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Triflusal

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Contents

Summary

▲ Triflusal is an antiplatelet agent structurally related to the salicylate group of compounds, but it is not derived from aspirin (acetylsalicylic acid). Platelet antiaggregant properties of triflusal and its active 3-hydroxy-4-trifluoro-methylbenzoic acid metabolite are primarily mediated by specific inhibition of platelet arachidonic acid metabolism.

▲ Triflusal, compared with placebo for 6 months, significantly reduced the incidence of nonfatal myocardial infarction in patients with unstable angina.

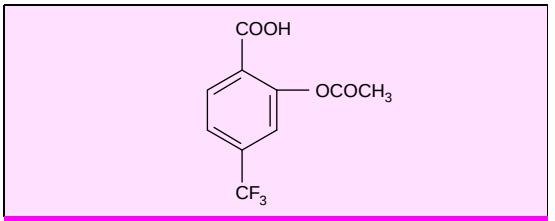
▲ In patients with peripheral arteriopathy, total and pain free walking distances were markedly improved in triflusal compared with placebo recipients.

▲ The cumulative event rate for stroke, ischemic cardiopathy and vascular death was lower, but not significantly different, in patients with atherothrombotic stroke who received triflusal than in aspirin recipients. Differences were significant, and favoured triflusal, in a subgroup of patients with >70% carotid stenosis.

▲ Prophylaxis with triflusal for 6 months after aortocoronary vein grafting reduced the number of new distal anastomosis occlusions and the graft attrition rate more than aspirin or placebo. The incidence of deep vein thrombosis or pulmonary embolism in more than 500 patients undergoing hip surgery was similar for these 3 treatments.

▲ The amount of blood transfused was significantly reduced in triflusal compared with aspirin recipients who underwent hip surgery. Risk of haemorrhage was also reduced in ischemic stroke patients receiving triflusal versus aspirin.

Features and properties of triflusal	
Indications	
Prevention and/or treatment of vascular thromboembolism	Launched
Mechanism of action	
Platelet antiaggregant	Inhibition of platelet arachidonic acid metabolism; stimulation of platelet cAMP production
Dosage and administration	
Usual dosage in clinical trials	300mg 2-3 times daily
Route	Oral
Pharmacokinetic profile (single 900mg dose)	
Peak plasma concentration	Triflusal: 11.6 mg/L 3-Hydroxy-4-trifluoro-methylbenzoic acid (HTB): 92.7 mg/L
Time to peak plasma concentration	Triflusal: 0.88h HTB: 4.96h
Clearance	Triflusal: 45.4 L/h HTB: 0.18 L/h
Terminal elimination half-life	Triflusal: 0.53h HTB: 34.29h
Adverse events	
Most frequent	Gastric pain, vomiting, nausea, erythema



Triflusal

1. Pharmacodynamic Profile

Triflusal is structurally related to the salicylate group of compounds.[1] Although it is not derived from aspirin (acetylsalicylic acid), triflusal does have an antiaggregant effect on platelets; however, the mechanisms of action for these 2 compounds are thought to differ in some respects (fig. 1). In the clinical setting, aspirin is considered the 'gold standard' for inhibition of platelet aggregation; therefore, where appropriate, triflusal has been discussed in comparison with aspirin.

Selective Effects on Platelet Arachidonic Acid Metabolism

• *In vitro* and *ex vivo* studies in healthy volunteers,[2] patients with type 1 diabetes[3] and patients with prosthetic heart valves[4] revealed that thromboxane B_2 (TxB_2) production was significantly reduced by both triflusal and aspirin. In 25 volunteers who received triflusal 600 to 900 mg/day or aspirin 500 mg/day for 7 days, basal TxB_2 levels were significantly decreased 2 hours after initial drug administration by approximately 25% for triflusal ($p < 0.05$) and by >90% for aspirin; this degree of inhibition with aspirin was maintained for the duration of the study ($p < 0.01$; from graph). By day 7, TxB_2 levels were reduced by approximately 85% with triflusal.[2]

• Ten days after treatment withdrawal, TxB_2 levels remained 35 to 40% below basal levels with triflusal 600 to 900 mg/day ($p < 0.05$ for 900 mg/day) and 20% below with aspirin 500 mg/day;[2] TxB_2 levels returned to within 10% of basal levels 30 days after triflusal 900 mg/day withdrawal.[4] These data indicate that triflusal, like aspirin, inhibits arachidonic acid metabolism in platelets (see fig. 1).

• In patients with type 1 diabetes, serum levels of TxB_2 were greatly reduced with both triflusal and aspirin after 15 days (by 85 and 99%; $p < 0.05$). However, reductions in serum 6-keto-prostaglandin-$F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) levels were negligible with triflusal compared with aspirin (8.8 *vs* 97.8%; $p < 0.001$) [fig. 2].[3] These data suggest that triflusal has selective activity for platelet arachidonic acid metabolism, whereas aspirin inhibits both platelet and vascular endothelial arachidonic acid metabolism (see fig. 1).

