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Oral Challenge with Alternative Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Paracetamol in Patients Intolerant to these Agents

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Summary

The reliability and safety of the oral challenge procedure were evaluated in the diagnosis and prevention of intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs). 112 NSAID-intolerant patients were submitted to oral challenge with aspirin (acetylsalicylic acid), dipyron, paracetamol, imidazole-hydroxybenzoate or nimesulide to confirm historic intolerance and to evaluate tolerance to other NSAIDs. A significant correlation was demonstrated between history of intolerance and the results of oral challenge in aspirin-intolerant patients ($p < 0.001$). Of 237 challenges with various NSAIDs and paracetamol in 101 patients, 19 challenges were positive and 2 patients developed anaphylactic shock. The ratio of positive : total challenges with alternative NSAIDs and paracetamol were as follows: 7 of 83 for paracetamol, 2 of 49 for imidazole-hydroxybenzoate and 0 of 30 for nimesulide. On the basis of these results, nimesulide was evaluated as an alternative NSAID in a second group of 284 NSAID-intolerant patients. Challenge with nimesulide elicited a positive response in 14 patients (in 6 patients the response was delayed), although adverse reactions were mild in all instances. In conclusion, a positive history of intolerance to a given NSAID is a sufficient reason to contraindicate its use even for diagnostic purposes, e.g. oral challenge. Oral challenge should therefore be restricted to the assessment of the tolerability of alternative NSAIDs. In the present study nimesulide appeared to be the safest currently available alternative in patients with NSAID intolerance.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may provoke or exacerbate bronchial asthma, rhinitis and urticaria/angioedema. Although these conditions are often clinical manifestations of atopy, the pathogenesis of NSAID intolerance is not clear and there are no convincing data to support an allergic involvement. Against this background, we evaluated the reliability and safety of oral challenge in the diagnosis and prevention of intolerance to NSAIDs.

1. Patients and Methods

A total of 112 adult patients (39 male and 73 female) aged 14 to 74 (mean 35) years with a history of NSAID and paracetamol intolerance were recruited for this study after giving written informed consent. Intolerance was manifested by the presence of urticaria-angioedema ($n = 92$), syncope ($n = 7$), asthma ($n = 6$), rhinitis ($n = 3$), anaphylactic shock ($n = 3$) or cutaneous pruritus ($n = 1$).

		OC	
		+	-
H	+	2	3
	-	0	14
		*	

Fig. 2. Correlation between a clinical history of intolerance to pyrazolone derivatives and dipyrone oral challenge in 101 NSAID-intolerant patients. H = history; OC = oral challenge; * $p = 0.057$.

tive history of intolerance to other NSAIDs tested with oral challenge does not permit significant correlation to be reached.

The results of 237 oral challenges with various NSAIDs and paracetamol in 101 patients are summarised in table II. A total of 19 challenges were positive. Two patients developed anaphylactic shock, 1 after dipyrone 25mg and the other after paracetamol 15mg. Another patient had a severe reaction (laryngeal oedema) to paracetamol challenge. Challenge with paracetamol, imidazole-hydroxybenzoate or nimesulide was performed in patients who either demonstrated a reaction to other NSAIDs during the test or had a history of intolerance to other NSAIDs to evaluate the tolerability of each of these drugs in order to identify an alternative treatment. Seven reactions to paracetamol, 2 reactions to imidazole-hydroxybenzoate and none to nimesulide were observed. Aspirin 100mg initiated a reaction in 7 of 8 patients and the remaining patient reacted to aspirin 900mg. Mean provocative doses were as follows: 100mg (range 15 to 350mg) for paracetamol, 23mg (range 6 to 40mg) for dipyrone, and 180mg (range 40 to 320mg) for imidazole-hydroxybenzoate.

