ANTIPLATELET THERAPY: NEW INSIGHTS ON THE SECONDARY PREVENTION OF STROKE

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ABSTRACT

Antiplatelet agents represent an important part of the therapeutic armamentarium in the prevention of stroke. Among them, aspirin is the gold standard but its chronic use has been associated with gastric intolerance, gastrointestinal and systemic hemorrhages and drug-resistance. Triflusal is a new antiplatelet agent from the family of salicylates but is not derived from aspirin and has a more selective mechanism of action: inhibition of thromboxane A2 in the platelet with no effect on prostacyclin biosynthesis in the endothelium. In the quest for the search of new antiplatelet agents, triflusal has shown a similar relative risk reduction than aspirin for the prevention of stroke but with reduced severe hemorrhagic side effects. The efficacy and better safety profile of triflusal vs aspirin in the secondary prevention of stroke has been demonstrated in major, randomized and double blind clinical trials and confirmed after a long term study with a mean follow up of 17 years, as well as in a Cochrane meta-analysis. Aspirin, but not triflusal, increased antihypertensive therapy requirements during long term treatment in the secondary prevention of stroke. In patients with atrial fibrillation, the combination of oral anticoagulants with triflusal has shown increased efficacy versus the standard oral single anticoagulation treatment with no increase of haemorrhagic risk. Studies have shown that the risk of upper gastrointestinal bleeding associated with the use of triflusal was negligible whereas the hemorrhagic risk associated with the use of aspirin, including low doses aspirin, was evident. Triflusal was well tolerated in asthmatic patients with aspirin-exacerbated respiratory-diseases. The efficacy of triflusal in secondary prevention of stroke and its better safety profile when compared to aspirin has been recognized in important International Guidelines including the European Stroke Organization Guidelines.

Key words: triflusal, antiplatelet therapy, stroke, secondary prevention.

INTRODUCTION

Antiplatelet agents represent an important part of the therapeutic armamentarium in the prevention of stroke. In this sense, the meta-analysis of the Antithrombotic Trialists [1], formerly the Antiplatelet Trialists [2], evidenced that in patients with previous stroke/transient ischemic attack (TIA), treatment with antiplatelet agents leads to an absolute reduction in the risk of having a serious vascular event (myocardial infarction, stroke, or vascular death) of 3.6%.

It is well accepted that aspirin is the gold standard antiplatelet drug for secondary prevention of cardiovascular events in patients at risk [3-9]. However, its use is associated with adverse events such as bleeding, drug-resistance [9], or aspirin-induced asthma (AIA) [10].

Aspirin-induced impairment of primary hemostasis cannot be separated from its antithrombotic effect and is similar at doses < 75 mg/day [9]. The balance between preventing vascular occlusion and causing excess bleeding with aspirin depends critically on the absolute thrombotic risk versus hemorrhagic risk of the patient [9].

The term aspirin resistance has been used to describe a number of different phenomena,
including the inability of aspirin to accomplish the following: (1) to protect individuals from thrombotic complications; (2) to cause a prolongation of the bleeding time; (3) to reduce thromboxane A2 (TXA2) production; or (4) to produce an anticipated effect on one or more in vitro tests of platelet function [11]. A variable proportion of patients (up to one quarter) with cerebrovascular disease achieve only partial inhibition of platelet aggregation at initial testing, and some (up to one third) seem to develop resistance to aspirin over time, even with increasing dose [12-14].

Aspirin-induced asthma (AIA), also called aspirin-sensitive or aspirin-intolerant asthma, is an aggressive mucosal inflammatory disease combined with precipitation of asthma and rhinitis attacks after ingestion of aspirin and most nonsteroidal anti-inflammatory drugs (NSAIDs) [10]. AIA affects about 10% of adults with asthma, more often women than men [15].