• The mean concentrations of triflusal required to produce 50% inhibition (IC_{50}) of TxB_2 and 6-keto-$PGF_{1\alpha}$ *in vitro* were similar (0.47 and 0.34 mmol/L). However, for the active triflusal metabolite (3-hydroxy-4-trifluoro-methylbenzoic acid; HTB), the IC_{50} value for TxB_2 was about 3.5 times less than that for 6-keto-$PGF_{1\alpha}$ (1.32 and 4.73 mmol/L).[5] Triflusal was therefore more potent than HTB, but aspirin was more potent than either of them: aspirin IC_{50} values were 0.00033 mmol/L for 6-keto-$PGF_{1\alpha}$ and 0.0009 mmol/L for TxB_2.

Effects on Platelet Aggregation

In Platelet Rich Plasma

• *In vitro* in human platelet rich plasma (PRP), IC_{50} values for the inhibition of platelet aggregation induced by arachidonic acid (0.8 to 1 mmol/L) ranged from 0.7 to 0.8 mmol/L for triflusal and 0.06 to 0.11 mmol/L for aspirin.[2,5] With HTB, 1 study reported an IC_{50} value of 2.33 mmol/L;[5] in another, 80% inhibition was achieved with 4 mmol/L.[2] The aspirin metabolite, salicylic acid, was the least effective compound: it produced 10% inhibition at 4 mmol/L and <50% at 5 mmol/L.

• *Ex vivo* in human PRP, 65% inhibition of arachidonic acid-induced (0.05 mmol/L) platelet aggregation was apparent 24 hours after a single 600mg dose of triflusal ($p < 0.05$).[2] Repeated administration of triflusal (600mg daily for 7 days) resulted in 50 to 75% inhibition of platelet aggregation induced by arachidonic acid (0.5 to 1

