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CLINICAL REPORT

Intolerance Reactions due to the Selective Cyclooxygenase Type II Inhibitors Rofecoxib and Celecoxib

Results of Oral Provocation Tests in Patients with NSAID Hypersensitivity

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Intolerance reactions due to the ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) are frequent emergencies. It is thought that inhibition of the isoenzyme cyclooxygenase type I (COX-1) is responsible for the common NSAID-associated adverse effects, whereas inhibition of COX-2 is mainly responsible for the therapeutic effects. The goal of our study was to estimate the frequency of intolerance reactions due to ingestion of the two newly approved selective COX-2 inhibitors, rofecoxib or celecoxib. In a sample of 13 patients who had previously documented NSAID hypersensitivity reactions to non-selective COX inhibitors, 2 patients (15.3%) showed intolerance reactions (2 of 9 patients with rofecoxib, 1 of 5 patients with celecoxib). These drugs cannot therefore be administered uncritically to patients with known NSAID hypersensitivity. Selective COX-2 inhibitors can only be used as alternative drugs in these patients after assessing their specific tolerability in a properly performed provocation test. ***Key words: drug intolerance; non-steroidal anti-inflammatory drugs (NSAIDs); skin reaction.***

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Intolerance reactions due to the ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) are frequent emergencies. These reactions may comprise erythema, urticaria, angioedema, rhinitis, conjunctivitis, dyspnea, tachycardia, hypotension or shock, and the inhibition of cyclooxygenase (COX) as the central enzyme in the synthesis of prostaglandins may be essential for these reactions. Alternative drugs for the treatment of pain and inflammation are needed in affected patients. It is thought that the inhibition of cyclooxygenase type II (COX-2) is responsible for the therapeutic (analgesic and anti-inflammatory) effects, whereas the inhibition of COX-1 is responsible for the common NSAID-associated adverse effects (including the upper GI tract). Most of the currently used NSAIDs are non-selective inhibitors of both COX-1 and COX-2. Rofecoxib and celecoxib are newly approved selective COX-2 inhibitors.

Several recent studies examining the effect of oral challenge with selective COX-2 inhibitors in patients with or without the history of hypersensitivity reactions against NSAID led to conflicting results. Some studies showed a complete absence of intolerance reactions (1–4), whereas in others positive reactions in a variable proportion of the challenged patients were observed (5, 6). In addition, further case reports present anaphylactoid reactions in single patients after the intake of selective COX-2 inhibitors (7–9).

Our study aimed to estimate the frequency of intolerance reactions due to the controlled ingestion of the two selective COX-2 inhibitors rofecoxib and celecoxib in an independent sample of 13 patients who had a previously documented NSAID hypersensitivity to non-selective cyclooxygenase inhibitors.

PATIENTS AND METHODS

The relevant histories of intolerance reactions of the 13 patients are given in detail in Table I. All patients had a documented intolerance reaction to non-selective NSAID (e.g. aspirin, diclofenac, ibuprofen). Every patient gave informed consent to the oral challenge test, a routine diagnostic tool in allergology. No patient had taken antihistamines at least in the 10 days prior to testing. Because of a sulfonamide moiety of celecoxib, a previous allergic reaction to sulfonamides was a contraindication for this drug. Nine of the 13 patients received the standardized escalating oral doses of rofecoxib (Vioxx®) up to a cumulative oral dose of 25 mg, and 5 patients received celecoxib (Celebrex®) up to a cumulative oral dose of 200 mg. (In 1 of the 13 patients, both rofecoxib and celecoxib was given.) During the challenge procedure, and for 24 h after the last oral dose, all patients were monitored for blood pressure, pulse rate and the appearance of skin signs. Unequivocal erythema, rhinitis, conjunctivitis, urticaria, angioedema, dyspnea, tachycardia, hypotension or shock were considered as positive reactions to the oral challenge test.