Other drugs such as ticlopidine and clopidogrel are also considered effective for prevention of stroke and other vascular events in patients with cerebrovascular disease [9]. However, the haematological toxicity associated to ticlopidine, mainly neutropenia and thrombotic thrombocytopenic purpura [16], have reduced the use of this drug in therapies due to a non optimal risk-benefit balance. For clopidogrel, efficacy data came from the Clopidogrel versus Aspirin in Patients at risk of Ischemic Events (CAPRIE) study [17] that studied 3 different clinical entities: myocardial infarction, ischemic stroke or symptomatic peripheral arterial disease. Although overall results were favourable for clopidogrel, no differences compared with aspirin were found when subgroups of ischemic stroke and myocardial infarction were analyzed. Patrono et al [18], reported that a formal test of heterogeneity of the 3 treatment effects in the CAPRIE study was statistically significant, suggesting that the true benefit of clopidogrel may not be identical for each type of disease. Thus, the evidence of clopidogrel efficacy, given as single medication, in patients with stroke does not proceed from a clinical trial specifically performed in patients with stroke.

More recent antiplatelet agents, prasugrel (Efient®) and ticagrelor (Brilique®), are not indicated for the secondary prevention of stroke. In particular, prasugrel is contraindicated in patients with history of previous stroke or transient ischaemic attack (TIA). They are only indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (i.e., unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI) as shown in the currently approved Efient® and Brilique® SPCs (Summary of Product Characteristics) leaflets. In addition, in the approved indication, both drugs need to be co-administered with aspirin.

For the above-mentioned reasons, antiplatelet drugs with demonstrated efficacy and a better safety profile than aspirin and other antiplatelet agents in the secondary prevention of stroke are welcome. Triflusal is an antiplatelet agent structurally related to salicylates but not derived from acetylsalicylic acid that presents a unique pharmacological profile and advantages over aspirin.

**TRIFLUSAL: PHARMACOLOGICAL PROFILE**

Like aspirin, triflusal irreversibly acetylates cyclo-oxygenase isoform 1 (COX-1) and therefore inhibits thromboxane biosynthesis [19,20]. The main metabolite of triflusal, 2-hydroxy-4-(trifluoromethyl) benzoic acid (HTB) has reversible inhibitory effects on the COX pathway. Aspirin, triflusal and HTB are able to stimulate nitric oxide (NO) synthase, increasing NO synthesis in several cell lines including monocytes [19]. Nitric oxide can be transferred to platelets, where it exerts an antiaggregant effect by potentiating cGMP synthesis [21]. Triflusal, in addition, inhibits platelet phosphodiesterase, the enzyme responsible for degrad-
ing cAMP and cGMP, both of which have antiaggregant effects [22]. Triflusal blocks the activation of nuclear transcription factor (NF-κB) and therefore is able to inhibit the expression of both vascular and neuronal inflammatory markers and adhesion molecules [23, 24]. Unlike aspirin, the endothelial synthesis of prostacyclin is preserved with triflusal [19].

Triflusal is rapidly absorbed after oral administration, with an absorption half life (t1/2 ka) of 0.44 hours [20]. Clearance values were 45.4 L/h for triflusal and and 0.18 L/h for HTB and terminal elimination half life (t1/2? values were 0.53 h and 34.29 hours for triflusal and HTB, respectively [25]. Pharmacokinetic parameters of triflusal are shown in Table 1.

Table 1. Pharmacokinetic parameters of triflusal

<table>
<thead>
<tr>
<th>Absorption:</th>
<th>Fast, not affected by food</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism:</td>
<td>Plasma hydrolysis, giving rise to active metabolite HTB</td>
</tr>
<tr>
<td>Maximum concentration:</td>
<td>Triflusal: 1 hour HTB: 5 hours</td>
</tr>
<tr>
<td>Biological half-life (T1/2):</td>
<td>Triflusal: 30 minutes HTB: 35 hours</td>
</tr>
<tr>
<td>Elimination:</td>
<td>Renal</td>
</tr>
<tr>
<td>Initial activity:</td>
<td>2 hours after intake</td>
</tr>
</tbody>
</table>

There was no plasma accumulation of the parent compound or its main metabolite HTB in elderly volunteers (mean age 80 years) or in young volunteers (mean age of 23 years) after 13 days' administration of twice-daily triflusal 300 mg, or in young volunteers who received triflusal 300 mg every 8 hours for 13 days, or 600 mg every 24 hours for 13 days [26, 27].

