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Original article

Safety of triflusal (antiplatelet drug) in patients with aspirin-exacerbated respiratory diseases

Background and aims: Aspirin, a cyclo-oxygenase (COX)-1 and COX-2 inhibitor, is the antiplatelet drug of choice to prevent serious vascular events. Adverse reactions to aspirin are frequent particularly among patients with asthma, chronic rhinosinusitis and nasal polyps. COX-1 inhibitors but not COX-2 inhibitors precipitate asthma attacks. Triflusal is a preferential COX-2 inhibitor antiplatelet agent that is as effective as aspirin in the prevention of serious vascular events. The aim of the study was to assess the tolerability of triflusal in patients with aspirin-exacerbated respiratory disease (AERD).
Methods: We studied 26 asthma patients [11 males, aged 52 (23–75) years] who had suffered asthma episodes triggered by one or more (23% of patients) non-steroidal anti-inflammatory drugs. Aspirin sensitivity was confirmed by either intranasal or oral aspirin challenge. All subjects underwent a single-blind, placebo-controlled oral challenge with three doses of triflusal separated by 1 week (first cumulative dose = 225 mg; second cumulative dose = 450 mg; third cumulative dose = 900 mg). Cutaneous, respiratory, general symptoms and lung function were monitored for 4 h in the laboratory and for 24 h at home.
Results: No clinical reactions to triflusal were observed. There were no significant changes in lung function measurements.
Conclusion: Our study appears to demonstrate that triflusal is a suitable alternative to aspirin as antiplatelet agent to prevent AERD.

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Key words: AIA; antiplatelet agents; aspirin-exacerbated respiratory disease; asthma; cyclo-oxygenase; triflusal.

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Aspirin-induced asthma, also called aspirin-exacerbated respiratory disease (AERD), is a syndrome characterized by the combination of asthma, chronic rhinosinusitis with nasal polyps and episodes of bronchospasm and rhinitis precipitated by the ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs; 1). The prevalence of AERD is thought to be 4–11% based on clinical history alone but it may be as high as 15–30% when asthmatic patients are challenged with oral aspirin (1). In patients with AERD, acute symptoms are superimposed on a background of chronic asthma. Nonsteroidal anti-inflammatory drugs are frequent precipitants of life-threatening attacks of asthma (2, 3).

The pathogenesis of AERD appears to involve both the cyclo-oxygenase (COX) and the lipoxygenase (LO) pathway of arachidonic acid metabolism (4). COX is found in different isoforms known as COX-1 and COX-2. COX-1 is a 'constitutive' enzyme that has the capacity to control various physiological functions, such as blood clotting and tissue homeostasis. In contrast, COX-2 is an inducible enzyme responsible for the synthesis of prostaglandins (PGs) in a variety of inflammatory diseases. Prostaglandin E_2 (PGE_2) is synthesized through the COX-1 and COX-2 pathways. It is commonly accepted that, under conditions of inflammation, COX-2 is upregulated and, as a result, PGE_2 production is increased (4). However, for reasons that are as yet unclear, the expected upregulation of COX-2 and increased production of PGE_2 do not occur in the inflamed airway mucosa of AERD patients (5–9). This appears to be a specific abnormality of AERD as COX-2 is upregulated, and the production of PGE_2 markedly increased, in other inflammatory airway diseases, such as cystic fibrosis (10).

Arachidonic acid can also be metabolized through the 5-lipoxygenase (5-LO) pathway. 5-Lipoxygenase converts AA into leukotriene A_4, which in turn can be transformed into either LTB_4 or cysteinyl leukotrienes (Cys-LTs) by specific enzymes (4). Patients with AERD usually synthesize excessive amounts of Cys-LTs (11). After aspirin challenge, Cys-LT levels rise significantly above the baseline values in urine (11) and in brochoalveolar (12) and nasal (13) lavage fluids. Nasal (7) and bronchial (14) biopsies have shown that the expression of the enzyme leukotriene C4 synthase involved in the synthesis of Cys-LTs is greater in NSAID-intolerant asthma patients than in tolerant asthmatics, which could explain why the

former synthesize more Cys-LT than the latter in basal conditions and after aspirin challenge.