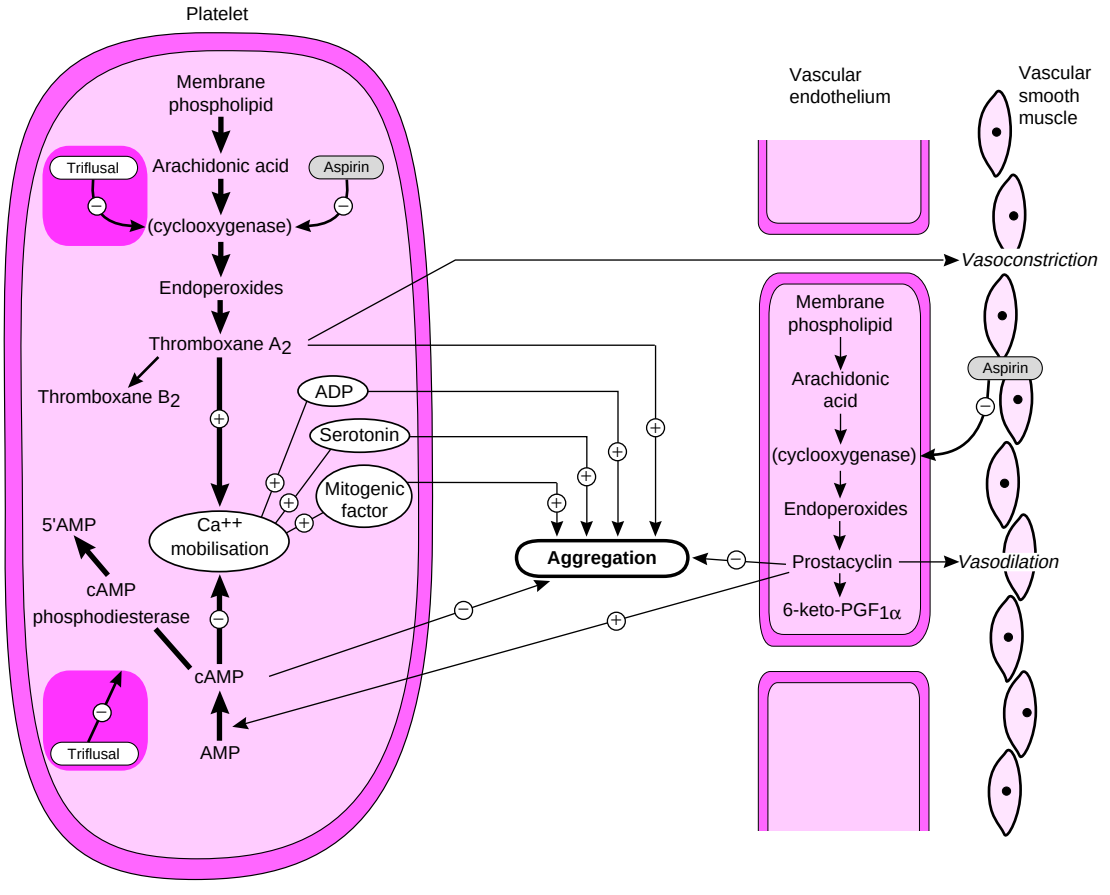


Fig. 1. Schematic representation (not to scale) of the interaction of platelet aggregating factors located in platelets and the vascular endothelium, and the sites of action for triflusal and aspirin. *Abbreviations and symbols:* 6-keto-$PGF_{1\alpha}$ = 6-keto-prostaglandin-$F_{1\alpha}$; ADP = adenosine diphosphate; AMP = adenosine monophosphate; cAMP = cyclic AMP; Ca^{++} = calcium ions; + = stimulation; – = inhibition.

mmol/L), adenosine diphosphate (ADP; 2 μmol/L), epinephrine (adrenaline; 5 μmol/L) and collagen (5 to 10 mg/L). Ten days after treatment cessation, inhibition was significant for stimulation with arachidonic acid 0.5 mmol/L only ($p < 0.05$ *vs* baseline), otherwise platelet response was fully recovered.

In Whole Blood

- *Ex vivo*, in blood from volunteers who received triflusal 600 mg/day or aspirin 400 mg/day for 15 days, ADP-induced platelet aggregation was reduced by 24.3% with triflusal and 9.8% with aspirin ($p < 0.005$ *vs* aspirin). Collagen-induced platelet aggregation was reduced by 78.7% with triflusal and 95.7% with aspirin (both $p < 0.005$ *vs* baseline).[6]

- *In vitro* in whole human blood, IC_{50} values for the inhibition of arachidonic acid (1 mmol/L)-induced platelet aggregation were 0.048, 0.2 and 0.0009 mmol/L, respectively, for triflusal, HTB and aspirin; salicylic acid induced a <20% inhibition at 5 mmol/L.[5] At these concentrations triflusal and aspirin did not inhibit platelet aggregation in PRP, which suggests that red blood cells may enhance the antiaggregant properties of these agents.[5]

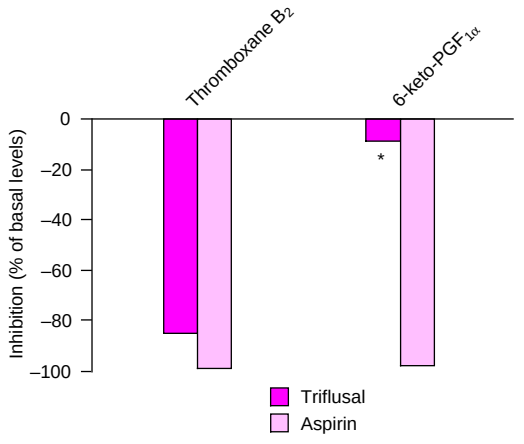


Fig. 2. Inhibition of serum thromboxane B_2 and 6-keto-prostaglandin-$F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) levels after 15 days' therapy with triflusal 600 mg/day or aspirin 400 mg/day in patients with type 1 diabetes.[3] * $p < 0.001$ *vs* aspirin.

• In 13 healthy volunteers who received twice-daily triflusal 300mg for 15 days, *ex vivo* inhibition of platelet aggregation was significantly different in whole blood and PRP ($p < 0.001$):[7] the potency ratios of whole blood : PRP were 10.6, 3.1, 1.8 and 1.3, respectively, against platelet aggregation induced by ADP, epinephrine, collagen and arachidonic acid.[7] Results were similar in blood from patients with type 1 diabetes:[3] the inhibitory effects of triflusal on induced platelet aggregation were 30 to 50% less in PRP than in whole blood; aspirin was 10 to 65% less effective in PRP than in whole blood (fig. 3).

• HTB >37.5 μmol/L appears to enhance the platelet antiaggregant effect of triflusal:[7] the IC_{50} value for triflusal against collagen-induced human platelet aggregation decreased from 82 μmol/L to 42, 25 and 4.4 μmol/L, respectively, in the presence of 75, 150 and 500 μmol/L HTB.[7]

Effects on Platelet-Subendothelial Interactions

• Blood taken from volunteers who received triflusal 600 mg/day or aspirin 400 mg/day for 15 days was subsequently used to compare the effects of the drugs on platelet-subendothelium interactions in perfusion studies with rabbit aortic preparations.[6] Both triflusal and aspirin significantly ($p < 0.01$) reduced subendothelial platelet coverage compared with pretreatment values (by 92.1 and 61.3%; $p < 0.05$ *vs* aspirin).