TRIFLUSAL: CLINICAL EFFICACY AND SAFETY. FOCUS ON STROKE PREVENTION

Evidence of the efficacy and safety of triflusal is derived from pivotal controlled clinical trials performed in patients with unstable angina [28], acute myocardial infarction [29], stroke [30,33], prevention of aortocoronary vein-graft occlusion [34], atrial fibrillation [35], prevention of thromboembolism after valve replacement [36] and asthmatic patients intolerant to aspirin and/or non-steroidal antiinflammatory drugs (NSAID) [37]. The evidence is reinforced by a published systematic review comparing efficacy and safety of triflusal with aspirin in patients with stroke or transient ischemic attack or acute myocardial infarction [38]. Two observational case-control studies [39,40] assessed the risk of upper gastrointestinal bleeding associated with triflusal and other drugs. In this paper we will focus the attention in clinical trials that have demonstrated the efficacy and safety of the drug in the prevention of stroke.

STROKE PREVENTION

Promising efficacy and safety results of two preliminary studies [31,32] of triflusal in comparison with aspirin in the prevention of stroke prompted to perform larger studies.

Two main studies [30,33] have been performed with triflusal in stroke.

THE TACIP STUD

The Triflusal versus Aspirin in Cerebral Infarction Prevention (TACIP) study [33] was a randomized, double-blind, parallel, multicenter clinical trial to assess the potential benefit of triflusal compared with aspirin in patients with stroke or transient ischemic attack. 2113 patients aged 40 or more years that had suffered from a transient ischemic attack or non-disabling stroke within the previous six months were randomized to receive treatment with tri-
flusal at a daily dose of 600 mg or aspirin at a daily dose of 300 mg, during 1-3 years.

2107 patients were evaluable for safety and for the intention to treat efficacy analysis. The primary composite end point of vascular death, nonfatal ischemic stroke, or non fatal myocardial infarction occurred in 138 (13.1%) of 1055 triflusal treated patients and in 130 (12.4%) of 1052 aspirin treated patients (HR: 1.09; 95% CI: from 0.85 to 1.38).

Concerning safety evaluation 54.3% of patients in the triflusal group and 52.8% in aspirin group presented at least 1 adverse event (p = 0.485). Gastric/peptic ulcer was lower in the triflusal group than in aspirin group (0.8% versus 0.1%; p = 0.021).

Of special interest is that the incidence of major systemic haemorrhage was 1.2% in the triflusal group and 2.9% in the aspirin group (HR: 0.42; 95% CI: from 0.22 to 0.81; p = 0.006) and the incidence of any cerebral or major systemic haemorrhage was 1.9% in the triflusal group and 4.0% in the aspirin group (HR: 0.48; 95% CI: from 0.28 to 0.82). Both, major systemic haemorrhage and any cerebral or major systemic haemorrhage were defined as secondary endpoints of the trial. The overall incidence of haemorrhage was lower in the triflusal group than in the aspirin group: 16.7% versus 25.2% (OR: 0.76; 95% CI: from 0.67 to 0.86; p < 0.001) (Table 2).

