Review Article

Triflusal: An Old Drug in Modern Antiplatelet Therapy. Review of Its Action, Use, Safety and Effectiveness

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Despite preventive measures and improved long-term prognosis, the prevalence of cardiovascular diseases in the majority of the industrialised countries is still high. The epidemic of obesity, diabetes, and metabolic syndrome, and the increasing age of the population are the major contributors to this epidemiological fact, whose socio-economic consequences are of profound importance.[1-4] Over 200,000 people in the US experience recurrent stroke annually, representing 29% of the total annual number of strokes.[5] Considering that the annual cost of strokes reaches $55.8 billion, recurrent attacks may incur costs of $16 billion each year.[1] In the Greek population, the overall incidence of first stroke reaches 343.6/100,000, ranging from 7.3 to 2661.1/100,000 depending on age and sex. The 1-year mortality is 35.9% in men and 41.8% in women.[6] Apparently, the incidence of stroke in our population is relatively high—possibly because of elevated salt intake and the high prevalence of hypertension.

Atherothrombotic episodes are associated with progression of the atheromatous disease and the influence of haemodynamic factors. The contribution of a hypercoagulable state is important. Platelets have a central role in the development of arterial thrombosis and subsequent cardiovascular events. This realisation has made antiplatelet therapy the cornerstone of atherosclerotic disease management.[7,8] Numerous guidelines and recommendations have documented the cardinal role of aspirin administration in the primary and secondary prevention of myocardial ischaemia.[1] All patients with acute coronary syndromes should receive antiplatelet medication, both during and after the acute episode, with at least one agent. Aspirin remains the first choice and should be combined with clopidogrel, which can substitute for aspirin in case the latter is contraindicated.[9-11] For thromboprophylaxis in patients with atrial fibrillation aspirin is an acceptable alternative in cases where anticoagulants are contraindicated or in patients at low risk for stroke.[12,13]

Prevention of stroke

Acetylsalicylic acid 50-325 mg/day or 50 mg plus dipyridamole 200 mg twice daily are considered first-line treatment for preventing recurrent stroke in patients with a previous non-cardioembolic cerebrovascular event. Alternatively, clopidogrel alone can be used. In the 2008 guidelines for stroke management from the European Stroke Organization, triflusal was for the first time recommended as lone therapy, as an alternative to the above-mentioned medica-

tions for secondary prevention of atherothrombotic stroke. This recommendation was based on the double-blind, randomised TACIP and TAPIRSS trials, which found triflusal to be equally as effective as aspirin in preventing post-stroke vascular events, while having a more favourable safety profile.[14-16]

In the early postoperative period following valve replacement with a bioprosthesis, anticoagulation with heparin and subsequently vitamin K antagonists or aspirin is endorsed, depending on the valve replaced. Among surgical centres remarkable variety is observed regarding the antithrombotic medication. Small clinical trials suggest that antiplatelet therapy with ticlopidine or triflusal is a promising alternative to warfarin for the primary prevention of thromboembolism in this clinical setting.[17-19]

Problems related to treatment with aspirin

Despite the well established effective clinical functions and the universal acceptance aspirin enjoys, its administration in various settings, such as in the geriatric population, is frequently problematic because of an increased risk of bleeding complications, especially in the presence of other comorbidities and concomitant use of other drugs. Gastrointestinal bleeding is a widely recognised consequence associated with acetylsalicylic use; it is dose related and potentially severe.[20,21] Even low dosage administration in individuals over 60 years of age can be blamed for almost 1/3 of all severe episodes of gastrointestinal haemorrhage. Aspirin also exhibits frequent adverse effects in patients with asthma, chronic sinusitis and nasal polyps.[22] Furthermore, its therapeutic action, like that of clopidogrel, is reduced in a significant part of the population that may reach 15%,[23] as a result of genetically controlled mechanisms of resistance.[24-27] Certain controversy exists regarding its use in cases of G-6PD deficiency, although the frequency of haemolytic complications is low, and its administration seems safe, especially in low doses.[28,29]

In other words, it has become evident that the use of antithrombotic drugs is far from optimised, mostly because of difficulty in their use and adverse effects. Therefore, the introduction of new agents with sufficient effectiveness, fewer cases of drug resistance, and with a reduced potential for treatment-related bleeding or airway over-responsiveness would represent a useful addition to the therapeutic options available at this time.