On the basis of the above results a second group of 284 patients (91 male, 193 female; mean age 41 years) with a history of intolerance to NSAIDs and paracetamol were enrolled. Intolerance was attributable to aspirin ($n = 90$), pyrazolone derivatives ($n = 78$), diclofenac ($n = 22$), propionic acid derivatives ($n = 18$), paracetamol ($n = 4$), aspirin plus pyrazolone derivatives ($n = 22$), aspirin plus para-

cetamol ($n = 6$), aspirin plus pyrazolone derivatives plus paracetamol ($n = 4$), aspirin plus pyrazolone derivatives plus others ($n = 13$), aspirin plus others ($n = 10$), pyrazolone derivatives plus paracetamol ($n = 9$), pyrazolone derivatives plus others ($n = 6$) and diclofenac plus others ($n = 2$). Intolerance was manifested clinically as urticaria/angioedema ($n = 253$), syncope ($n = 12$), asthma ($n = 8$), rhinitis ($n = 6$), anaphylactic shock ($n = 3$) or cutaneous pruritus ($n = 2$). All patients were challenged with nimesulide to assess the tolerability of this alternative NSAID.

Of the 284 patients tested, 14 (4.9%) demonstrated a positive response to challenge with nimesulide. Skin reactions occurred in 13 patients (all with a history of cutaneous adverse reactions to NSAIDs) and mild rhinitis was observed in 1 patient. Adverse reactions were mild in all instances and only 1 patient with urticaria-angioedema required therapy with an oral antihistamine (loratadine 10mg). Six of these 14 patients had a delayed reaction, i.e. a reaction occurring more than 2 hours after the last administered dose. Symptoms resolved in all patients within 12 hours of their occurrence. The provocative nimesulide dose was 100mg in 12 patients and 30 and 5mg in the remaining 2 patients. An oral challenge with an alternative NSAID or paracetamol was performed in 10 patients who showed a positive reaction to nimesulide. Of the 8 patients challenged with paracetamol, only 1 had a positive response; 2 patients were challenged with either etodolac or glafenine and showed no response.

Table II. Results of oral challenge with various NSAIDs

Drug	Total no. of challenges	Total no. of positive challenges
Aspirin	56	8
Dipyrone	19	2
Paracetamol	83	7
Imidazole-hydroxybenzoate	49	2
Nimesulide	30	0
Total	237	19

At present, oral challenge appears to be the most reliable procedure for the diagnosis of NSAID intolerance. However, such a challenge performed with the suspected drug involves a high risk of provoking a life-threatening reaction. Therefore, a positive history of intolerance to a given NSAID appears to be a sufficient reason for contraindication, either clinically or in an oral challenge test. Accordingly, we recommend the use of oral challenge tests in clinical practice only to evaluate the tolerability of alternative drugs. Paracetamol has often been considered a safe alternative drug in almost all patients with a positive history of NSAID intolerance, especially those intolerant to aspirin (Samter & Beers 1968; Spector et al. 1979; Stevenson 1985; Szczeklik 1987). This drug may be safe in asthmatic patients, since it has few inhibitory effects on cyclo-oxygenase (Szczeklik et al. 1977; Stevenson 1984; Stevenson & Simon 1988). Despite these observations, the present study did not confirm paracetamol to be a safe alternative in patients intolerant to NSAIDs. This may be explained by the clinical characteristics of the patients recruited, who were mainly affected with urticaria/angioedema. In conclusion, the results obtained in

our patient population suggest that nimesulide is a sufficiently safe alternative drug in patients with a history of intolerance to other NSAIDs.

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Renal Effect Subjects

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Summary

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Glomerular filtration plasma flow (RPF) depends on a complex interplay between vasoconstrictor and vasodilator influences. In euovolemia, the contribution of intrarenal prostaglandins to the resting tone of renal resistance is minimal. In contrast, when renal resistance is increased, both PGs and thromboxane become major determinants of GFR. Suppression of prostaglandin synthesis under these circumstances results in a haemodynamically mediated decrease in GFR. The result of the unopposed effect of the renin-angiotensin systems