Table 2. Haemorrhagic adverse events in patients with TIA or stroke treated with triflusal or aspirin in the TACIP study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Aspirin n=1052</th>
<th>Triflusal n=1055</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANY MINOR</td>
<td>233</td>
<td>160</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ANY MAJOR*</td>
<td>42</td>
<td>20</td>
<td>0.004</td>
</tr>
<tr>
<td>ANY MAJOR OR MINOR</td>
<td>265</td>
<td>176</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>89</td>
<td>59</td>
<td>0.01</td>
</tr>
<tr>
<td>Skin haematoma</td>
<td>82</td>
<td>47</td>
<td>0.001</td>
</tr>
<tr>
<td>Respiratory</td>
<td>74</td>
<td>56</td>
<td>n.s.</td>
</tr>
<tr>
<td>Urinary</td>
<td>24</td>
<td>20</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cerebral</td>
<td>11</td>
<td>7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ocular</td>
<td>11</td>
<td>6</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

*Include: systemic and cerebral haemorrhage, fatal and non-fatal

THE TAPIRSS STUDY

The Triflusal versus Aspirin for Prevention of Infarction: a Randomized Stroke Study (TAPIRSS) study [30] was a multicenter, double-blind, randomized, parallel groups, pilot clinical trial to explore the efficacy and safety of triflusal versus aspirin in the prevention of vascular complications in patients with previous TIA or ischemic stroke in a Latin American population.

Patients were randomized to receive treatment with a daily single dose of either triflusal 600 mg or aspirin 325 mg. To avoid interferences with acute-phase treatments, patients were enrolled after 15 days from onset of the qualifying event. Treatment and follow-up extended from a minimum of 1 year to a maximum of 2 years from inclusion.

Primary endpoint was the first occurrence of the composite of either vascular death, nonfatal ischemic stroke, nonfatal acute myocardial infarction, or major bleeding.

Secondary endpoints were the occurrence of each of the above events separately as well
A total of 692 adverse events (358 aspirin, 334 triflusal) were reported by 248 patients, 127 (58.8%) of whom had been assigned to aspirin and 121 (56.5%) to triflusal. Less than one half of adverse events were considered treatment related (35.7% in aspirin and 43.1% in triflusal).

Four hundred thirty patients were evaluable for safety and 429 were evaluable for efficacy. The primary composite end-point of either vascular death, nonfatal ischemic stroke, nonfatal acute myocardial infarction, or major bleeding was achieved in 30 patients (13.9%) in the aspirin group and 27 patients (12.7%) in the triflusal group (OR: 1.11; 95% CI: 0.64 to 1.94; p = 0.711). No statistically significant differences were observed in secondary efficacy variables. End-points by treatment group are shown in Table 3.

### Table 3. End-points by treatment groups in patients with stroke or TIA in the TAPRIRSS study

<table>
<thead>
<tr>
<th>Primary end-point</th>
<th>Treatment</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin n=216</td>
<td>Triflusal n=213</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>Combined primary end-point</td>
<td>30</td>
<td>13.9%</td>
<td>27</td>
<td>12.7%</td>
</tr>
<tr>
<td>Secondary end-points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal cerebral infarction</td>
<td>16</td>
<td>7.40%</td>
<td>17</td>
<td>8.00%</td>
</tr>
<tr>
<td>Non-fatal AMI</td>
<td>5</td>
<td>2.30%</td>
<td>4</td>
<td>1.90%</td>
</tr>
<tr>
<td>Vascular death</td>
<td>8</td>
<td>3.70%</td>
<td>5</td>
<td>2.30%</td>
</tr>
<tr>
<td>Major haemorrhage</td>
<td>7</td>
<td>3.20%</td>
<td>1</td>
<td>0.50%</td>
</tr>
<tr>
<td>Non-vascular death</td>
<td>5</td>
<td>2.30%</td>
<td>1</td>
<td>0.50%</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>13</td>
<td>6.00%</td>
<td>6</td>
<td>2.80%</td>
</tr>
<tr>
<td>Minor systemic haemorrhage</td>
<td>13</td>
<td>6.00%</td>
<td>5</td>
<td>2.30%</td>
</tr>
<tr>
<td>Overall haemorrhage</td>
<td>18</td>
<td>8.30%</td>
<td>6</td>
<td>2.80%</td>
</tr>
<tr>
<td>Non-fatal systemic thromboembolism</td>
<td>2</td>
<td>0.90%</td>
<td>3</td>
<td>1.40%</td>
</tr>
</tbody>
</table>

