever. Oral challenges were not performed with the drugs reported as causes of previous reactions.

To identify alternative drugs that might be better tolerated, all 150 patients were subjected to oral challenges with floctafenine (2,3 dihydroxypropyl N-[8-trifluoromethyl 4 quinolyl] anthranilate) (Idarac - Roussel Pharma, Milan, Italy); 101 were also tested with nimesulide (Aulin - Boehringer Mannheim, Milan, Italy) and paracetamol (Tachipirina - Angelini, Ancona, Italy). At the time of testing, at least 8 weeks had passed since the last adverse reaction (1 to 2 years in 58% of the cases, 6 months to 1 year in 24%, and 2 to 6 months in 18%). None of the patients had clinically relevant respiratory tract symptoms, and pulmonary function tests showed stable FEV_{1,s} >

80% of predicted values in all cases. Antihistamines had been discontinued seven days or more before challenges (8 weeks in the case of astemizole) and no drugs of any type were taken during the 48 hours prior to testing. Informed consent was obtained from each patient.

The oral challenges were administered during the morning after an overnight fast. Under single-blinded conditions, 1/4 of the therapeutic dose (floctafenine, 200 mg; nimesulide, 100 mg; paracetamol, 500 mg) was initially administered; the remaining 3/4 of the dose was given one hour later if no symptoms had developed with the initial administration. In a preliminary session, each patient had received a placebo (lactose) challenge administered in the same manner. In patients tested with all three drugs, an interval of at least three days elapsed between challenges; in view of the refractory period that generally follows positive reactions,¹⁴ patients who reacted positively were not rechallenged until 1 week had passed. Emergency resuscitation equipment was available during all challenges. The patients remained for a day in the hospital under medical supervision for six hours after each challenge and were seen in the outpatient department the next day to determine whether any reactions had occurred after discharge. Any symptoms that occurred after the outpatient interview were to be reported to our staff by telephone. In patients with histories of rhinitis and/or bronchial asthma unrelated to drug use and those whose adverse reactions had included bronchospastic or rhinitic symptoms, the FEV₁ was measured with computerized spirometry (Pony Spirometer, Cosmed, Roma, Italy) before the challenge, at 30-minute intervals during the first two hours after administration of the drug and every hour thereafter up to the sixth postchallenge hour. The response to the challenge was considered positive if any of the following symptoms developed: erythema, pruritus accompanied by erythema, urticaria/angioedema, rhinorrhea, nasal obstruction, sneezing, dyspnea or cough associated

with a decrease of at least 20% in the FEV₁, hypotension.

Differences between the percentages of positive reactions observed in the two subgroups were assessed with the chi-square test.

RESULTS

Of the 150 adults with histories of adverse reactions to nonsteroidal anti-inflammatory agents considered here, 83 (55.3%) had histories of allergies or allergy-like diseases. Thirty-two (38.5%) suffered from chronic idiopathic urticaria/angioedema syndromes (with negative findings in routine tests used to evaluate these symptoms). Thirty-six (24%) had histories of chronic respiratory symptoms. Rhinitis was reported by 23 of these 36 patients, including 14 with skin-test positivity for one or more common airborne allergens (Dermatophagoides in eight cases, Parietaria in three, grass, and olive pollen in one) and 9 subjects with negative allergologic findings. Two of the latter had previously undergone nasal polypectomies and ear, nose, and throat examinations had been negative in the remaining seven. Six others reported bronchial asthma associated with negative allergologic findings. The remaining seven had histories of both rhinitis and bronchial asthma. Of these, two presented negative findings in allergologic tests and the remaining five were skin-test positive for Dermatophagoides (three cases), grass pollens (one case), or Parietaria (one case). None of the patients presented nasal polyps at the time of our study and none had histories of sinusitis. According to the GINA classification,²⁷ all of the patients with histories of asthma were considered to have mild, intermittent disease that was controlled with PRN drug therapy.

