Peer reviewed article

Tolerance to celecoxib in patients with a history of adverse reactions to nonsteroidal anti-inflammatory drugs

Antonie Roll, Brunello Wüthrich, Peter Schmid-Grendelmeier, Günther Hofbauer, Barbara K. Ballmer-Weber

Allergy Unit, Department of Dermatology, University Hospital, Zurich, Switzerland

Summary

Background: Adverse reactions to nonsteroidal antiinflammatory drugs (NSAIDs) are frequently reported, particularly among asthmatic patients. To date, there is no causal treatment available apart from tolerance induction. Therefore, the search for safe alternative drugs is of pivotal importance in clinical practice.

Objective: The aim of our prospective study was to investigate the tolerance to celecoxib, a selective cyclooxygenase-2 inhibitor, in a large group of patients with positive case history of NSAID intolerance in comparison to paracetamol and nimesulide.

Methods: 106 NSAID-sensitive patients, 46 (43.4%) of whom had experienced reactions only to one NSAID (single hypersensitivity), 60 (56.6%) to several NSAIDs (multiple hypersensitivity), were included in a single-blinded drug challenge protocol with cumulative doses of 175 mg of celecoxib, 875 mg of paracetamol and 175 mg of nimesulide. Objective and subjective symptoms during challenge were documented.

Results: Of 261 challenges in 106 patients, 31 challenges were positive: 5 of 106 (4.7%) for celecoxib, 10 of 64 (15.6%) for paracetamol and 16 of 91 for nimesulide (17.6%). Adverse reactions to celecoxib were mainly mild in character: three patients reported subjective symptoms including generalised pruritus and thoracic oppression, whereas two patients reacted with angio-oedema.

Conclusions: Our results demonstrate that celecoxib is well tolerated by the majority of patients with NSAID intolerance. However, since adverse reactions to celecoxib cannot be ruled out completely, a controlled oral challenge test is still mandatory for proper management of patients with NSAID intolerance.

Key words: Celecoxib; nonsteroidal anti-inflammatory drugs (NSAIDs); hypersensitivity; tolerance; intolerance; oral challenge

Introduction

NSAIDs are widely described drugs for treatment of pain, fever, arthritis or other inflammatory diseases because of their high safety profile [1]. Since more than ten years COX-2 selective NSAIDs, ie celecoxib, are preferably used for these indications, especially because of fewer gastrointestinal adverse events [2]. The use of NSAIDs may be accompanied by intolerance reactions of the skin (urticaria, angio-oedema, pruritus, flush), respiratory symptoms (dyspnoea, rhinitis) or eventually even by anaphylactic-like reactions [3, 4]. Manifestations usually occur within 3 hours after drug intake [5]. NSAID intolerance is one of the most common causes of adverse drug reactions (ADRs) accounting for 44.7% of all reported ADRs, only surpassed by ADRs induced by antimicrobials [6, 7]. While the prevalence of adverse reactions to NSAIDs is about 0.3–0.9% in the normal population it mounts to 23–28% in patients with asthma and chronic urticaria [8–13].

Due to cross-intolerance between different NSAIDs, many patients report a history of reactions to various drugs of this class and thus alternative drug treatment of these patients can be challenging.

Financial support provided by Pfizer AG, CH-8048 Zürich

Abbreviations

ASA	= acetylsalicylic acid
ADR(s)	= adverse drug reaction(s)
COX	= cyclooxygenase
coxibs	= cyclooxygenase inhibitors
n.s.	= non significant
NSAID(s)	= nonsteroidal anti-inflammatory drug(s)
FEV_1	= peak expiratory flow

To date, the pathogenesis of NSAID intolerance is still unclear. NSAIDs exert their anti-inflammatory effects by blockage of cyclooxygenase (COX). So far, two isoforms of COX have been described (COX-1 and COX-2), which are expressed by various tissues. COX-1 is constitutively expressed in most tissues, including endothelial cells, platelets and the gastric mucosa; in contrast, COX-2 represents the inducible isoform, which is mainly expressed in response to pathologic stimuli (eg TNF-α) leading to the production of several inflammatory cytokines such as PGE_2 [14, 15]. COX-2 specific inhibitors exert their effect without interfering with the homeostatic functions mediated by COX-1-derived prostanoids resulting in better tolerance. Adverse reactions to NSAIDs are thought to be dependent on their inhibitory effect on COX. Most studies were performed in patients suffering from aspirin intolerant asthma [16, 17]. In these patients NSAIDs may trigger adverse reactions via COX-1 inhibition by reducing prostaglandin E_2-dependent suppression of leukotrienes, which are potent bronchocontrictors. In addition, there is a profound overrepresentation in bronchial biopsies of patients with ASA intolerance of cells expressing LTC_4 synthase which is associated with increased bronchial responsiveness to inhaled aspirin [18]. It is suggested that genetic polymorphisms lead to overexpression of LTC_4 synthase in the bronchial wall of aspirin intolerant patients and, thereby, cause chronic overproduction of cys-Leukotrienes, which is exacerbated when non-selective NSAIDs suppress the endogenous PGE "brake" generated by COX-1 activity. In NSAID-induced cutaneous reactions such as acute urticaria and angio-oedema a similar pathway is hypothesised, but a direct stimulation of histamine by NSAIDs is assumed too [19].