A total of 692 adverse events (358 aspirin, 334 triflusal) were reported by 248 patients, 127 (58.8%) of whom had been assigned to aspirin and 121 (56.5%) to triflusal. Less than one half of adverse events were considered treatment related (35.7% in aspirin and 43.1% in triflusal). A total of 69 serious adverse events were reported (43 aspirin, 26 triflusal); 17 (14 aspirin, 3 triflusal) were considered treatment related. The most frequently reported were dyspepsia (three aspirin, none triflusal), angina pectoris (three aspirin, none triflusal), and cerebrovascular disorder (one aspirin, two triflusal).

The triflusal-treated group showed a favourable trend in hemorrhagic events, with an incidence of major hemorrhages of 7 patients (3.2%) in the aspirin group vs 1 patient (0.5%) in the triflusal group (OR: 7.1; 95% CI: 1.15 to 43.52; p = 0.068) and an incidence of minor hemorrhages of 13 patients (6%) in the aspirin group vs 5 (2.3%) in the triflusal group (OR: 2.66; 95% CI: 0.93 to 7.61; p = 0.058). In a post hoc analysis, all bleeding episodes, including first major and minor hemorrhages, were significantly more frequent in the aspirin group (OR: 3.13; 95% CI: 1.22 to 8.06; p = 0.013) (Figure 1). The gastrointestinal tract was the most frequently reported bleeding site, with a favourable trend toward fewer episodes in triflusal treated patients (p = 0.062). Differences were particularly evident after the first year of follow-up.
The Cochrane Collaboration Systematic Review of triflusal versus aspirin in stroke and acute myocardial infarction

A systematic review comparing efficacy and safety of triflusal with aspirin in patients with stroke or transient ischemic attack or acute myocardial infarction has been published [38]. Five studies (four in stroke or transient ischemic attack [2994 patients] and one in acute myocardial infarction [2275 patients]) comparing triflusal with aspirin were included.

The comparative efficacy of triflusal versus aspirin (OR > 1 favours triflusal), showed no significant differences were found between triflusal and aspirin neither for the primary outcome, defined as non-fatal myocardial infarction, non-fatal ischemic or hemorrhagic stroke, or vascular death (OR: 1.04; 95% confidence interval: 0.87 to 1.23) nor for each of the individual outcomes that contributed to the primary outcome: vascular death (OR: 1.11 [0.86 to 1.45]), non-fatal stroke (OR: 1.1 [0.86 to 1.40]), and non-fatal acute myocardial infarction (OR: 0.90 [0.61 to 1.31]). In general, differences for the secondary outcomes were not found. The exceptions, all favouring triflusal, were non-fatal hemorrhagic stroke (OR: 2.83 [1.2 to 6.68]), fatal and non-fatal hemorrhagic stroke (OR: 2.15 [1.15 to 4.04]) and fatal ischemic stroke (OR: 2.71 [1.12 to 6.55]).

The comparative safety of triflusal versus aspirin (OR > 1 favours triflusal) was also studied. No differences were detected in the number of patients with at least one adverse event, although the number of patients with serious adverse events related to medication was higher with aspirin than with triflusal (OR: 1.36 [1.04 to 1.78]). Triflusal was safer than aspirin concerning the following variables: overall hemorrhagic adverse events (OR: 1.73 [1.44 to 2.08]), number of patients with any intracranial hemorrhage or other major systemic hemorrhage (OR: 2.34 [1.58 to 3.46]), number of patients with any major systemic hemorrhage (OR: 2.34 [1.41 to 3.86]), number of patients with any minor hemorrhage (1.60 [1.31 to 1.95]) and number of patients with gastrointestinal hemorrhage (OR: 1.83 [1.35 to 2.48]).

