Drugs of the Future 2006, 31(10): 867-873

CCC: 0377-8282/2006
DOI: 10.1358/dof.2006.031.10.1038241

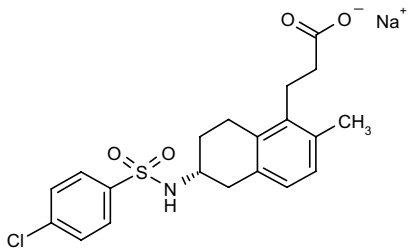
Terutroban Sodium

Prop INNM

Prostanoid TP Receptor Antagonist
Antithrombotic Agent
Antiatherosclerotic Agent

S-18886
S-18204 (racemate)

3-[6(R)-(4-Chlorophenylsulfonamido)-2-methyl-5,6,7,8-tetrahydronaphth-1-yl]propionic acid sodium salt



$C_{20}H_{21}ClNNaO_4S$
Mol wt: 429.8936

CAS: 609340-89-8

CAS: 165537-73-5 (racemate, free acid)

CAS: 165538-40-9 (free acid)

EN: 223481

Abstract

Thromboxane A_2 (TxA_2) is an unstable metabolite of arachidonic acid formed by the cyclooxygenase pathway and released from activated platelets, monocytes and damaged vessel walls, causing irreversible platelet aggregation, vasoconstriction and smooth muscle cell proliferation. From efforts to discover novel compounds that could block the deleterious actions of TxA_2, the 2-aminotetralin derivative terutroban sodium (S-18886) emerged as a potent, orally active, long-acting, selective antagonist of thromboxane (TP) receptors. The agent was able to inhibit TP agonist-induced platelet aggregation and vasoconstriction and was selected for further development as an antiplatelet and antithrombotic agent. Terutroban has been shown to be effective in animal models of thrombosis, atherosclerosis and diabetic nephropathy and is currently undergoing phase III development for the secondary prevention of acute thrombotic complications of atherosclerosis.