Since coxibs like celecoxib do not inhibit COX-1 mediated prostaglandin synthesis it was suggested that they might be better tolerated by this group of patients [17].

Since there is no reliable *in vitro* test, which identifies NSAID-sensitive patients with high sensitivity, clinicians have to rely on oral challenges with alternative NSAIDs.

The purpose of this study was to determine the tolerance of celecoxib (Celebrex®), a diaryl substituted pyrazole, in patients with a history of NSAID-intolerance and to compare it with the tolerability of paracetamol (Paracetamol®), an acetaminophen, and nimesulide (Aulin®), belonging to the sulfonamide family. Both, paracetamol and nimesulide are to date the most frequently used alternative drugs in patients with NSAID-intolerance.

Materials and methods

Patients

A total of 106 patients (33 men, 73 women), aged 13 to 76 years (mean age: 41.7 ± 11.7 years) with a well-documented history of NSAID intolerance were included after giving informed consent to the protocol approved by the ethical committee of the University of Zurich. Exclusion criteria were pregnancy, breast feeding, chronic renal failure and other kidney diseases, liver diseases, FEV_1 <70%, infectious diseases, intolerance to sulfonamide, celecoxib, paracetamol, nimesulide, drug intake of lithium, warfarine, fluconazole, ketotifen (within the last 14 days), corticosteroids (within the last 14 days) and antihistamines (within the last 3 days; astemizole: 6 weeks).

Skin tests

Skin tests were performed by scratch method with propyphenazone, acetylicsalicylic acid, paracetamol, chinine, phenobarbital, novaminsulfone, diclofenac, mefenamic acid, nimesulide, celecoxib and the NSAIDs responsible for the reported reaction in each patient. Drugs were pulverised and redissolved with PBS (phosphate-buffered saline). In addition, a positive skin prick test with histamine (10 mg/ml) and a negative control scratch test with PBS were performed.

Oral challenge tests

Oral provocation tests were carried out in a single-blinded fashion at the Allergy Unit of the University Hospital of Zurich. Before and during the challenge procedure, cardiovascular parameters, nasoocular, pulmonary, and cutaneous symptoms were monitored in all patients. In patients with a history of bronchial asthma or respiratory symptoms after NSAID-intake, a pulmonary function test was performed before each provocation step. The following drug doses were applied: paracetamol 125, 250 and 500 mg on test day one, nimesulide 25, 50 and 100 mg on test day two and celecoxib 25, 50 and 100 mg on test day three. Between oral challenges with the three different drugs an interval of at least one day, usually two to seven days, was kept. Tablets were administered orally with an interval of one hour. After the challenge test, patients remained under medical supervision for up to 120 minutes. When objective symptoms (flush, urticaria, angio-oedema, rhinitis, conjunctivitis, dyspnoea or cough associated with fall of FEV_1 >20%, hypotension) appeared, the application of the drug was stopped and the test regarded as positive. Subjective symptoms (itching, vertigo, headache, abdominal pain) alone were not considered as an adequate proof of intolerance or a valid reason for terminating the challenge test. Any symptoms that developed when the patients were out of the hospital were reported to our staff by telephone. For treatment of delayed-type reactions, all patients received an emergency set (2 capsules of 8 mg acrivastine and 2 tablets of 50 mg prednisone).

In patients who reliably tolerated either paracetamol or nimesulide, or who had a history of paracetamol or nimesulide intolerance, we renounced to oral provocation with these two drugs.

Statistical analysis

The Chi-Square test by Pearson was used to analyse the data and, a p value <0.05 was considered significant (SPSS for Windows, version 10.0).

Results

The 106 patients presented at our Allergy Unit after an average of 18.6 months after the most recent ADR to an NSAID.