Triflusal versus Aspirin in the prevention of stroke: long term follow up study

Mean follow-up of clinical trials with antiplatelet agents in the secondary prevention of atherothrombotic stroke ranges between 1.5 and 3.5 years, and the safety and efficacy of these drugs at more long term is unknown. In this study the long term safety and efficacy of Triflusal and
Aspirin in patients with atherothrombotic stroke was assessed (mean follow-up: 17.2 years) [41].

Patients with atherothrombotic ischemic stroke were included. The recruitment period was between 1983 and 1999. All patients received antiplatelet treatment: Aspirin or Triflusal. Possible adverse events and vascular events along the follow-up were registered. Statistical analysis to assess if there were differences between the two kind of antiplatelet agents was performed by means of the software SPSS 15.0.

Four hundred and forty one patients aged 51.1 ± 12.4 years were studied. Three hundred and five (69.2%) were men. Two hundred eighty eigth (65.3%) were treated with Triflusal and 153 (34.7%) with Aspirin. Concerning adverse events it should be emphasized that Aspirin treated patients presented more serious hemorrhagic complications during the follow-up (18.3% vs 5.6%, p < 0.001). There were no significant differences concerning new recurrences of stroke (49.7% Aspirin vs 46.5% Triflusal, p = 0.529), ischemic heart disease (54.9% vs 55.6%, p = 0.895), mortality of vascular origin (25.5% vs 24%, p = 0.728) and global mortality (42.5% vs 42%), p = 0.924).

In conclusion, a very long term treatment with Triflusal is safer and equally effective than Aspirin in the secondary prevention of ischemic stroke of atherothrombotic ethiology.

Antihypertensive therapy requirements during long term antiplatelet treatment in the secondary prevention of stroke: a TACIP subanalysis

Requirements of antihypertensive drugs (Ca-blockers, diuretics, beta-blockers, ACE-inhibitors) in the population of the TACIP study [33] in the long term secondary prevention of stroke have been studied [42]. Patients randomly assigned to triflusal 600 mg or aspirin 325 mg daily were compared for antihypertensive therapy requirements. 2107 patients (1052 aspirin, 1055 triflusal) were followed for a mean follow-up of 30.1 months. Percentage of patients with hypertension at baseline was balanced (62.2% aspirin; 60.9% triflusal) as well as in the proportion of the consumption of the different antihypertensives. During treatment, the percentage of patients in the aspirin group that were treated with antihypertensive drugs increased significantly from 58.2% (start) to 71.4% (end) but not in the triflusal group (58.1% start; 58.6% end). This difference can be due to a negative interaction between aspirin and some antihypertensive drugs not observed with triflusal, probably as a consequence of a different mechanism of action of both drugs [43].

Atrial fibrillation: The NASPEAF study

The published National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF) study [35] evidenced the efficacy and tolerability of triflusal plus moderate intensity anticoagulation in patients with atrial fibrillation. It was a prospective, multicenter, randomized clinical trial, performed in 1209 patients with atrial fibrillation, that were divided into two groups based on risk for thromboembolism: the high-risk group included patients with nonvalvular plus prior embolism and patients with mitral stenosis with and without prior embolism. All others were included in the intermediate-risk group. Patients in the intermediate-risk group were randomized to one of the three arms: oral anticoagulation with acenocoumarol to a target INR of 2 to 3, triflusal 600 mg daily, or a combination of both with a target INR of 1.25 to 2. Acenocoumarol is a vitamin K antagonist commonly used in Europe that can be considered equivalent and interchangeable to warfarin [44,45]. In the high-risk group, the triflusal-only arm was omitted and subjects were assigned to anticoagulation with a target INR of 2 to 3 or the combination therapy with a target INR of 1.4 to 2.4. Primary outcome was a composite of vascular death, TIA and nonfatal stroke or systemic embolism, whichever came first. After a median follow-up of 2.76 years, primary outcome was lower in the combined therapy than in the anticoagulant arm in both the intermediate risk group (hazard ratio [HR]: 0.33 [95% confidence interval: 0.12 to 0.91]; p = 0.02) and in the high-risk group (HR: 0.51 [0.27 to 0.96]; p = 0.03) (Figure 2).
Similar results were not demonstrated in previous trials combining low-dose warfarin and aspirin [46-48].