Based on history data, 76 (50.7%) of the patients were classified as SI and 74 (49.3%) were considered to have MI. Of the 101 patients that were challenged with nimesulide and paracetamol, as well as with floctafenine, 64.3% were from the SI group and 35.7% had MI.

Table 1 shows the drugs reported by the patients as causes of their adverse reactions. The most commonly implicated drugs were acetylsalicylic acid and pyrazolone derivatives, followed by (in decreasing order of frequency) paracetamol, propionic acid derivatives (naproxen, ketoprofen, and ibuprofen), diclofenac, indomethacin, and piroxicam. Regarding the adverse reactions themselves, 60% of the patients (44 SIs and 46 MIs) reported exclusively cutaneous symptoms (urticaria and/or angioedema, erythema), 32.7% (20 SIs and 29 MIs) had experienced both cutaneous and respiratory symptoms, and the remaining 7.3% (3 SIs and 8 MIs) reported only respiratory symptoms (rhinitis and/or asthma).

None of the patients reacted to the placebo challenge. Positive responses to the floctafenine challenge were observed in 13/150 patients (8.7%), the vast majority of whom had been classified as having MI (MI versus SI: $P < .05$) (Table 2). Nimesulide challenges were positive in 9/101 cases (8.9%) (Table 3); a similar percentage of positive responses was seen with the paracetamol challenge (Table 4). In these latter two cases, the percentage of positive responses observed in the MI group was higher than that seen

Table 2. Positive Reactions to Oral Challenges with Floctafenine in Patients with Histories of Intolerance to Single (SI group) and Multiple (MI group) Nonsteroidal Anti-inflammatory Drugs

Group*	No. Challenged	Negative	Positive	%
SI	76	73	3	3.9
MI	74	64	10	13.5

* SI versus MI: Chi-square test $P < .05$.

Table 3. Positive Reactions to Oral Challenges with Nimesulide in Patients with Histories of Intolerance to Single (SI group) and Multiple (MI group) Nonsteroidal Anti-inflammatory Drugs

Group*	No. Challenged	Negative	Positive	%
SI	55	52	3	5.4
MI	46	40	6	13.0

* SI versus MI: Chi-square test, ns.

among the SI patients, but not significantly so. None of the 101 patients tested with all three drugs reacted to more than one of the challenges.

All of the positive reactions occurred within 24 hours after administration of the second dose. Twelve of the 13 patients that reacted to floctafenine experienced only cutaneous

Table 4. Positive Reactions to Oral Challenges with Acetaminophen in Patients with Histories of Intolerance to Single (SI group) and Multiple (MI group) Nonsteroidal Anti-inflammatory Drugs

Group*	No. Challenged	Negative	Positive	%
SI	55	51	4	7.2
MI	46	41	5	10.8

* SI versus MI: Chi-square test, ns.

symptoms: six presented diffuse erythema, five developed urticaria, and one experienced angioedema of the lips. Six of these 12 had histories of idiopathic urticaria. The 13th patient (who had a history of allergic rhinitis and bronchial asthma) reacted to the floctafenine challenge with rhinorrhea, nasal obstruction, and sneezing. Of the nine patients who reacted to nimesulide challenge, four experienced erythema, four urticaria, and one became mildly hypotensive (blood pressure dropping from 140/85 to 95/65 mmHg). Five of these nine patients had histories of idiopathic urticaria. All nine of the reactions to paracetamol were manifested by cutaneous symptoms (erythema in six cases, urticaria in two, and angioedema in one). Four of these nine patients had histories of idiopathic urticaria. All symptoms resolved within a few hours after administration of terfenadine or loratadine. The patient who became hypotensive following the floctafenine challenge required no drug therapy or fluid replacement; the blood pressure promptly returned to baseline level after the patient was placed in the supine position.