The NSAIDs reported by the patients to induce intolerance reactions are shown in table 1. 46 patients (43.4%) experienced reactions only to one NSAID (single hypersensitivity), 60 (56.6%) to more than one NSAID (multiple hypersensitivity) (29.2% to two, 8.5% to three, 5.7% to more than three NSAIDs).

Intolerance to acetylsalicylic acid (ASA) was reported by 22.6% patients of the single hypersensitivity group (24/46) and by 57.5% of all patients (61/106). Mefenamic acid was not tolerated by 14.2% (15/46) and 32.1% (34/106), respectively. A significant increase in reported ASA intolerance was observed among asthmatics compared to patients without asthma (15/18; 83.3% *vs* 46/88; 52.3% (p = 0.015)). Furthermore, we observed more intolerance reactions to ASA than to other NSAIDs in patients with nasal polyposis (87.5%, p = .075). There was no significant increase in reported acetylsalicylic acid intolerance compared to other NSAIDs among patients with atopic diseases or urticaria (p >0.05). Six out of eight patients with polyposis nasi were diagnosed to suffer from ASA exacerbated respiratory disease. Overall, adverse reactions were reported after intake of 176 drugs in 106 patients. Cutaneous symptoms such as urticaria combined with angio-oedema were most common (42.5%), followed by isolated urticaria (26.4%), and angio-oedema (14.2%); 13.2% of patients experienced urticaria and dyspnoea (table 2).

Skin scratch tests with propyphenazone, acetylicsalicylic acid, paracetamol, chinine, phenobarbital, novaminsulfone, diclofenac, mefenamic acid, nimesulide, celecoxib and other NSAIDs were negative in all patients.

Table 1

NSAIDs reported to induce intolerance reaction in 106 patients.

Drugs	Patients	
	n	%
Single hypersensitivity group (46 patients = 43.4%)		
ASA	24	22.6
Mefenamic acid	15	14.2
Diclofenac	7	6.6
Pyrazolon	6	5.7
Paracetamol	4	3.8
Ibuprofen	1	0.9
Piroxicam	1	0.9
Naproxen	1	0.9
Multiple hypersensitivity group (60 patients = 56.6%)		
ASA and pyrazolon	10	9.4
ASA and mefenamic acid	4	3.8
ASA and ibuprofen	5	4.7
ASA and paracetamol	2	1.9
ASA and diclofenac	1	0.9
ASA and clonixidin	1	0.9
Mefenamic acid and pyrazolon	2	1.9
Mefenamic acid and paracetamol	2	1.9
Mefenamic acid and diclofenac	1	0.9
Ibuprofen and acetmetacin	1	0.9
Diclofenac and nimesulide	1	0.9
Diclofenac and pyrazolon	1	0.9
ASA, ibuprofen and pyrazolon	2	1.9
ASA, ibuprofen and paracetamol	2	1.9
ASA, mefenamic acid and diclofenac	2	1.9
ASA, mefenamic acid and paracetamol	2	1.9
ASA, diclofenac and acetmetacin	1	0.9
Other combinations	6	5.7
Unknown	1	0.9

Table 2

Symptomes reported by 106 patients after NSAID intake.

Symptoms	Patients	
	n	%
Cutaneous symptoms		
urticaria	28	26.4
angio-oedema	15	14.2
urticaria and angio-oedema	45	42.5
pruritus	1	0.9
flush	0	0
Respiratory symptoms		
dyspnoea	11	10.4
rhinitis and/or conjunctivitis	9	8.5
Cutaneous and respiratory symptoms	14	13.2
urticaria and dyspnoea	2	1.9
urticaria and rhinitis and/or conjunctivitis	9	8.5
urticaria, angio-oedema and dyspnoea	7	6.6
angio-oedema and dyspnoea	1	0.9
angio-oedema and flush	2	1.9
angio-oedema, dyspnoea and flush	7	6.6
angio-oedema and rhinitis and/or conjunctivitis	1	0.9
angio-oedema, and rhinitis and/or conjunctivitis	1	0.9
dyspnoea and flush		
Gastrointestinal symptoms (nausea and/or emesis and/or diarrhoea)	4	3.8
cutaneous and gastrointestinal symptoms	6	5.7
respiratory and gastrointestinal symptoms	2	1.9
cutaneous, respiratory and gastrointestinal symptoms	9	8.5
Anaphylaxis	2	1.9

Table 3
Results of oral challenge with celecoxib, paracetamol and nimesulide.