**Triflusal in asthmatic patients intolerant to aspirin and/or non-steroidal anti-inflammatory drugs**

A single-blind placebo-controlled study to evaluate the tolerance to triflusal was performed in 26 asthmatic patients intolerant to aspirin and/or non steroidal antiinflammatory drugs (NSAID) [37]. In visit 1 one placebo capsule was administered followed by two placebo capsules after 2 hours. Total doses of triflusal were 225 mg in visit 2 (one 75 mg capsule and two 75 mg capsules after 2 hours), 450 mg in visit 3 (one 150 mg capsule and two 150 mg capsules after 2 hours) and 900 mg in visit 3 (one 300 mg capsule and two 300 mg capsules after 2 hours). No patient presented intolerance to triflusal, defined as the appearance of respiratory, nasal, ocular or cutaneous symptoms and/or a decrease of 20% or more of forced expiratory volume in 1 second (FEV1) or peak expiratory flow (PEF) with respect to the basal value.

**Observational case-control studies assessing the risk of upper gastrointestinal bleeding**

Two case-control studies evaluated the risk of upper gastrointestinal bleeding associated with non-aspirin cardiovascular drugs, analgesics and NSAID [39] and with antiplatelet drugs [40], respectively. In the first study [39], including 1122 cases and 2231 controls, triflusal was not associated with increased risk of upper gastrointestinal bleeding. In the second study [40], including 2813 cases and 7193 controls, the individual risks of upper gastrointestinal bleeding for the studied antiplatelet agents were (OR; 95% CI) aspirin: 4.0 (3.2-4.9), clopidogrel: 2.3 (0.9-6.0), dipyridamole: 0.9 (0.4-2), ticlopidine: 3.1 (1.8-5.1) and triflusal: 1.6 (0.9-2.7). These results are compatible with those found in triflusal clinical trials.

**Triflusal in National and International Guidelines for the prevention of stroke**

Triflusal is included in National and International Guidelines for the secondary prevention of stroke. In particular triflusal is included, among others, in:

Guidelines from the "European Stroke
Organization (ESO)" for Management of Ischemic Stroke and Transient Ischaemic Attack 2008 (Cerebrovasc Dis 2008; 25:457-507)

In this guideline is classified as **Class I and level A** of recommendation (maximum level) for the secondary prevention of stroke (p. 473) and it is specifically worded the following:

"**Triflusal reduces stroke recurrence with similar efficacy to aspirin but with fewer adverse events**" (p. 474)

Guidelines from the "Spanish Society of Neurology" (SEN) for the Diagnosis and Treatment of Stroke (2006, Prous Science Eds).

In this guideline triflusal is recommended as Grade IA (maximum level) and it is specifically worded the following:

"...Its administration at doses of 300 mg every 12 hours has demonstrated an efficacy similar to that of ASA with a lower number of long term haemorrhagic complications (Grade IA), that in the case of ASA increase exponentially throughout the years. Because of that it could be also considered as a first choice antiplatelet agent or as an alternative to ASA" (p 156-157)


In these guidelines Triflusal is recommended as Grade 2B for stroke prevention in patients with a history of cardioembolic stroke or TIA. In page e623 and table 21 (p. e626S) it is worded that Triflusal, compared to Aspirin, caused a reduction in nonfatal major extracranial hemorrhage (6 fewer bleeding events per 1000), and the quality of evidence (Grade) is "High".