• *In vitro*, thrombus formation on rabbit vascular subendothelium was significantly reduced by 47, 18 and 56%, respectively, by human blood preincubated with triflusal (1 mmol/L), HTB (1 mmol/L) or aspirin (0.05 mmol/L) [$p < 0.05$ *vs* control for all agents];[6] corresponding reductions in platelet coverage of the tissue were 57, 49 and 45% ($p < 0.01$ *vs* control). Adhesions (platelets spread and firmly bound onto the subendothelium, forming layers <5 μm high) were reduced by 25% with triflusal or HTB ($p < 0.05$ *vs* control) and by 1% with aspirin. Contacts (platelets attached but not spread onto the subendothelium) were increased by 55 and 42% for triflusal and HTB ($p < 0.01$ *vs* control) and by 25% for aspirin. Salicylic acid did not inhibit any of the platelet interactions.

Effects on Nitric Oxide Production and Platelet Cyclic AMP Metabolism

• In human PRP, neutrophils were required to achieve a dose-related inhibition of thrombin-induced platelet activation with triflusal or aspirin (0.15 to 5 mmol/L).[8] At a concentration of 3.3 mmol/L for each drug, triflusal was significantly more potent than aspirin (61 *vs* 43% inhibition; $p < 0.05$).[9] Preincubation of neutrophils with N^w-Nitro-L-arginine methyl ester (L-NAME), which inhibits nitric oxide production, reduced the antiaggregant effects of triflusal and aspirin *in vitro* by about 55 and 45%, respectively (results presented graphically).[8]

• The production of [^{3}H]L-citrulline in [^{3}H]L-arginine–loaded neutrophils (an indicator of nitric oxide production) was significantly stimulated by 3.3 mmol/L triflusal or aspirin (by 150 and 60%; $p < 0.05$ *vs* basal level).[8] HTB alone or in combination with aspirin had no effect on [^{3}H]L-citrulline accumulation. Basal levels of cyclic GMP (18

pmol/L) were increased to ≈88, ≈50 and ≈23 pmol/L by triflusal, aspirin and HTB, respectively ($p < 0.05$ *vs* basal level; results presented graphically).[8]

- *Ex vivo*, in neutrophils isolated from 7 healthy volunteers after triflusal 600 mg/day for 4 days, [^{3}H]L-citrulline production was significantly increased compared with baseline by 38.5% ($p < 0.05$).[9]

- In *in vitro* animal studies, triflusal was 5 times more potent than aspirin at inhibiting cyclic AMP (cAMP) phosphodiesterase.[10] Inhibition of this enzyme leads to an increase in platelet cAMP levels and thus a decrease in calcium mobilisation and subsequent platelet aggregation (see fig. 1).

- At therapeutic concentrations (1 mmol/L) HTB increased basal levels of cAMP in washed rat platelets more than triflusal (49 and 36%; $p < 0.01$ *vs* control for triflusal);[11] at 5 mmol/L, compared with control, increases in cAMP levels were 102% for HTB ($p < 0.02$) and 76% for triflusal ($p < 0.01$). At 5 mmol/L, aspirin and salicylic acid did not significantly increase basal cAMP levels (0 and 34%).

The differences in nitric oxide production and cAMP metabolism exhibited by triflusal and aspirin may account for their different antiaggregant potencies *in vitro*.

Effects on Bleeding Time

- In a comparative study in healthy volunteers, bleeding time was not significantly different from basal levels after 3 to 7 days of placebo or triflusal 600 to 900 mg/day;[2] after aspirin 500 mg/day, however, bleeding time was increased by approximately 80% ($p < 0.01$ *vs* basal and triflusal levels).[2]

Effects on Cerebrovascular Occlusion

- In rats, single-dose oral administration of triflusal or aspirin 50 mg/kg protected 33 and 38% of animals from arachidonic acid-induced cerebrovascular occlusion.[12] Repeated administration (once daily for 5 days) significantly increased the rate of protection in the triflusal compared with the aspirin group (60 *vs* 27%; $p < 0.01$).