Drugs	Total no. of challenges	Total no. of positive challenges	Adverse reactions	Dose (mg)
Celecoxib	106	**5 (4.7%)**	Objective symptoms (2)	
			angio-oedema (2)	25/50
			Subjective symptoms (3)	25/50
			generalised pruritus (2)	25
			generalised pruritus, thoracic oppression (1)	
Paracetamol	64	**10 (15.6%)**	Objective symptoms (8)	
			urticaria (1)	500
			urticaria, angio-oedema (2)	125/500
			flush, generalised pruritus (1)	500
			angio-oedema, generalised pruritus (2)	125/500
			$FEV_1\downarrow$ (2)	500
			Subjective symptoms (2)	125/500
			generalised pruritus (2)	
Nimesulide	91	**16 (17.6%)**	Objective symptoms (10)	
			urticaria (1)	100
			angio-oedema, flush, conjunctivitis (1)	50
			angio-oedema, conjunctivitis (1)	25
			flush, thoracic oppression (1)	25
			$FEV_1\downarrow$ (2)	100/100
			rhinitis and/or conjunctivitis (2)	50/100
			rhinoconjunctivitis, generalised pruritus, nausea, vertigo (1)	100
			nausea, emesis (1)	25
			Subjective symptoms (6)	25/25/50/50
			dyspnoea, generalised pruritus (1)	25
			generalised pruritus (4)	
			nausea (1)	
Total	**261**	**31 (11.9%)**		

Table 4
Frequency of adverse reactions during oral challenges in defined subgroups of patients.

Intolerance reactions during oral challenges among patients		%
with asthma	(n = 18)	38.9
without asthma	(n = 88)	19.3
with polyposis	(n = 8)	50
without polyposis	(n = 98)	20.4
with atopic diseases	(n = 32)	28.1
without atopic diseases	(n = 74)	20.3
with urticaria	(n = 13)	30.8
without urticaria	(n = 93)	21.5

The results of 261 oral challenges with celecoxib, paracetamol and nimesulide in 106 patients are summarised in tables 3 and 4.

A total of 31 challenges were positive. Patients with a history of asthma, both allergic and nonallergic, tended to develop more intolerance reactions (7/18; 38.9%) during oral challenges than nonasthmatic patients (17/88; 19.3%), although there was no significant difference between both groups (p = .071). However, none of the asthmatic patient reacted to celecoxib. Similarly, presence or absence of polyposis did not result in a significant difference in intolerance reactions (4/8; 50% *vs* 20/98; 20.4%; p = .058); the same was true for patients with atopic diseases or urticaria as compared to nonatopic patients and patients without urticaria, respectively (9/32; 28.1% *vs* 15/74; 20.3%, p = 0.273 and 4/13; 30.8% *vs* 20/93; 21.5%, p = 0.737, respectively).

Only two patients responded with objective symptoms to the celecoxib provocation, ie after a cumulative dose of 25 mg and 50 mg, respectively. In addition, three patients complained about subjective symptoms such as thoracic oppression after 25 mg celecoxib in one patient, not accompanied by a drop in FEV_1, and generalised pruritus in two patients.

Under provocation with paracetamol six patients responded with objective skin symptoms, ie flush, urticaria or angio-oedema after intake of cumulative doses between 125 mg and 875 mg. Furthermore, 875 mg of paracetamol initiated a drop of FEV_1 >20% (39 and 32%, respectively) in two patients. Generalised pruritus was reported by two patients.

The symptoms that we observed under provocation with nimesulide were more diverse. Skin symptoms such as flush, urticaria, generalised pruritus or angio-oedema were seen in four subjects after a cumulative dose of 25 to 175 mg. Rhinitis or rhinoconjunctivitis occurred in three patients after intake of a cumulative dose of 75 to 175 mg, respectively. A drop of FEV_1 of 19% and 33% was

observed in two patients, both after a cumulative dose of 175 mg. Another patient reacted with nausea and emesis after a cumulative dose of 175 mg. Subjective symptoms, ie generalised pruritus, nausea and mild dyspnoea were reported by six patients.

Discussion

Analgetic and anti-inflammatory treatment in patients with a positive case history of NSAID intolerance is an important problem in clinical practice since patients often show hypersensitivity to mulitple nonsteroidal anti-inflammatory drugs.

In the present study, we investigated 106 patients with a positive case history of NSAID intolerance by oral challenges with celecoxib, paracetamol and nimesulide to provide them with a safe alternative drug. Our study population reported all kinds of intolerance reactions to NSAIDs, but the major part of the included patients responded with skin symptoms.