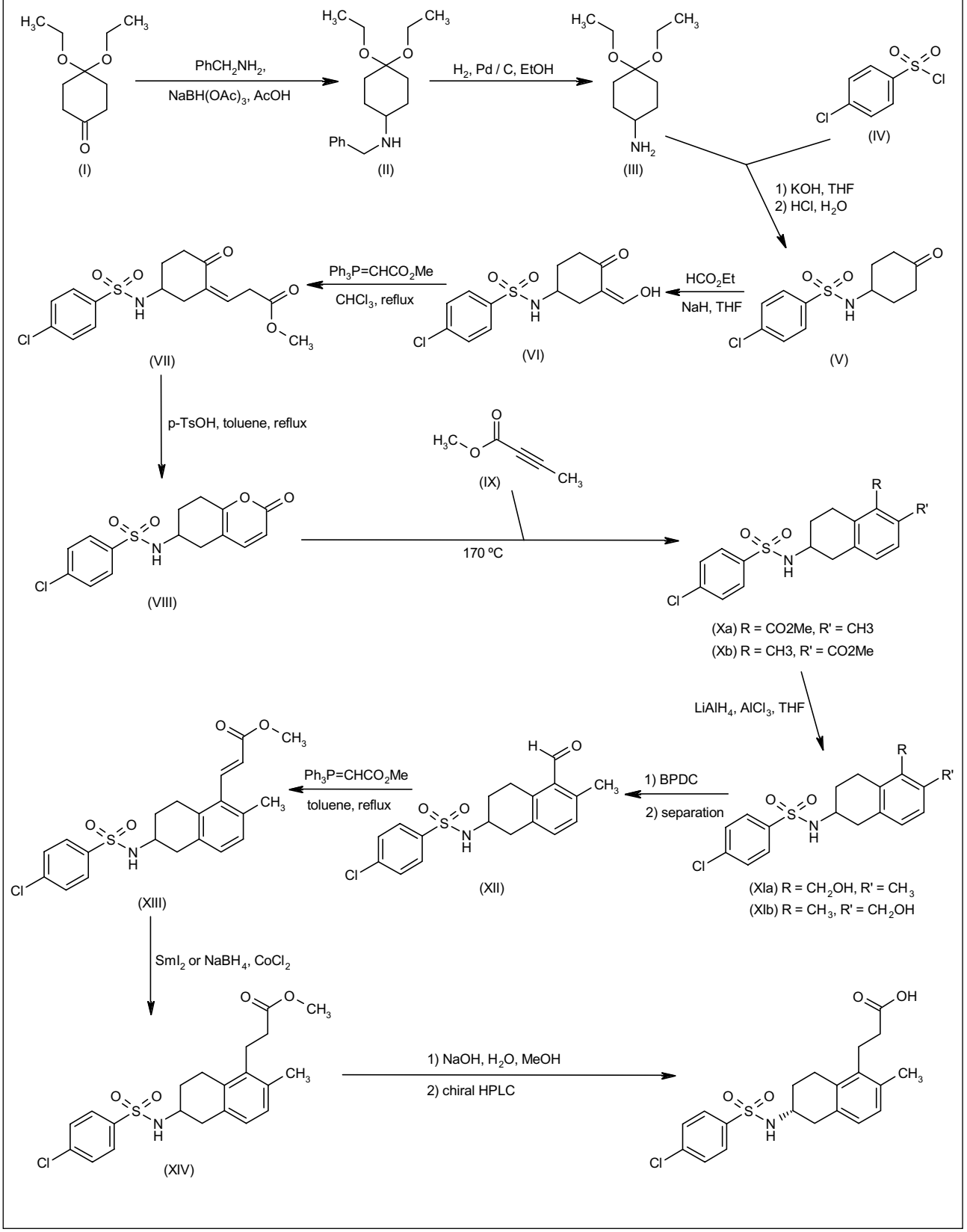
Synthesis

Terutroban is obtained by resolution of the racemate S-18204. Reductive amination of 4,4-diethoxycyclohexanone (I) with benzylamine in the presence of sodium triacetoxyborohydride affords the amino ketal (II), which is debenzylated to (III) by hydrogenation over Pd/C. Subsequent acylation of amine (III) with 4-chlorobenzenesulfonyl chloride (IV), followed by acidic ketal hydrolysis, provides the sulfonamide ketone (V). Claisen condensation of (V) with ethyl formate yields the hydroxymethylene ketone (VI), which is subjected to a Wittig reaction with (methoxycarbonylmethylene)triphenylphosphorane to give the ester (VII). Benzopyranone (VIII) is then obtained by intramolecular cyclization of (VII) under acidic conditions. Subsequent Diels-Alder cycloaddition between methyl butynoate (IX) and benzopyranone (VIII) leads to a mixture of two regioisomeric tetrahydronaphthalenes (Xa) and (Xb), which, without separation, are reduced with $LiAlH_4$, yielding alcohols (XIa) and (XIb). After oxidation of (XIa,b) to the corresponding aldehydes with 4-benzylpyridinium dichromate, separation of the resulting mixture by column chromatography furnishes the desired isomer (XII). Wittig condensation of aldehyde (XII) with (methoxycarbonylmethylene)triphenylphosphorane gives the conjugated ester (XIII), which is further reduced to the saturated ester (XIV) by using either samarium iodide or sodium borohydride/cobaltous chloride. Finally, saponification of the methyl ester (XIV) affords the racemate (1, 2), which is finally resolved utilizing chiral HPLC (3). Scheme 1.