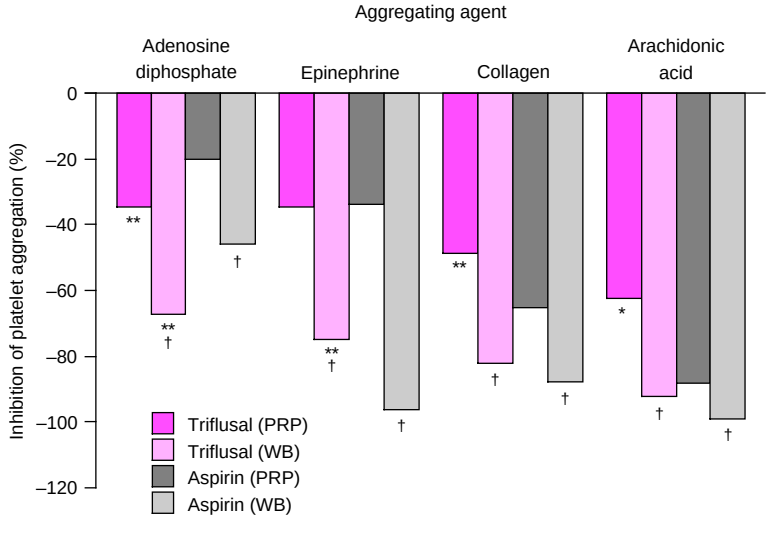


Fig. 3. *Ex vivo* inhibition of platelet aggregation induced by a variety of agents in human platelet rich plasma (PRP) or whole blood (WB) from patients with type 1 diabetes who received triflusal 600 mg/day or aspirin 400 mg/day for 15 days.[3] *Symbols:* * $p < 0.05$, ** $p < 0.01$ *vs* aspirin; † $p < 0.05$ *vs* PRP.

• Formation of microthrombi subsequent to experimentally induced brain ischemia was significantly reduced in rats given triflusal 12.5 to 50 mg/kg/day for 6 days after surgery ($p < 0.002$ *vs* placebo[13] but $p < 0.05$ *vs* sham operation[14]). Aspirin also reduced microthrombus formation at 12.5 and 25 but not 50 mg/kg/day ($p < 0.05$ *vs* sham operation).[14]

2. Pharmacokinetic Profile

• Oral triflusal is rapidly metabolised and eliminated from the plasma.[15-17] Therefore, most of the available pharmacokinetic data pertain to the active HTB metabolite.

• In 8 healthy volunteers (mean age 27 years) who received a single 900mg oral dose of triflusal, mean maximum plasma concentrations (C_{max}) of triflusal and HTB were 11.6 and 92.7 mg/L.[17] The time to C_{max} was much shorter for the parent compound than the metabolite (0.88 *vs* 4.96 hours). However, both compounds were detectable in the plasma at similar time intervals after triflusal administration (t_{lag}; 0.23 and 0.31 hours for triflusal and HTB) which suggests a rapid biotransformation of the parent compound.[17]

• An absorption half-life ($t_{½}Ka$) of 0.44 hours and a terminal elimination half-life ($t_{½\beta}$) of 0.53 hours for triflusal indicate that the parent compound is rapidly absorbed and eliminated; the corresponding values for HTB were 2.44 and 34.29 hours. The area under the concentration-time curve $(AUC)_{\infty}$ value was 20.26 mg/L · h for triflusal 900mg and 4227 mg/L · h for HTB. There was also a large difference between triflusal and HTB with respect to volume of distribution and clearance parameters:[17] these values were 34L and 45.4 L/h for triflusal and 8.96L and 0.18 L/h for HTB.

• There was no plasma accumulation of the parent compound in elderly volunteers (mean age 80 years) after 13 days' administration of twice-daily triflusal 300mg.[15] However, C_{max} values of the active metabolite increased significantly from day 1 to day 13 (39.88 *vs* 120.42 mg/L; $p < 0.001$) with an accumulation factor of 6.64.[15] Similar results were seen in young volunteers (mean age 23 years) who received triflusal 300mg every 8 hours for 13 days: C_{max} values for HTB were 36.4 mg/L on day 1 and 177.8 mg/L on day 13 with an accumulation factor of 6.35 (no statistical analysis provided).[16] C_{max} values for HTB also increased (to 152.9 mg/L) after 13 days' triflusal 600mg every 24 hours in the young volunteers, however, the accumulation factor was reduced (2.77).[16]

• In elderly volunteers, steady-state plasma HTB concentrations (mean 102.21 mg/L) were attained after 4 to 5 days' administration of twice-daily triflusal 300mg therapy;[15] peak and trough plasma concentrations ranged from 114.64 to 93.70 mg/L with this 12-hour dosing regimen.[15] In younger volunteers, mean steady-state plasma HTB concentrations were 168 mg/L with triflusal 300mg every 8 hours and 123 mg/L with triflusal 600mg every 24 hours.[16] Peak and trough variations were about 10 mg/L with the 8-hour dosing regimen and about 30 mg/L with the 24-hour dosing regimen.

• Mean HTB AUC values after a single 300mg dose of triflusal were 1624 mg/L · h in young[16] and 2156 mg/L · h in elderly volunteers.[15] After 13 days' therapy in young volunteers, the mean steady-state AUC values for HTB were 1301 mg/L · h with triflusal 300mg every 8 hours and 2924 mg/L · h with once-daily triflusal 600mg.[16] In the elderly, the mean HTB AUC value was 1226 mg/L · h with twice-daily triflusal 300mg.[15]

• The $t_{½\beta}$ values for HTB were similar in the elderly[15] and in the young[16] and after single (300mg) or repeated (600 to 900 mg/day for 13 days) administration of triflusal:[15,16] reported values ranged from 44.5 to 54.6 hours.[15,16]