Both the anti-factor Xa and antithrombin agents have been developed for oral use and have provided impressive clinical outcomes for the post-surgical prophylaxis of venous thrombosis. In animal models melagatran has been proven effective in preventing thrombus formation in mechanical valves.[30] Anti-factor Xa rivaroxaban and otamixaban are potent antithrombotic factors, comparable to enoxaparin and unfractionated heparin in the prevention of venous thromboembolism after major orthopaedic surgery and in percutaneous coronary interventions, respectively.[31,32] However, safety concerns related to liver enzyme elevations and thrombosis rebound have been reported with their use.[33] Newly studied antiplatelet agents, such as prasugrel, present a significant reduction in ischaemic events compared to clopidogrel in acute coronary syndromes, but at the cost of a significant increase in major bleeding.[34]
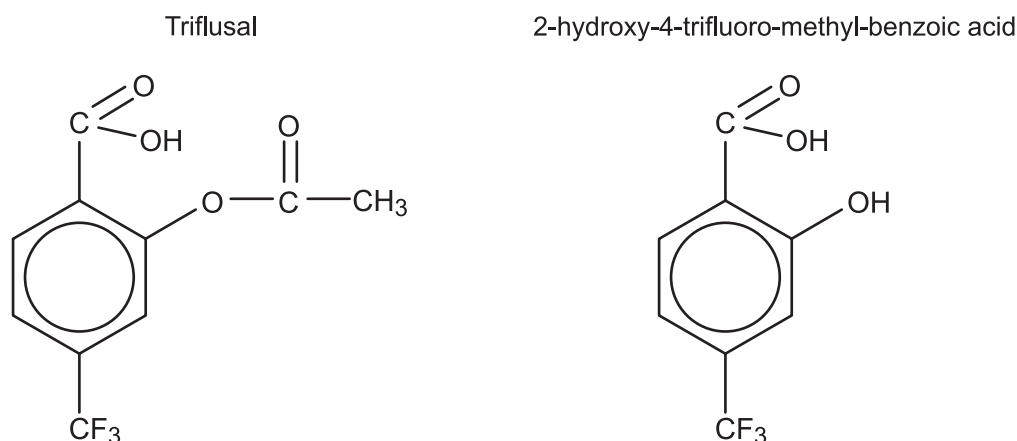
Triflusal

Triflusal represents a challenging and promising alternative to aspirin. It is chemically related to acetylsalicylic acid and inhibits cycloxygenase-1 in platelets, but seems to leave intact the arachidonic acid metabolic pathway in endothelial cells. It also favours the production of NO and increases the concentration of cyclic nucleotides. Thanks to this multiplicity of actions, this drug presents comparable antiplatelet activity to aspirin while presenting a more favourable safety profile.[35]

Chemical properties and pharmacokinetics of triflusal

Triflusal, or 2-acetyloxy-4-trifluoromethyl benzoic acid, is structurally related to acetylsalicylic acid, although its chemical synthesis is different, having a trifluoromethyl group in position 4 (Figure 1). It is produced as white crystals with a melting point of 110°C.[36] The drug is administered orally. It is absorbed in the small intestine and its bioavailability ranges from 83% to 100%.[37,38] It binds to plasma proteins almost entirely (99%) and crosses organic barriers readily. During passage through the liver it is deacetylated, forming its main metabolite 2-OH-4-trifluoromethyl benzoic acid (HTB). The half-life of triflusal in healthy humans is 0.5 ± 0.1 h, while that of HTB is 34.3 ± 5.3 h. Elimination is primarily renal. Unchanged triflusal, HTB and HTB glycine conjugate have been identified in the urine. Renal clearance is 0.8 ± 0.2 L/h and 0.18 ± 0.04 L/h for triflusal and HTB, respectively. Steady state for HTB is reached after 8-10 days of treatment.[39,40]