Our observations suggest that celecoxib is an appropriate alternative drug with an excellent tolerance in subjects with a history of adverse reactions to ASA and/or to other NSAIDs, confirming the low rate of cross-intolerance of this COX-2 specific drug with other NSAIDs. Information about the safety of these new anti-inflammatory drugs is scarce except for possible cardiovascular side-effects in long-term use ("Adenoma Prevention with Celebrex" Study (APC) [20]).

Skin tests with multiple NSAIDs were negative in all patients. This confirms the general experience that hypersensitivity reactions to NSAIDs are mainly not IgE-mediated [21].

In our study only two subjects responded with objective symptoms related to celecoxib (1.9%, 2 of 106 challenges), while 8 of 64 (12.5%) paracetamol and 10 of 91 (11%) nimesulide challenges were positive. Celecoxib did not cause asthmatic attacks in patients, but mainly triggered angio-oedema. Thus, a cumulative dose of 175 mg celecoxib was safely ingested by most of our patients with history of NSAID intolerance.

The finding that only 13.2% of patients experienced urticaria and dyspnoea is of particular interest, since it is generally suggested that the pathophysiology of ASA induced-asthma and ASA-induced cutaneous reactions such as acute urticaria might be similar [19]. Having observed in our population of patients either dermatological or respiratory symptoms in most subjects with NSAID intolerance seems to suggest that different mechanisms inducing asthma or urticaria might be activated when ingesting NSAIDs.

In line with our results, other investigations in patients with a history of intolerance reactions to NSAIDs also revealed an excellent tolerance to COX-2 specific NSAIDs [22]: out of the 76 subjects that were challenged with three COX-2 specific anti-inflammatory drugs (rofecoxib, celecoxib and meloxicam), 6.6% (4/72) reacted to 100 or 200 mg of celecoxib, 1.3% (1/75) showed a reaction to the recently withdrawn rofecoxib and 4.1% (3/73) to meloxicam. Pacor et al. assessed tolerance of rofecoxib in a group of 104 NSAID-intolerant patients in a double-blinded, placebo-controlled challenge test. In that study, no intolerance reactions were observed under intake of rofecoxib [23]. In a study by Liccardi et al., safety of celecoxib was examined in 72 patients with well-documented adverse reactions to nimesulide. Only two patients (2.77%) developed objective adverse events during oral challenge up to a cumulative dose of 400 mg, again indicating a very good tolerance in NSAID sensitive patients [24]. In a very recent and well-conducted study Martin-Garcia et al. demonstrated a high tolerance of rofecoxib among NSAID intolerant patients with asthma [17]. Only patients who had experienced asthma attacks with at least two different NSAIDs were included and in all 40 tested patients rofecoxib (25 mg) was proven to be well tolerated. Another Spanish group conducted single-blind, placebo-controlled oral challenges with rofecoxib and celecoxib in 33 patients with NSAID-induced anaphylactoid reactions. In all patients both drugs were well tolerated [25]. The only study, in which a tendency for celelecoxib to induce a high rate of reactions was shown, was performed by Sánchez Borges et al. [26]. They investigated clinical tolerance to COX-2 inhibitors in 110 patients with cutaneous symptoms attributable to classic NSAIDs by oral challenges with four different COX-2 inhibitors (nimesulide, meloxicam, rofecoxib and celecoxib). Celecoxib induced a rate of intolerance reactions of 33.3%, whereas the reaction rate for rofecoxib was only 3.0%. On the other hand, it has to be noted that celecoxib can also induce severe, true immune-mediated hypersensitivity reactions, especially in patients with previous sulfonilamid allergy. Also cutaneous hypersensitivity to celecoxib has been reported, however occuring very rarely, in the form of urticaria and exanthmematic pustulosis up to toxic epidermal necrolysis [27–34].

Paracetamol has often been considered a safe alternative drug in many patients with NSAID intolerance since its anticyclooxygenase activity *in vivo* is very low [35, 36]. For instance Jenkins et al. proved that less than 2% of asthmatic patients were sensitive to both aspirin and paracetamol [36]. However, they showed that intolerance reactions to paracetamol also occur in a dose dependent way in patients with NSAID intolerance: patients who are highly sensitive to aspirin are more likely to be sensitive to paracetamol than those requiring higher doses of aspirin to elicit a response [37–39].

Among the challenged patients we observed a

paracetamol intolerance rate of 15.6% (n = 10). Taking into account additionally those patients who consistently reported tolerance to paracetamol (n = 30) and who were therefore not challenged, the tolerance rate to paracetamol among the whole investigated population was 79.3% (84/106).