3. Therapeutic Trials

Effects in Cardiovascular Disease

• In patients (mean age 59 years) with unstable angina, the occurrence of nonfatal myocardial infarction was significantly reduced in those randomised to receive triflusal 300mg (n = 143)

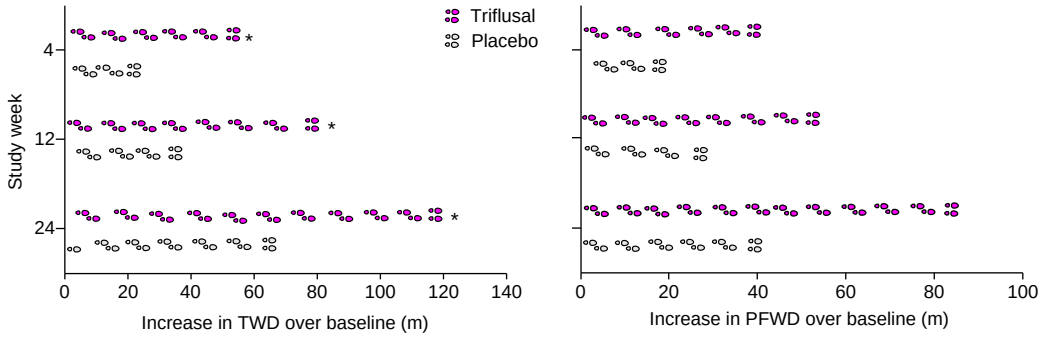


Fig. 4. The effect of 24 weeks of triflusal 600 mg/day (n = 59) or placebo (n = 63) on total walking distance (TWD) and pain free walking distance (PFWD), assessed as increase over baseline distance, in patients with chronic peripheral arteriopathy.[21] *Symbol:* * p = 0.05 *vs* placebo.

compared with placebo (n = 138) 3 times daily for 6 months (4.2 *vs* 12.3%; p < 0.013).[18] The cardiac or vascular death rate was low (2 from the triflusal group and 0 from the placebo group; statistical analysis not practical). In addition, there was no significant difference in the number of patients requiring revascularisation (16.8% for triflusal and 20.3% for placebo).

- In a nonrandomised study, 352 patients with atrial fibrillation, myocardiopathy or postinfarct anterior aneurysm received triflusal 600 mg/day therapy for a mean of 12.48 months, and 69 received dicoumarol (dosage determined by prothrombin time) for 24.6 months (p < 0.05 *vs* triflusal group).[19] The percentage of systemic embolisms/patient/year was significantly less in the triflusal than dicoumarol group (0.96 *vs* 2.16; p < 0.05). A total of 8 embolisms were recorded: the 3 in the triflusal group occurred within the first 8 weeks of switching from dicoumarol to triflusal, or starting triflusal therapy. Although there was no significant difference between the groups regarding the incidence of atrial fibrillation, the follow-up time (duration of therapy) and percentage of patients with previous embolisms (15.29 *vs* 32.17%; p < 0.01) were significantly greater in the dicoumarol group.

- In a second, similar study in patients with mitral valve disease, 190 patients received triflusal 600 mg/day and 119 received dicoumarol (dosage determined by prothrombin time) for respective mean durations of 14.3 and 22.7 months.[20] Three of the 4 embolisms reported occurred in the triflusal group; the percentage of embolism/patient/year was 1.44% for triflusal and 0.36% for dicoumarol (no p value provided). The percentage of patients with atrial fibrillation (86.92 *vs* 49.45%; p < 0.05) or previous embolisms (47.7 *vs* 13.6%; p < 0.01) was significantly greater in the dicoumarol group, as was the follow-up time (p < 0.05).

Effects in Peripheral Vascular Disease

- In a 24-week randomised, double-blind trial, triflusal 600 mg/day (n = 59) compared with placebo (n = 63) markedly improved total (TWD) and pain free (PFWD) walking distances and clinical symptoms (paraesthesia, sense of heaviness and sense of cold) in patients (mean age 64 years) with chronic obliterative peripheral arteriopathy.[21] Overall success, defined as ≥40% increase in baseline TWD, was achieved in 63.6% of triflusal and 22.5% of placebo recipients. Continuous improvements in TWD and PFWD were observed throughout the treatment period (fig. 4): after 24 weeks, mean TWD had improved by 120.9m over basal distance in triflusal recipients and by 67.7m in placebo recipients (p = 0.05 *vs* placebo; fig. 4). The corresponding, statistically nonsignificant, increases over basal PFWD were 87.7m and 40.9m (fig. 4).

- In patients with chronic obliterative peripheral arteriopathy, the mean 'sum of symptoms' scores

were reduced by 61 and 27% with triflusal and placebo (p = 0.003).[21] However, there were no significant differences between the treatments with respect to reduction in the 'sum of signs' (colour, thermotaxis, tibial pulse) scores, or the Winsor index. Time required to recover from the treadmill tests was similar in both groups and did not improve significantly during the treatment period.