The concentration of HTB in the cerebrospinal

Triflusal

2-hydroxy-4-trifluoro-methyl-benzoic acid

Figure 1. Chemical structure of triflusal and its metabolite 2-hydroxy-4-trifluoro-methyl-benzoic acid.

fluid ranges from 0.011-0.341 μg/ml, which is reported to be within a range that may, according to *in vitro* data from a study in human neuroblastoma cells, have a protective effect in Alzheimer's disease.[41] The pharmacokinetic profiles of triflusal or HTB do not appear to have clinically significant differences in elderly or younger volunteers.[35,40] No plasma accumulation of the parent compound was noticed in volunteers >80 years old who received triflusal 300 mg × 2/day for 13 days.[42] Although values for $t_{1/2}$ were greater in elderly compared to younger individuals (triflusal 0.92 h vs. 0.53 h, HTB 64.6 h vs. 34.3 h) such differences were not considered to be clinically significant or to necessitate dosage adjustments in aged people. Conventional haemodialysis is reported to have no major influence on plasma HTB concentrations.[35]

As mentioned above, at therapeutic concentrations 98-99% of HTB is bound to plasma proteins. This binding is not significantly influenced by theophylline, enalapril, caffeine or warfarin, but the free fraction of this compound is increased by non-steroidal anti-inflammatory drugs (diclofenac, ibuprofen, piroxicam, naproxen). Furthermore HTB may, in high concentrations, impair protein binding of non-steroidal anti-inflammatory drugs, glisentide or warfarin[35] and therefore may increase their free fractions and require dosage reductions.

In contrast to other inhibitors of prostaglandin synthesis, such as non-steroidal anti-inflammatory drugs or aspirin, triflusal, probably because of its multiple mechanisms of action, seems to interfere to a lesser degree with the effectiveness of antihypertensive medication. Data from the TACIP study suggest that the need for antihypertensive therapy was signifi-

cantly less in triflusal than in aspirin recipients.[43,44] In the specific case of angiotensin-converting enzyme inhibitors, an analysis of the TIM study reported that concurrent administration of aspirin, but not triflusal, may impede their antihypertensive action and potentially affect patient survival.[45] Notably, the recommended dosage in adults is 600-900 mg/day, administered as a single dose of 600 mg or in two or three doses of 300 mg, preferably during or after meals.

Mechanism of action

Triflusal inhibits platelet aggregation and interaction with subendothelium. Its effect has been documented in experimental animals and in humans in *in vitro* and *ex vivo* studies and in *in vivo* models of thrombogenesis in animals.[46-48] The drug irreversibly inhibits cyclooxygenase-1 (COX-1) and reduces thromboxane B2 (TXB2) production, but to a lesser degree compared to aspirin, and its action declines within 30 days from withdrawal.[49] The reduction in serum 6-keto prostaglandin F1 levels was negligible with triflusal (8.8% vs. 97.8% with aspirin), suggesting that this compound inhibits COX-1 and arachidonic acid metabolism selectively in platelets, sparing the metabolic function of vascular endothelial cells. The main metabolite, HTB, is pharmacologically active; triflusal is more potent in inhibiting COX-1 and reducing TXB2 than HTB but is less potent than aspirin. However, HTB potentiates triflusal's effect on COX-1 inhibition, whereas aspirin's metabolite, salicylic acid, competes with the parent compound for its binding to COX.[48]

In vitro, triflusal inhibits platelet aggregation with a significantly smaller IC$_{50}$ when tested in whole blood

compared to platelet rich plasma. This fact suggests that red blood cells may somehow enhance the drug's anti-aggregant properties. In studies regarding the platelet-endothelium interactions, where blood from volunteers receiving triflusal or aspirin circulates in contact with rabbit aorta subendothelium, triflusal reduced platelet coverage by 92% (aspirin: 62%). The arterial area occupied by aggregates was reduced by 89% (aspirin 75%). The surface occupied by adhesions (platelets spread and firmly bound onto the subendothelium forming layers <5 μm, a function dependent on decreased levels of cyclic adenosine monophosphate, cAMP) was reduced by 25% (aspirin 3%).[40]