RESULTS

Thirteen patients were challenged with a selective COX-2 inhibitor (for details see Table I). Six of these patients were challenged before with a non-selective COX inhibitor (ibuprofen or naproxen). In 2 of 9 patients

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Table I. *Oral provocation tests with selective COX-2 inhibitors in 13 patients with non-steroidal anti-inflammatory drug hypersensitivity*

Patient	Hypersensitive to:	Symptoms (history)	1st challenge Drug	Outcome	2nd challenge Drug	Outcome	3rd challenge Drug	Outcome
1	Ibuprofen	Generalized pruritus, dyspnea, tachycardia	Rofecoxib	No reaction				
2	ASA	Angioedema with dyspnea	Ibuprofen	Angioedema with dyspnea after a few hours	Rofecoxib	No reaction		
3	Pyrazolon, Phenopropazon	Generalized erythema and pruritus as well as dyspnea	Rofecoxib	No reaction				
4	Piroxicam, Diclofenac	Anaphylactic shock (with cardiac arrest)	Celecoxib	No reaction				
5	Diclofenac, Ibuprofen	Urticaria	Celecoxib	No reaction				
6	ASA	Urticaria, oedema of the tongue, tachycardia, hypotension, tinnitus, visual disorder	Rofecoxib	No reaction				
7	Diclofenac	Circulatory disorder and hypotension	Ibuprofen	Enoral paraesthesia, globus sensation, dizziness shortly after a cumulative dose of 175 mg	Rofecoxib	Enoral paraesthesia globus sensation, dizziness shortly after a cumulative dose of 12 mg		
8	ASA, Ibuprofen	Generalized "rash"	Rofecoxib	No reaction				
9	Diclofenac	Dyspnea	Ibuprofen	Dyspnea shortly after a dose of 25 mg	Celecoxib	No reaction		
10	Diclofenac	Generalized "rash"	Naproxen	Facial erythema, globus sensation, sensation of restlessness, nausea after intake of low doses	Rofecoxib	Facial erythema, globus sensation, sensation of restlessness, nausea after intake of low doses	Celecoxib	Facial erythema, globus sensation, sensation of restlessness, nausea after intake of low doses
11	ASA	Generalized "rash", angioedema and dyspnea	Ibuprofen	Generalized urticaria	Rofecoxib	No reaction		
12	Ibuprofen	Rash including swelling of fingers	Rofecoxib	No reaction				
13	ASA	Exacerbation of chronic-relapsing urticaria	Ibuprofen	Urticaria after a few hours	Celecoxib	No reaction		

ASA: acetylsalicylic acid, aspirin

an intolerance reaction after rofecoxib was observed. Interestingly, 1 of these 2 patients showed in addition an intolerance reaction to celecoxib. Furthermore, both of these patients had a previously diagnosed intolerance to non-selective COX inhibitors (patients 7 and 10).

DISCUSSION

In our study group, after challenge with rofecoxib or celecoxib 2 (15.3%) of 13 patients showed an intolerance reaction; one of the two patients showed an intolerance reaction to both rofecoxib and celecoxib (2 of 9 and accordingly 22.2% with rofecoxib, 1 of 5 and accordingly 20% with celecoxib). Our results are compatible with the results of Asero (5), who detected an intolerance reaction to rofecoxib in 17% of NSAID-sensitive patients. Sanchez-Borges et al. (6) documented an intolerance reaction in 3% of patients challenged with rofecoxib and in 33% of patients tested with celecoxib. In contrast, Berges-Gimeno et al. (1) and Zollner et al. (4) did not observe any intolerance reaction in 33 patients and in 37 unselected patients (including 3 patients with aspirin-sensitive asthma), respectively. The pathophysiology of the aspirin-sensitive asthma group of intolerance patients is different from other NSAID intolerance patients. This may be the reason why studies with solely aspirin-sensitive asthma patients consistently did not show any intolerance reaction to COX-2 inhibitors (2, 3, 10).

In agreement with the recent literature, our study demonstrates that the selective COX-2 inhibitors, rofecoxib or celecoxib, may be useful in the anti-inflammatory treatment of patients with a history of NSAID intolerance. In addition, our study indicates that there may be two further groups of patients with NSAID intolerance: one with intolerance to all COX inhibitors and a second with intolerance only to COX-1 inhibitors.

It has to be emphasized that not every NSAID-intolerant patient tolerates COX-2 inhibitors. These drugs cannot therefore be administered uncritically to patients with NSAID intolerance. Selective COX-2 inhibitors can only be used as alternative drugs in these patients (as well as in patients with aspirin-sensitive asthma) after assessing their specific tolerability in a properly performed provocation test.

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