Effects in Cerebrovascular Disease

- In 217 patients (mean age 43 years) with atherothrombotic stroke, the cumulative event rate for stroke, ischemic cardiopathy and vascular death was lower, but not significantly different, in those receiving triflusal 900 mg/day for a mean 48.3 months than in aspirin 330 mg/day recipients for a mean 46.3 months (19.8 *vs* 28.8%).[22,23] The corresponding rates in a subgroup of patients (n = 70) with >70% carotid stenosis were 38.1 and 67.9% (p < 0.05).[22]

- Recurrent cerebrovascular attacks were prevented in 92.6% of 110 patients receiving triflusal 600 mg/day and 94% of 111 receiving aspirin 300 mg/day over a mean period of 47 months.[24]

- Triflusal 600mg/day for 12 months compared with control, significantly reduced cognitive deterioration in a total of 73 patients with vascular dementia.[25] In patients who completed 12 months' treatment, negative response (≥10% reduction in Cognitive Mini Examination score) was recorded in 3 of 35 (8%) triflusal recipients and 8 of 24 (33%) of those receiving no treatment (p = 0.0375)

Prophylactic Use after Cardiovascular or Orthopaedic Surgery

- In a randomised, double-blind, placebo-controlled study in patients undergoing aortocoronary vein grafting, there was no difference in the angiographic parameters assessed 9 days after surgery in 161 patients who received triflusal 300mg plus dipyridamole 75mg, aspirin 50mg plus dipyridamole 75mg, or placebo 3 times daily.[26] Reassessment in 138 of the patients after 6 months' continued treatment revealed fewer new distal anastomosis occlusions in the triflusal group (2.6%) compared with the aspirin (10%) or placebo (12%) groups (p = 0.056). In addition, the graft attrition rate was lower in patients receiving triflusal than aspirin or placebo: the respective number of new graft occlusions at 6 months was 1, 9 and 12% (p = 0.04).

- In a retrospective study,[27] the number of postoperative complications (defined as acute myocardial infarction, death or emergency surgery) in 197 patients who underwent percutaneous transluminal coronary angioplasty was significantly less with antiplatelet therapy (either 300mg triflusal 3 times daily or 330mg aspirin plus dipyridamole 75mg 3 times daily at least 48 hours before surgery) than without it (9.1 *vs* 23.1% within 48 hours of the procedure; p < 0.01). There was no significant difference between triflusal or aspirin treatment with respect to the number of complications reported (8.3 *vs* 10.0%).

- Two studies in more than 500 patients undergoing hip surgery revealed no significant difference in the incidence of deep vein thrombosis (DVT)[28,29] or pulmonary embolism[29] with triflusal 300mg, aspirin 200[29] or 250mg[28] or placebo[29] given 3 times daily for 15[28] or 18[29] days postoperatively. Triflusal was given 12 hours before surgery (except in patients with hip fracture[29]), whereas aspirin and placebo were given immediately after surgery.[28,29] In addition, in the placebo-controlled study all patients received heparin 7500IU 2 hours before surgery and every 12 hours for 10 days afterwards.[29] Rates of DVT were about 14% for triflusal,[28,29] 18[29] or 22%[28] for aspirin and 18% for placebo.[29] The incidence of pulmonary embolism was 5% for aspirin or placebo and 2% for triflusal.[29]

Other Effects

- Ophthalmological evaluation during 2 years' therapy in patients with type 1 diabetes revealed that, compared with control (n = 8), triflusal 900 mg/day (n = 9) significantly reduced the number of

microaneurysms (21% decrease *vs* 129% increase from baseline; $p < 0.025$) and degree of colorant leakage (-0.5 *vs* +0.5 on a scale of 1 to 4; $p < 0.02$).[30] There was no difference between the groups with respect to percent variation in visual acuity (10 *vs* 6.5% increase) or the computerised perimetry (28% decrease *vs* 6.2% increase).

• Triflusal 900 mg/day for 5 days significantly decreased baseline microalbuminuria (from 59 to 33 μg/min; $p < 0.01$) and increased renal plasma flow rate (from 648 to 722 ml/min; $p < 0.005$) in 9 normotensive patients with type 1 diabetes.[31] This suggests a protective effect of the drug in diabetic nephropathy.