It is now generally accepted that the inhibition of COX-1, rather than COX-2, precipitates asthma attacks, and there is accumulated evidence indicating that the highly selective COX-2 inhibitors are well tolerated and can be safely used in these patients (1, 15). It is also known that the administration of PGE_2 via airways inhibits both bronchospasm induced by NSAIDs and the increased synthesis of Cys-LTs (16). Given the bronchoprotective effect of PGE_2 and the control that this prostanoid exerts in the release of Cys-LTs, the reduction in the production of PGE_2 found in aspirin-sensitive asthmatics could make these patients more susceptible to the inhibition of COX-1 (4). In patients with AERD, COX-1 might perform the task of controlling Cys-LT release, which seems to be assumed by COX-2 in inflammatory tissues. This would explain the sudden release of Cys-LT when this enzyme is inhibited by an NSAID. This could also explain the impunity with which these same patients can take selective COX-2 inhibitors. Because it is inactive, COX-2 has no control over the release of Cys-LT and therefore its inhibition causes no such Cys-LT release (4).

Aspirin is the antiplatelet drug of choice to prevent serious vascular events in a variety of clinical conditions such as stable angina (17), acute coronary syndromes (18) and stroke (19) and it is widely used. Aspirin-exacerbated respiratory disease can be a serious problem in a significant number of patients requiring antiplatelet therapy worldwide and thus, well-tolerated antiplatelet drugs in patients with cardiovascular diseases and AERD would be welcome.

Triflusal is an antiplatelet agent structurally related to salicylates but not derived from acetylsalicylic acid. In patients with an acute myocardial infarction or with ischaemic stroke, triflusal was as effective as aspirin in the prevention of serious vascular events, but the risk of haemorrhagic complications was lower (20–22). One study (23) demonstrated that the inhibitory effect on PGE_2 production in the stomach, which is mainly due to COX-1, is six times less with triflusal than with aspirin and that triflusal is 10 times more selective for COX-2 over COX-1 than aspirin. These pharmacological characteristics allow us to hypothesize that triflusal could be an alternative to aspirin in patients with AERD who need an antiplatelet agent. This study was performed to test this hypothesis.

Methods

Patients

Asthmatic outpatients of both sexes and an age of more than 18 years were assessed for eligibility. To be included in the study, patients must have documented in their clinical histories at least one episode of bronchospasm after administration of aspirin or an NSAID in the previous 5 years. In addition, a positive nasal provocation (24) test with lysine acetylsalicylate or a positive oral provocation test with aspirin (25) was required. Before admittance to the study, patients were required to give their written informed consent.

Table 1. Previous history of intolerance

Drug	*N* (%)
Aspirin	24 (96)
Dipyrone	4 (15.4)
Dicloflenac	1 (3.8)
Naproxen	1 (3.8)
Ibuprofen	1 (3.8)

Six patients (23%) had intolerance to more than one drug.

Patients were ineligible for the study if they showed at least one of the following conditions: (i) forced expiratory volume in 1 s (FEV_1) $< 70\%$ or < 1.5 l; (ii) severe asthma requiring systemic corticosteroids; (iii) treatment with antiplatelet drugs during the previous month or need for treatment with these drugs during the study period; and (iv) chronic urticaria.

Twenty-six patients [11 males, aged 52 (23–75) years] were included in the study. The patients' history of NSAID intolerance and the drugs involved are shown in Table 1.

Study design

It was a single-blind study. Five consultations were scheduled, including an inclusion consultation (consultation 0) and four further experimental consultations (consultations 1–4). The inclusion consultation and the first experimental session were separated by 24–48 h. The first three experimental sessions were separated by 7 days, whereas the period between the third and the fourth experimental session was 14 days. Prior to the first experimental session, there was a washout period of 2 weeks for the last oral glucocorticoid treatment, 4 days for antihistamines and 12 h for bronchodilators or inhaled corticosteroids.

At consultation 0, the medical histories were completed. Forced expiratory volume in 1 s, forced vital capacity and peak expiratory flow (PEF) were measured. Patients were instructed how to measure their PEF.

Eligible patients received treatment with placebo and triflusal capsules containing 75, 150 and 300 mg. All triflusal and placebo capsules were identical in appearance. At consultation 1, one placebo capsule and two placebo capsules were administered after 2 h. The total doses of triflusal were 225 mg at consultation 2 (one 75 mg capsule and two 75 mg capsules after 2 h), 450 mg at consultation 3 (one 150 mg capsule and two 150 mg capsules after 2 h) and 900 mg at consultation 3 (one 300 mg capsule and two 300 mg capsules after 2 h). The second dose of placebo or triflusal was given only if the following conditions were fulfilled: absence of intolerance, previous FEV_1 (see below) higher than 70% of the predicted normal value and absence of serious adverse events. The usual recommended dose of trifusal ranges from 600 to 900 mg/day.