DISCUSSION

In the present study, 150 patients with histories of adverse reactions to one or more nonsteroidal anti-inflammatory drugs were subjected to oral challenges to identify alternative agents that should be better tolerated. The approach used is one that we have found

Table 1. Nonsteroidal Anti-inflammatory Drugs Reported as Causes of Adverse Reactions by 150 Patients

Drug	No. of Patients	Percentage of total
SI group* (76 pts)		
Pyrazolone derivatives	36	24
ASA	31	20.7
Paracetamol	4	2.7
Propionic acid derivatives	3	2
Others	2	1.3
MI group† (74 pts)		
Pyrazolone derivatives + ASA	20	13.3
Pyrazolone derivatives + others	13	8.7
Pyrazolone derivatives + ASA + paracetamol	11	7.3
ASA + others	11	7.3
Pyrazolone derivatives + Paracetamol	8	5.3
Pyrazolone derivatives + ASA + others	7	4.7
Paracetamol + others	4	2.7
Total	150	100

* Single-intolerance group.

† Multiple-intolerance group.

to be rapid and reliable for routine use in a clinical setting. The patients considered in this study, however, were classified as SI or MI on the basis of histories alone, and the drugs that had reportedly been associated with adverse events were not tested. This omission may have led to the inclusion of a certain number of false positives among the population we studied. It is also important to recall that oral challenges with these drugs, and aspirin in particular, can be hazardous, especially in patients with histories of asthma or anaphylaxis.²⁸ These challenges must be performed by trained physicians with easy access to equipment and personnel for intubation and other emergency treatment, should the patient fail to respond to standard therapeutic measures. Our decision to defer challenge confirmation of the patients' reports was thus designed to limit patient risk and discomfort, although the question of time also had its influence. A recent study of patients who had experienced adverse reactions to nonsteroidal anti-inflammatory drugs has, however, shown significant correlation between history data and the results of oral challenges in patients reporting aspirin intolerance and, to a lesser extent, in those who claimed to have reacted to pyrazolone drugs.¹⁹ In clinical practice, a patient's report of intolerance to a given nonsteroidal anti-inflammatory drug is, thus, generally considered to be a valid contraindication to use of the drug for both therapeutic and diagnostic purposes.

Our findings confirm those of other investigators regarding the use of nimesulide and paracetamol in patients who do not tolerate aspirin or other nonsteroidal anti-inflammatory agents^{2,16,17,19,20} although the percentage of reactions to nimesulide observed in the present study is somewhat higher than that reported by some other groups.^{17,19,20} The low incidence of adverse reactions to these drugs is probably due to the limited degree of cyclo-oxygenase inhibition they exert.^{1,11,29-35} Our findings indicate that the tolerability of floctafenine, which is also a relatively weak cyclooxygenase inhibitor, is similar to that of the above two

drugs. At doses of 200 mg, floctafenine has been found to be equipotent to 50 mg pentazocine,³⁶ 30 mg dihydrocodeine,³⁷ 200 mg ibuprofen³⁸ and more effective than 130 mg dextropropoxyphene³⁹ in relieving mild to moderate pain. Based on subjective and objective evaluation of its effects in osteoarthritic patients, the analgesic effects of floctafenine (1.2 g/day) have proved to be equivalent to or greater than that of enteric-coated aspirin (2.6 mg/day).⁴⁰ These findings indicate that floctafenine may prove to be a safe and effective alternative for many patients who react adversely to other nonsteroidal anti-inflammatory drugs.

Positive reactions to the oral challenges were, on the whole, less common in those patients classified as SI. This finding may reflect a difference in the mechanisms involved in multiple and single forms of intolerance. Previous reports indicate that reactions to a single nonsteroidal anti-inflammatory drug, particularly those provoked by a pyrazolone drug, are more commonly caused by immune mechanisms.⁴ In these cases, the patient will probably be able to tolerate a number of other drugs in this class, including aspirin.² In contrast, cases of adverse reactions to multiple nonsteroidal anti-inflammatory drugs are more likely to reflect intolerance to cyclo-oxygenase blockade in general. Weaker, prostaglandin inhibitors, such as the drugs considered here, may be better tolerated by these patients. The percentages of positive challenges observed in the two patient groups were significantly different only in the case of floctafenine, suggesting that this drug is more useful in patients with SI than those that have reacted to more than one nonsteroidal anti-inflammatory drug.

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