4. Tolerability

• In the studies reviewed, up to 15% of triflusal recipients reported adverse events;[18,26,29] the most common were nausea, vomiting, gastric and epigastric pain and erythema. The incidence of adverse events was significantly greater in triflusal than placebo recipients ($p < 0.05$) in 2 studies[26,29] but not in 2 others.[18,21] In addition, the incidence of adverse events was similar in triflusal and aspirin recipients.[26,29]

• Three to 5% of triflusal recipients stopped therapy because of gastric intolerance (3.5%), conjunctival haemorrhage and epistaxis (1.4%)[18] or vomiting (2.6%);[29] 4% of placebo recipients withdrew because of severe epigastric burning, and skin reaction.[18]

Bleeding Complications

• In patients with prosthetic heart valves, a mean pretreatment bleeding time of 6 minutes was increased by 2 minutes (33%) after 30 days' triflusal 900 mg/day therapy ($p < 0.05$), but returned to pretreatment time 1 month after therapy ceased.[4]

• Significantly more patients with atherothrombotic stroke receiving aspirin 330 mg/day (n = 106) than triflusal 900mg/day (n = 111) reported haemorrhagic events (10.8 *vs* 2.8%; $p < 0.05$):[22] gastrointestinal haemorrhage occurred in 4.5 and 0.9%, intracranial haemorrhage in 3.6 and 0.9% and 'other' haemorrhages in 2.7 and 0.9% of patients, respectively, receiving aspirin and triflusal.

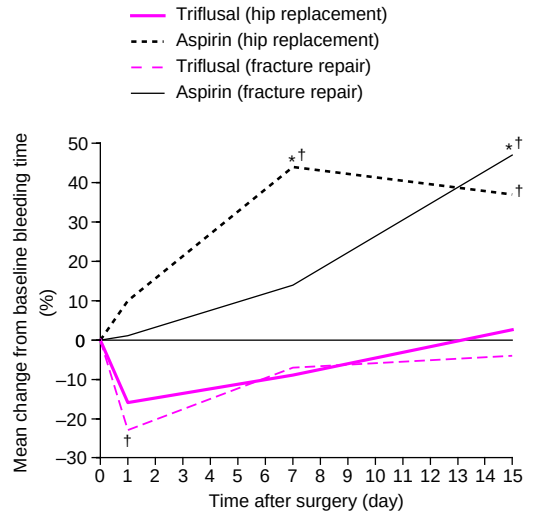


Fig. 5. Effect of 15 days' prophylaxis with triflusal or aspirin on bleeding time in patients undergoing elective hip replacement (n = 32) or corrective surgery for hip fracture (n = 46).[28] Triflusal was given 600mg preoperatively then 900 mg/day thereafter, and aspirin was given 750 mg/day postoperatively only (placebo given preoperatively). Observations were made on days 1, 7 and 15 after surgery. *Symbols:* * $p < 0.05$ *vs* triflusal; † $p < 0.05$ *vs* baseline.

• In patients undergoing aortocoronary vein grafting, perioperative bleeding was significantly different in triflusal than in placebo recipients (700 *vs* 562ml; $p = 0.025$),[26] and similar to that in aspirin recipients (601ml).

• After hip surgery, the mean bleeding time measured for 15 days postoperatively was not increased from baseline (preoperative) assessment in patients receiving prophylactic triflusal as it was in aspirin recipients (fig. 5).[28] In patients undergoing total hip replacement, the mean change from baseline bleeding time at day 7 was significantly different in triflusal and aspirin recipients (9% decrease *vs* 44% increase; $p < 0.05$). In addition, aspirin significantly increased the bleeding time from baseline at days 7 and 15 (by 44 and 37%; $p < 0.05$).

• Similar results were seen in patients undergoing corrective surgery for hip fracture (fig. 5).[28] An initial 23% decrease in mean bleeding time occurred at day 1 in triflusal recipients ($p < 0.05$ *vs* baseline); by day 15 mean changes were a 4% decrease for triflusal and a 47% increase for aspirin ($p < 0.05$ *vs* triflusal and baseline).

• In a second study in 151 patients undergoing elective hip replacement or corrective surgery for hip fracture, the amount of blood required during the first 24 hours after surgical intervention was significantly greater in aspirin recipients (0.4 units) than in those receiving triflusal or placebo (both 0.2 units; $p = 0.02$).[29]

5. Triflusal: Current Status

Triflusal is a platelet antiaggregant which has been approved in several countries for the prophylaxis and treatment of thromboembolic disease. It has shown clinical efficacy greater than that of placebo and generally similar to that of aspirin in the prevention or treatment of thromboembolism associated with cardio- and cerebrovascular disease. Unlike aspirin, triflusal did not increase bleeding time or the amount of blood transfused after hip surgery; compared with aspirin, it reduced the risk of haemorrhagic complications in patients with ischemic stroke. Gastric pain, nausea and vomiting and erythema were the most commonly reported adverse events. Several large (n = 400 to >2000) 2- to 3-year double-blind clinical trials are underway: these include the TAPIRSS[32] study (prevention of infarction in patients with ischemic attack or stroke), the TACIP[33] study (prevention of secondary cerebral infarction in patients with transient ischemic attack or stroke) and the TIM[34,35] study (comparative effects on the prognosis of patients with acute myocardial infarction). Results from these studies are eagerly awaited.

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