At consultations 1–4, spirometric measurements were performed in basal conditions, 2 h after the first dose, 3 h after the second dose and in the case of respiratory symptoms suggesting intolerance. Peak expiratory flow was evaluated in basal conditions and at hourly intervals between doses and during the 3 h following the second dose. Three consecutive measurements separated by 1 min were performed in basal conditions, the higher value being

considered as the reference for further comparisons. Respiratory, ocular, nasal and cutaneous signs or symptoms were evaluated in basal conditions and at hourly intervals during the patients' stay in the hospital for each experimental session. Three hours after the last dose, the patients received a PEF meter to record PEF at 2-h intervals, while respecting the night-time rest, and a self-assessment card to record clinical symptoms.

Adverse events evidenced by investigators or reported by patients were recorded. The study was performed after the local Ethics Committees and Spanish Health Authorities had given their approval, and was conducted in accordance with the Declaration of Helsinki and subsequent revisions.

Definition of triflusal intolerance

Triflusal intolerance was defined by at least one of the following criteria: (1) decrease of 20% or more of FEV_1 or PEF with respect to the basal value; (2) appearance of moderate or severe respiratory symptoms that, in the researcher's opinion, advise against the administration of a new dose of triflusal; and (3) appearance of moderate or severe ocular, nasal or cutaneous symptoms that, in the researcher's opinion, advise against the administration of a new dose of triflusal.

Statistical analysis

The changes in PEF and FEV_1 from baseline were analysed by a two-way analysis of variance with factors treatment and subject. A *P*-value of < 0.05 was considered to be significant.

Results

At the end of the challenge procedures, 100% of the patients tolerated all doses of triflusal, without any sign or symptom of intolerance (data not shown). There were no significant changes in the mean FEV_1 and PEF (Table 2).

None of the subjects experienced reactions to the placebo challenge. No adverse events were reported.

Table 2. Description of percentage changes in PEF and FEV_1

	Placebo		225 mg		450 mg		900 mg	
	PEF	FEV_1	PEF	FEV_1	PEF	FEV_1	PEF	FEV_1
N	26	26	26	26	26	26	26	26
Mean	6.2	1.4	1.3	0.8	1.6	0.9	3.9	1.8
SD	9.9	8.1	5.2	6.2	5.6	7.2	8.2	6.0
95% CI (lower)	2.2	−1.9	−0.8	−1.7	−0.7	−2.0	0.5	−0.6
95% CI (upper)	10.1	4.8	3.4	3.3	3.8	3.9	7.3	4.2

PEF, peak expiratory flow; FEV_1, forced expiratory volume in 1 s.

Discussion

Aspirin is the most widely studied antiplatelet drug. For this reason, alternative treatments for patients intolerant to aspirin who need antiplatelet therapy are welcome. Clopidogrel has been recommended in aspirin-intolerant patients with acute coronary syndromes (17, 18), ischaemic stroke or transient ischaemic attack (TIA) (26).

Our study shows that triflusal is well tolerated in patients with aspirin intolerance. This is an interesting finding because, in face-to-face comparisons, triflusal has demonstrated an efficacy equivalent to aspirin in the prevention of cardiovascular events in patients with acute myocardial infarction (20) and an efficacy similar to aspirin in patients with ischaemic stroke or TIA (21, 22). These results were confirmed in a meta-analysis (22).

The majority of patients with AERD tolerate preferential COX-2 inhibitors such as nimesulide and meloxican (1, 15). Although no specific face-to-face comparison studies between trifusal and meloxicam or nimesulide have been carried out, data from the literature suggest that triflusal is as or even less potent inhibitor of COX-1 than nimesulide and meloxicam (27, 28). This inhibitory COX-1/COX-2 profile of triflusal very close to that of preferential COX-2 inhibitors probably accounts for the good tolerability found in our study.

In conclusion, our results support the use of triflusal in asthmatic patients with intolerance to aspirin who need antiplatelet therapy to reduce vascular events after myocardial infarction, ischaemic stroke or TIA.

However, as a note of caution, it is important to keep in mind that, although preferential (meloxicam) and selective (coxibs) COX-2 inhibitors are usually well tolerated by NSAID-intolerant asthmatic patients (1, 15), recent studies have reported rare cases of asthma attacks precipitated by coxibs (29, 30). Because triflusal is a less selective COX-2 inhibitor than coxibs, our study does not guarantee that all NSAID-sensitive asthmatics will not adversely react to triflusal. Therefore, it is mandatory to check tolerance by administering the first full dose of triflusal under direct medical supervision before starting regular antiplatelet therapy.

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