In contrast to a previous study (40), our study showed that nimesulide, although being more selective for COX-2 than COX-1 and highly recommended in ASA sensitive asthmatics when given in a therapeutic dose, was precarious in patients with NSAID intolerance as oral challenge resulted in a high risk to develop adverse reactions. Almost 20% of all patients challenged with nimesulide did not tolerate it under oral challenge, thus, indicating a high degree of cross-intolerance to other nonsteroidal drugs. Although nimesulide is one of the most widely studied drugs in ASA sensitive patients, reporting tolerance percentages between 71% and 100%, we have to consider that only a few of these studies included patients with asthma attacks after NSAID-intake [40–43].

According to the literature, rhinorrhea and asthma are caused when nimesulide is ingested in higher doses, ie 100 mg [44, 45]. Our patients, however, developed rhinorrhoea or asthma after 25 and 75 mg, respectively. Additionally, nimesulide may induce abnormal liver enzyme levels with no symptoms or even fatal hepatic failure following a continued intake and therefore monitoring of liver enzymes after initiating therapy with nimesulide is mandatory and its use is more and more restricted [46].

It is important to notice that special security measures such as assessment of blood pressure, lung function and skin condition have to be followed when challenging patients with NSAIDs. The personnel involved in the challenge procedure must be specially trained in management of acute intolerance reactions and equipment for resuscitation (including adrenaline for injection and oxygen) must be readily available.

Our results demonstrate that celecoxib is well tolerated by the majority of patients with NSAID intolerance and may serve as an alternative therapeutic option up to a cumulative dose of 175 mg. However, since adverse reactions to celecoxib cannot be ruled out completely and life-threatening anaphylactic reactions to celecoxib have been reported in a few cases, a controlled oral challenge test is still mandatory for proper management of patients with NSAID intolerance and long-term evaluation on larger series of patients is required before general treatment of NSAID-sensitive patients with celecoxib can be recommended

We are grateful for the excellent assistance of the nurses of the Allergy Unit.

Correspondence:
PD Dr. med. Barbara K. Ballmer-Weber
Allergy Unit
Department of Dermatology
University Hospital
Gloriastrasse 31
CH-8091 Zürich
E-Mail: Barbara.Ballmer@usz.ch

References

1 Guidelines for the management of rheumatoid arthritis. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Arthritis Rheum. 1996;39:713–22.
2 Schnitzer TJ, Truitt K, Fleischmann R, Dalgin P, Block J, Zeng Q, et al. The safety profile, tolerability, and effective dose range of rofecoxib in the treatment of rheumatoid arthritis. Phase II Rofecoxib Rheumatoid Arthritis Study Group. Clin Ther. 1999; 21:1688–702.
3 Christie PE, Smith C, Arm JP, Lee TH. Aspirin sensitive asthma. Clin Exp Allergy. 1992;22:171–5.
4 Slepian IK, Mathews KP, McLean JA. Aspirin-sensitive asthma. Chest. 1985;87:386–91.
5 Yates AB, deShazo RD. Allergic and nonallergic drug reactions. South Med J 2003;96:1080–7.
6 Naldi L, Conforti A, Venegoni M, Troncon MG, Caputi A, Ghiotto E, et al. Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. Br J Clin Pharmacol. 1999;48:839–46.
7 Namazy JA, Simon RA. Sensitivity to nonsteroidal anti-inflammatory drugs. Ann Allergy Asthma Immunol 2002;89:542–50; quiz 550, 605.
8 Settipane GA. Aspirin sensitivity and allergy. Biomed Pharmacother. 1988;42:493–8.
9 Zeitz HJ. Bronchial asthma, nasal polyps, and aspirin sensitivity: Samter's syndrome. Clin Chest Med. 1988;9:567–76.
10 Falliers CJ. Aspirin and subtypes of asthma: risk factor analysis. J Allergy Clin Immunol. 1973;52:141–7.
11 Sanchez-Borges M, Capriles-Hulett A. Atopy and NSAID sensitivity. J Allergy Clin Immunol. 1997;100:143–4.
12 Sanchez-Borges M, Capriles-Hulett A. Atopy is a risk factor for non-steroidal anti-inflammatory drug sensitivity. Ann Allergy Asthma Immunol 2000;84:101–6.
13 Hoigne R, Schlumberger HP, Vervloet D, Zoppi M. Epidemiology of allergic drug reactions. Monogr Allergy. 1993;31: 147–70.
14 Motilva V, Alarcon de la Lastra C, Bruseghini L, Manuel Herrerias J, Sanchez-Fidalgo S. COX expression and PGE(2) and PGD(2) production in experimental acute and chronic gastric lesions. Int Immunopharmacol 2005;5:369–79.
15 Xie WL, Chipman JG, Robertson DL, Erikson RL, Simmons DL. Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. Proc Natl Acad Sci U S A. 1991;88:2692–6.
16 Stevenson DD, Simon RA. Lack of cross-reactivity between rofecoxib and aspirin in aspirin-sensitive patients with asthma. J Allergy Clin Immunol 2001;108:47–51.
17 Martin-Garcia C, Hinojosa M, Berges P, Camacho E, Garcia-Rodriguez R, Alfaya T, et al. Safety of a cyclooxygenase-2 inhibitor in patients with aspirin-sensitive asthma. Chest 2002; 121:1812–7.
18 Cowburn AS, Sladek K, Soja J, Adamek L, Nizankowska E, Szczeklik A, et al. Overexpression of leukotriene C4 synthase in bronchial biopsies from patients with aspirin-intolerant asthma. J Clin Invest. 1998;101:834–46.
19 Bernstein IL, Storms WW. Practice parameters for allergy diagnostic testing. Joint Task Force on Practice Parameters for the Diagnosis and Treatment of Asthma.The American Academy of Allergy, Asthma and Immunology and the American