Moreover, triflusal, via stimulation of the constitutive activity of NO synthase (cNOS), enhances the production of NO by neutrophils by 150%, whereas aspirin does so by 60%. It also increases levels of cyclic guanosine monophosphate and inhibits cAMP phosphodiesterase, leading to a rise in cAMP levels and thus a decrease in calcium mobilisation and subsequent platelet aggregation.[40]

Ex vivo, in rat brain slices triflusal was more potent than acetylsalicylic acid in reducing anoxia-reperfusion related cell death (21-47% vs. 0-26%) and other indices of cerebral oxidative stress (25-30% vs. 0-24% decrease in inducible nitric oxide synthase [iNOS] activity, 30-40% vs. 0-35% decrease in lipid peroxidation).[50] *In vitro*, in human mononuclear cells, it reduced the activation of NF-kB which is a gene expression regulatory factor participating among other things in the control of transcription of cytokine and COX-2 genes. Triflusal also inhibits vascular cell adhesion molecule-1 mRNA expression[51,52] as well as the production of various cytokines, such as interferon-γ, interleukins IL-2, IL-3 and IL-8, and tumour necrosis factor-alpha (TNF-α).[53]

In vivo animal models studies have established the antiplatelet action of triflusal. Brain ischaemia in rats—induced by intracarotid injection of arachidonic acid, which causes the formation of multiple small thrombi—is significantly reduced after the chronic administration of triflusal (60% protection compared to 27% with equivalent dose of aspirin).[54] Similar results are obtained when brain ischaemia is provoked by occlusion of the middle cerebral artery or electrical stimulation of the carotid artery.[55,56]

In humans, triflusal has been found more effective than acetylsalicylic acid in platelet aggregation inhibition, using electrical impedance aggregometry in whole blood. However, in a comparative study in healthy volunteers, bleeding time was not significantly different from baseline after 3-7 days of 600-900 mg/day triflusal administration.[57]

Apart from its antithrombotic effect, triflusal is thought to reduce the damage caused to the nervous system by various insults, such as ischaemic or cytotoxic, acting directly on this specific tissue. Given in a dosage of 30 mg/kg it reduced brain lesions provoked by N-CH$_3$-D aspartate (NMDA) injection,[58,59] while in doses of 1, 10 and 50 mg/kg it showed a neuroprotective action against anoxia-reperfusion damage in rat brain slices. In this setting it diminished LDH activity by 21%, 42% and 47%, respectively.[60] Acetylsalicylic acid exhibited a dose-dependent but quantitatively more limited effect. Similar differences between the two drugs were observed regarding their influence on the biochemical pathways of brain damage (oxidative stress, prostaglandin accumulation, NO pathways).[60] Several sites of action in the nervous tissue, which are interrelated via biochemical pathways with well established involvement in neuronal damage, have been proposed to account for the neuroprotective properties of this drug. Triflusal inhibits the excess lipid peroxidation resulting from anoxia-reoxygenation. HTB, on the other hand, enhances the endogenous glutathione antioxidant system in addition to inhibiting lipid peroxidation.[50] Triflusal's various actions are summarised and depicted in Figure 2.