**CONCLUSIONS**

Triflusal is an antiplatelet agent with a chemical structure of the family of salicylates but is not derived from aspirin. Like aspirin it blocks platelet cyclooxygenase and therefore inhibits thromboxane B2 formation. However, unlike aspirin, triflusal also inhibits platelet cAMP-phosphodiesterase and preserves the formation of prostacyclin in the vascular wall (endothelium cells), due to its negligible effect on vascular cyclooxygenase. These activities provide triflusal of a unique mechanism of action in the therapeutic armamentarium of antiplatelet agents and is more selective than that of aspirin.

Triflusal has demonstrated similar efficacy to Aspirin but with a better safety profile (lower haemorrhagic risk) in the long term prophylaxis of secondary stroke (mean follow up of up to 17 years).

Aspirin but not triflusal increased antihypertensive therapy requirements during long term therapy of the secondary prevention of stroke.

Triflusal plus moderate intensity oral anticoagulation is more effective than standard oral anticoagulation to prevent vascular events in patients with valvular and non-valvular atrial fibrillation and does so without increasing bleeding risk. Risk reduction was of 50%. This has not been demonstrated with aspirin.

The risk of upper gastrointestinal bleeding associated with the use of triflusal is negligible and much lower than that of other antiplatelet agents such as low doses aspirin and clopidogrel.

Triflusal was well tolerated and did not cause allergic effects in asthmatic patients with previously demonstrated aspirin-exacerbated respiratory diseases.

The efficacy of triflusal in the secondary prevention of stroke and its safety, better than that of Aspirin, has been recognized in National and International Clinical Practice Guidelines including the Guidelines of the European Stroke Organization, the Guidelines of the Spanish Society of Neurology and the Guidelines of The American College of Chest Physicians.
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Антиагреганты играют важную роль в медикаментозной профилактике инсульта. Среди них аспирин считается «золотым стандартом», однако длительное его использование сопровождается непереносимостью со стороны желудочно-кишечного тракта, желудочно-кишечными и системными кровотечениями, а также резистентностью к препарату. Трифлусал - новый антиагрегант, относящийся к группе салицилатов, но не являющийся производным аспирина, обладает более селективным механизмом действия: подавляет синтез тромбоксана А2 в тромбоцитах, но не влияет на биосинтез простациклина в эндотелии. Сравнивая антиагреганты, в профилактике инсульта трифлусал показал одинаковый с аспирином уровень снижения риска, но с меньшим показателем тяжелых геморрагических осложнений. Эффективность и лучший профиль безопасности трифлусала во вторичной профилактике инсульта, по сравнению с аспирином, были показаны в крупных, рандомизированных, двойных слепых клинических исследованиях и подтверждены продолжительным исследованием с длительностью наблюдения более 17 лет, а также мета-анализом Бьюкенена. При длительной терапии во вторичной профилактике инсульта, аспирин, но не трифлусал, требует увеличения дозы антигипертензивных препаратов. У пациентов с фибрилляцией предсердий комбинация трифлусала с оральным антикоагулянтом показала более высокую эффективность по сравнению со стандартной терапией только антикоагулянтом, без повышения риска кровотечений. Исследования показали, что при использовании трифлусала риск кровотечения из верхних отделов желудочно-кишечного тракта был незначительным, в то время как риск кровотечения, ассоциированный с приемом аспирина, в том числе в низких дозах, был очевидным. Трифлусал хорошо переносился пациентами с аспирин-ассоциированными респираторными заболеваниями и бронхиальной астмой. Эффективность трифлусала во вторичной профилактике инсульта и его лучший фармакологический профиль по сравнению с аспирином были подтверждены важнейшими международными клиническими протоколами, включая Европейскую Организацию Инсульта.

Ключевые слова: трифлусал, антиагрегантная терапия, инсульт, вторичная профилактика.
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Açar sözər: triflusal, antiqreqantterapiya, insult, ikincili profilaktika

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