College of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol. 1995;75:543–625.
20 Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005;352:1071–80.
21 Nettis E, Colanardi MC, Ferrannini A, Tursi A. Update on sensitivity to nonsteroidal antiinflammatory drugs. Curr Drug Targets Immune Endocr Metabol Disord 2001;1:233–40.
22 Senna G, Bilo MB, Antonicelli L, Schiappoli M, Crivellaro MA, Bonadonna P, et al. Tolerability of three selective cyclo-oxygenase-2 inhibitors, meloxicam, celecoxib and rofecoxib in NSAID-sensitive patients. Allerg Immunol (Paris) 2004;36: 215–8.
23 Pacor ML, Di Lorenzo G, Biasi D, Barbagallo M, Corrocher R. Safety of rofecoxib in subjects with a history of adverse cutaneous reactions to aspirin and/or non-steroidal anti-inflammatory drugs. Clin Exp Allergy 2002;32:397–400.
24 Liccardi G, D'Amato G, Canonica GW, Lobefalo G, Noschese P, Piccolo A, et al. Safety of celecoxib in patients with adverse reactions to nimesulide. Allergy 2005;60:708–9.
25 Quiralte J, Delgado J, Saenz de San Pedro B, Lopez-Pascual E, Nieto MA, Ortega N, et al. Safety of the new selective cyclooxygenase type 2 inhibitors rofecoxib and celecoxib in patients with anaphylactoid reactions to nonsteroidal anti-inflammatory drugs. Ann Allergy Asthma Immunol 2004;93:360–4.
26 Sanchez Borges M C-HA, Caballero-Fonseca F, Perez CR. Tolerability to new COX-2 inhibitors in NSAID-sensitive patients with cutaneous reactions. Ann Allergy Asthma Immunol 2001; 87:201–4.
27 Schuster C, Wuthrich B. Anaphylactic drug reaction to celecoxib and sulfamethoxazole: cross reactivity or coincidence? Allergy 2003;58:1072.
28 Grob M, Pichler WJ, Wuthrich B. Anaphylaxis to celecoxib. Allergy 2002;57:264–5.
29 Fontaine C, Bousquet PJ, Demoly P. Anaphylactic shock caused by a selective allergy to celecoxib, with no allergy to rofecoxib or sulfamethoxazole. J Allergy Clin Immunol 2005;115:633–4.
30 Gagnon R, Julien M, Gold P. Selective celecoxib-associated anaphylactoid reaction. J Allergy Clin Immunol 2003;111:1404–5.
31 Levy MB, Fink JN. Anaphylaxis to celecoxib. Ann Allergy Asthma Immunol 2001;87:72–3.
32 Perna AG, Woodruff CA, Markus RF, Hsu S. Toxic epidermal necrolysis as a complication of treatment with celecoxib. Dermatol Online J 2003;9:25.
33 Goeschke B, Braathen LR. Acute generalized exanthematic pustulosis: a case and an overview of side effects affecting the skin caused by celecoxib and other COX-2 inhibitors reported so far. Dermatology 2004;209:53–6.
34 Grob M, Scheidegger P, Wuthrich B. Allergic skin reaction to celecoxib. Dermatology 2000;201:383.
35 Szczeklik A. Analgesics, allergy and asthma. Drugs. 1986;32 (Suppl 4):148–63.
36 Jenkins C, Costello J, Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. BMJ 2004;328:434.
37 Settipane RA, Stevenson DD. Cross sensitivity with acetaminophen in aspirin-sensitive subjects with asthma. J Allergy Clin Immunol. 1989;84:26–33.
38 Szczeklik A. Aspirin-induced asthma: new insights into pathogenesis and clinical presentation of drug intolerance. Int Arch Allergy Appl Immunol. 1989;90(Suppl 1):70–5.
39 Barles PG, Duce Garcia F, Portillo Olmo JR, Perez Aznar J, Escuer Alarma JL. Adverse reaction of acetaminophen as an alternative analgesic in A.A.S. Triad. Allergol Immunopathol (Madr). 1988;16:321–5.
40 Ispano M, Fontana A, Scibilia J, Ortolani C. Oral challenge with alternative nonsteroidal antiinflammatory drugs (NSAIDs) and paracetamol in patients intolerant to these agents. Drugs. 1993; 46(Suppl 1):253–6.
41 Andri L, Senna G, Betteli C, Givanni S, Scaricabarozzi I, Mezzelani P, et al. Tolerability of nimesulide in aspirin-sensitive patients. Ann Allergy. 1994;72:29–32.
42 Bavbek S, Celik G, Ediger D, Mungan D, Demirel YS, Misirligil Z. The use of nimesulide in patients with acetylsalicylic acid and nonsteroidal anti-inflammatory drug intolerance. J Asthma. 1999;36:657–63.
43 Martin-Garcia C, Hinojosa M, Berges P, Camacho E, Garcia-Rodriguez R, Alfaya T. Celecoxib, a highly selective COX-2 inhibitor, is safe in aspirin-induced asthma patients. J Investig Allergol Clin Immunol 2003;13:20–5.
44 Kosnik M, Music E, Matjaz F, Suskovic S. Relative safety of meloxicam in NSAID-intolerant patients. Allergy. 1998;53: 1231–3.
45 Bianco S, Robuschi M, Petrigni G, Scuri M, Pieroni MG, Refini RM, et al. Efficacy and tolerability of nimesulide in asthmatic patients intolerant to aspirin. Drugs. 1993;46(Suppl 1): 115–20.
46 Weiss P, Mouallem M, Bruck R, Hassin D, Tanay A, Brickman CM, et al. Nimesulide-induced hepatitis and acute liver failure. Isr Med Assoc J. 1999;1:89–91.