Both the parent compound and the active metabolite not only decrease the prostaglandin synthesis and accumulation observed in ischaemic brain tissue as a result of anoxia-reoxygenation,[60] but they also interfere with the NO pathway. Excess production of NO leads to formation of peroxynitrites, which are highly reactive radicals and extremely toxic for the neuronal cells. These drugs substantially reduce the availability of free radicals, as a result of their antioxidant potential, and also decrease the activity of iNOS more powerfully than does acetylsalicylic acid. As a result, they limit the excessive synthesis of NO by the ischaemic neuronal tissue. Finally, as they also inhibit the inducible COX pathway (COX-2), they hinder the expression of numerous inflammatory mediators, such as IL-1β and TNF-α, as evident in models of NMDA neurotoxicity.[58] This effect appears to be mediated by a reduction of NF-kB synthesis and desensitisation of neurons to its action.[50,52,59,61] This mechanism has been proposed to underlie triflusal's neuroprotective properties in an experimental model of neurodegenerative diseases.[62]
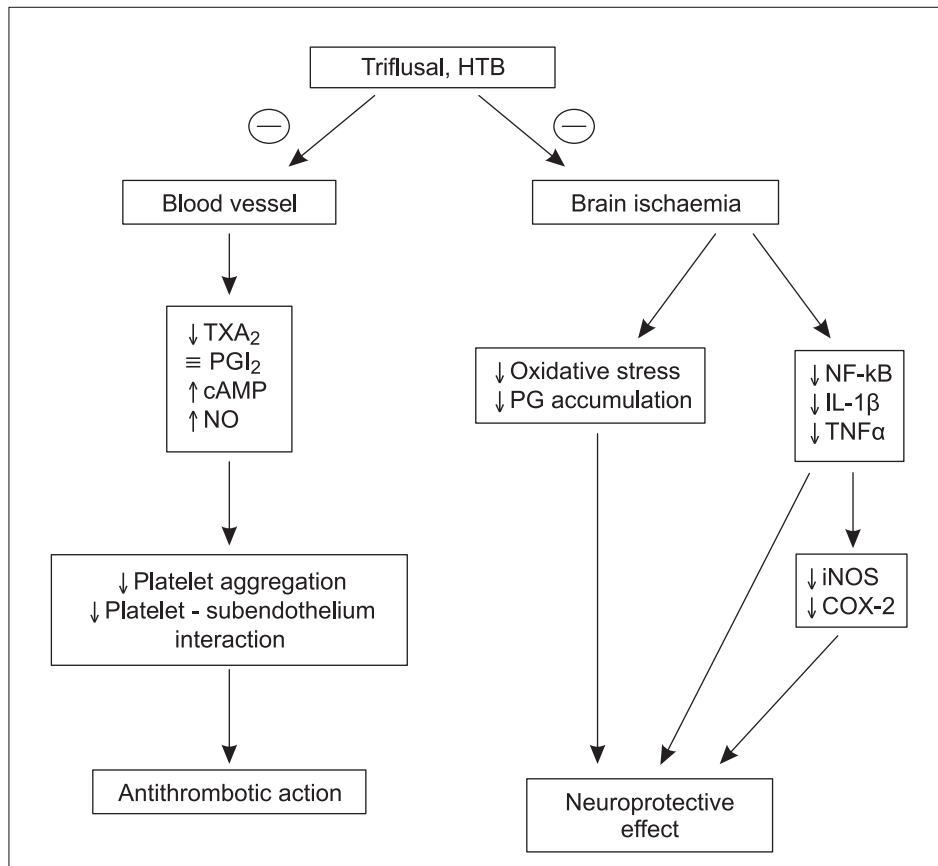
Figure 2. Antithrombotic and neuroprotective properties of triflusal.

Clinical trials

Several studies have been designed and conducted to evaluate the clinical efficacy and safety of novel antiplatelet medication in different clinical settings. The TIM study was undertaken to determine whether triflusal provides an efficacy advantage over aspirin in the prevention of vascular complications following acute myocardial infarction (AMI) and to qualify the relative safety benefit of the two drugs. It was a double blinded, randomised sequential parallel group study carried out at 29 centres in Spain, Portugal and Italy, in which 2275 patients with established AMI were randomised to receive either triflusal 600 mg/day or aspirin 300 mg/day for 35 days starting within the first 24 h after the onset of symptoms. The primary endpoint was a composite of death or non-fatal MI or non-fatal cerebrovascular event within 35 days. Secondary endpoints were defined individually as the incidence of death, non-fatal re-infarction, non-fatal cerebrovascular event, or urgent revascularisation procedure in the same period. Drug tolerability and safety, with particular regard to bleeding episodes, were also assessed.[63] There were no significant differences between treatments in the primary endpoints, the risk of death, non-fatal MI or revascularisation procedures. The risk of non-fatal cerebrovascular events was significantly lower with triflusal (63% less compared to aspirin). As far as adverse effects are concerned, the most frequently affected system was the gastrointestinal tract and the central and peripheral nervous system, with a similar incidence in both treatment groups. However, triflusal was associated with a lower incidence of central nervous system bleeding (p=0.033) and with a non-significant trend towards less frequent bleeding in all organs (p=0.09).[63]