Swiss
Medical Weekly

Official journal of
the Swiss Society of Infectious disease
the Swiss Society of Internal Medicine
the Swiss Respiratory Society

The many reasons why you should choose SMW to publish your research

What Swiss Medical Weekly has to offer:

- SMW's impact factor has been steadily rising, to the current 1.537
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website http://www.smw.ch (direct link from each SMW record in PubMed)

- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of our professional statistician for every article with statistical analyses

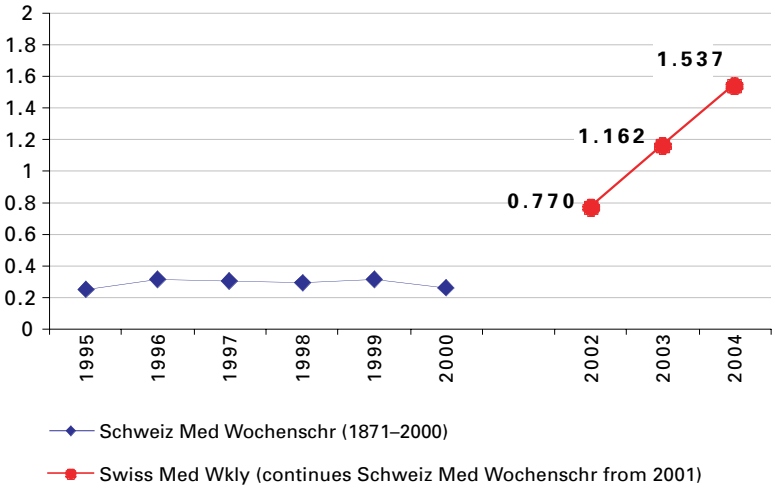
- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing
- No page charges and attractive colour offprints at no extra cost

We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:
http://www.smw.ch/set_authors.html

Impact factor Swiss Medical Weekly



EMH FMH Schwabe
Editores Medicorum Helveticorum

All manuscripts should be sent in electronic form, to:

EMH Swiss Medical Publishers Ltd.
SMW Editorial Secretariat
Farnsburgerstrasse 8
CH-4132 Muttenz

Manuscripts: submission@smw.ch
Letters to the editor: letters@smw.ch
Editorial Board: red@smw.ch
Internet: http://www.smw.ch