The TACIP study, a randomised, double blinded multi-centre trial, enrolled 2113 patients over 40 years of age with transient ischaemic attacks (TIA) or non-disabling stroke of neither haemorrhagic nor cardioembolic nature in the past 6 months. They were randomised to receive triflusal 600 mg/day or aspirin 325 mg/day for no less than 1 year and up to 3 years. Prima-

ry endpoints included vascular death, non-fatal ischaemic stroke or non-fatal MI. Secondary events were the occurrence of these events separately, as well as overall mortality, non-vascular death, non-fatal or any ischaemic stroke, non-fatal or any MI, any cerebral haemorrhage, and major systemic haemorrhage (requiring blood transfusion or hospital admission). No significant differences were noted with regard to the primary or secondary endpoints, except for the incidence of bleeding episodes: 2.9% of aspirin and 1.2% of triflusal recipients reported at least one major systemic haemorrhage, while 4% in the aspirin group and 1.9% in the triflusal group suffered cerebral or major systemic haemorrhagic episodes. Patients treated with aspirin showed a significantly higher overall incidence of bleeding adverse events (25% vs. 15.2%).[14] Notably, the 95% confidence intervals calculated for the relative effect of triflusal compared to aspirin were wide and thus the study would not show a superior efficacy of any treatment option; instead it documents that a substantial difference is unlikely.[14]

The TAPIRSS study was a multi-centre, double blinded, randomised, parallel group pilot clinical trial to develop data sufficient to conduct a larger trial in Latin America. Four hundred and thirty-one patients were recruited in 19 centres in Argentina among individuals 40 or more years old with TIA or established non-disabling cerebral infarction, non-haemorrhagic and non-cardioembolic, in the previous 6 months. The patients were randomly assigned to receive triflusal 600 mg/day or aspirin 325 mg/day for a mean of 586 days. Primary endpoints included vascular death, non-fatal ischaemic stroke, non-fatal MI or major bleeding; secondary outcome events were the occurrence of each of the above separately, as well as minor bleeding, non-vascular death or systemic thromboembolism. Follow up extended from 1 to 2 years. No significant differences were observed in terms of either primary or secondary endpoints; although in the triflusal group there were significantly more non-lacunar/large vessel infarcts, which are associated with a higher incidence of recurrence that reaches 9% annual risk compared to 6.1% for lacunar defects. However, the triflusal treated patients showed a favourable trend in bleeding events, with 0.5% major and 2.3% minor haemorrhages in comparison to 3.2% and 6%, respectively, in the aspirin group. In a *post hoc* analysis, all bleeding episodes were significantly more frequent in aspirin-treated subjects, the gastrointestinal tract being the dominant affected system.[15]

In primary prevention, triflusal's usefulness has been evaluated in preventing embolism in cases of atrial fibrillation (AF). The NASPEAF study compared the efficacy of triflusal 600 mg/day alone, in combination with acenocoumarol (INR 1.25-2.4), or acenocoumarol alone (INR 2-3), in patients with chronic or paroxysmal AF. Individuals at high risk of stroke (non-valvular AF with antecedents of embolism, mitral stenosis) received acenocoumarol or the combination of the two drugs. The primary endpoint was a composite of vascular death, TIA, non-fatal stroke, or systemic embolism. In the intermediate risk group the incidence of the primary endpoint was significantly lower with the combined therapy than with triflusal or acenocoumarol alone (0.92% vs. 3.8% vs. 2.7%, respectively). In the group of high-risk patients the combination was again more effective, showing a 2.44% incidence of the primary endpoint, compared to 4.7% in the acenocoumarol alone arm.[64] Another study comparing triflusal (600 mg/day) with acenocoumarol (INR 2-3) over an endpoint including thromboembolism, severe haemorrhage, or death related to vascular disease, in subjects undergoing aortic or mitral valve replacement with bioprostheses, failed to document any significant differences after a follow up of 30 days.[17]

In individuals undergoing coronary artery bypass grafting, 9 days' postoperative angiographic evaluation showed no significant difference in the rate of vein graft occlusion between aspirin 50 mg and triflusal 300 mg, both administered in combination with dipyridamole 75 mg three times a day. Nevertheless, re-evaluation after 6 months disclosed that the combination incorporating triflusal was superior in terms of maintaining vein graft patency.[65]

In a prospective, randomised, double-blind study with 459 patients operated on for a hip fracture and receiving unfractionated heparin, triflusal 300 mg and aspirin 200 mg thrice daily appeared equally affective in preventing deep vein thrombosis (DVT) or pulmonary embolism. Similar results regarding DVT incidence were obtained from another small randomised, double-blind trial enrolling 99 patients who received 250 mg of aspirin or 300 mg of triflusal 3 times a day after hip surgery.[66,67]

Adverse reactions/tolerability

Traditionally, antiplatelet drugs have been associated with an increased risk of bleeding complications. Aspirin increases the risk of severe extracranial haemorrhage by approximately 50%.[68,69] This is equivalent to

1-2 severe bleeding episodes per 1000 patients per year and 1-2 haemorrhagic strokes per 10,000 patients per year.[70]

The clinical trials evaluating triflusal's efficacy and safety showed that the rates of withdrawal and the incidence of side effects did not differ significantly between study groups, but the severity of the adverse events deserves further discussion. Major systemic haemorrhages were significantly lower with triflusal administration compared to aspirin.[14,15,63] This reduction was also evident in individuals receiving fibrinolytic therapy.[63] As expected, triflusal appears safer with regard to haemorrhagic events compared to acenocoumarol (INR 2-3) or the combination of the two (INR 1.25-2.4).[64] A meta-analysis by Costa et al[71] revealed that, although the frequency of non-haemorrhagic complications (abdominal pain, dyspepsia, peptic ulcer) was significantly higher in patients treated with triflusal, the incidence of haemorrhagic complications (fatal or non-fatal haemorrhagic stroke, intracranial or major systemic haemorrhage) was significantly lower than in aspirin-treated patients. In terms of gastrointestinal complaints, which were the most widely reported, dyspepsia was more frequent among triflusal-receiving participants, while peptic ulcer was reported mainly by aspirin recipients.

Usually, individuals on antiplatelet medication are also receiving other drugs for concomitant conditions; these complicate therapy and make the evaluation of drug interactions necessary, but difficult. Unlike aspirin, triflusal is less likely to interfere with the efficacy of antihypertensive drugs, especially angiotensin converting enzyme inhibitors, as suggested by data from the TACIP study.[14] However, HTB interacts with the serum protein binding of other pharmacological agents (non-steroidal anti-inflammatory drugs, glisentide, warfarin) to the same degree as aspirin, so that precautions must be taken when triflusal is used in combination with these substances.[72,73]

Conclusions

Current clinical practice with regard to antiplatelet therapy is highly demanding. This is not only a direct consequence of the high prevalence of cardiovascular diseases, but it is also a result of the realisation of the importance of platelet activity in the pathogenesis of the so-called atherothrombotic procedure. In the light of evolving, long-awaited new antithrombotic drugs that will shortly claim a role in everyday clinical practice, we ought to also take into consideration the established effectiveness of older drugs. Moreover,

the demographic changes in our population emphasise the need for safer drugs, given that the side effects of antiplatelet medications are even more prominent in elderly people, who represent the main candidates for such treatments. Triflusal is an antiplatelet agent that is chemically related to aspirin and has similar effectiveness, but appears to have a better tolerability profile. Empirical data and results from large-scale clinical trials suggest that its use may be preferable to that of aspirin, in several clinical settings where antiplatelet therapy is indicated. In selected populations, such as in geriatric patients or in cases of aspirin resistance, triflusal may be a choice worth considering. Furthermore, when combination antiplatelet-fibrinolytic or antiplatelet-anticoagulant therapy is needed, clinical data support triflusal use based on its efficacy and better safety than aspirin.

Although more large scale trials comparing antiplatelet drugs in various clinical settings would be useful in the effort to determine each agent's particular role in therapeutics, use of triflusal where indicated is an attractive therapeutic option, especially when safety and cost-effectiveness are prioritised.

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