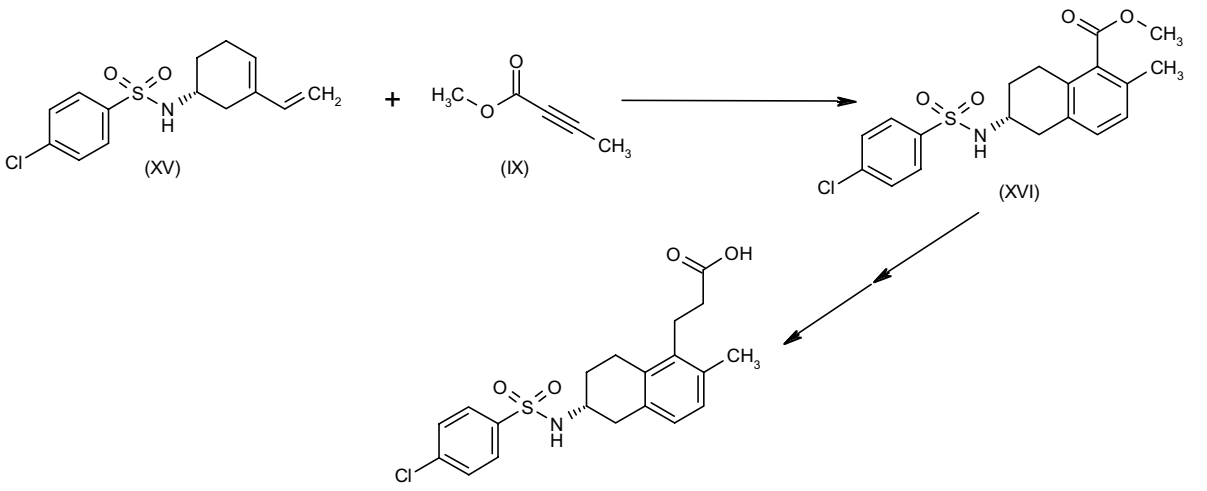
In an alternative synthesis, the resolved sulfonamido diene (XV) is subjected to Diels-Alder condensation with methyl butynoate (IX) to produce the optically active sulfonamidoaminotetralin (XVI), from which terutroban is readily accessible following conventional procedures (3). Scheme 2.

L.A. Sorbera, N. Serradell, J. Bolós, M. Bayés. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of Terutroban



Scheme 2: Synthesis of Terutroban



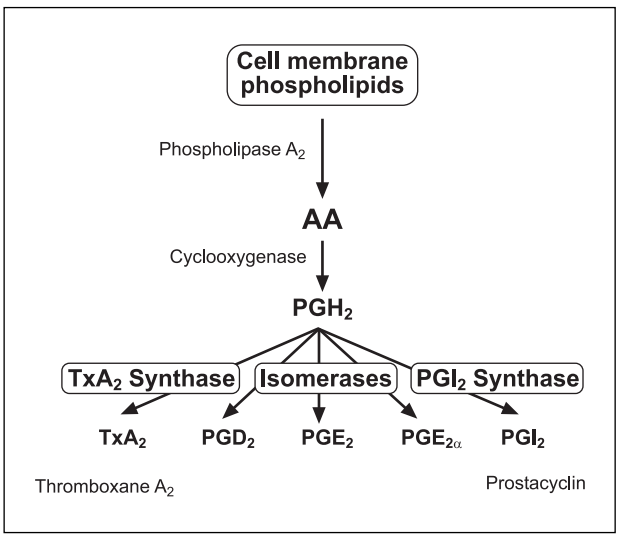


Fig.1. Arachidomic acid metabolism lipoxygenase/cyclooxygenase pathways.

Background

Thromboxane A_2 (TxA_2) is an unstable metabolite of arachidonic acid (AA) formed via the cyclooxygenase pathway (Fig. 1). The eicosanoid is released from activated platelets, monocytes and damaged vessel walls, causing irreversible platelet aggregation, vasoconstriction and smooth muscle cell proliferation. TxA_2 activity is mediated via TxA_2/prostaglandin (PG) H_2 receptors (TP receptor; TPα and TPβ in humans), which are extensively expressed on platelets and vascular smooth muscle (4, 5).

TxA_2 has been implicated in a wide range of circulatory and other disorders. Several TP receptor antagonists and TxA_2 synthase inhibitors have been reported as potential antiplatelet agents. However, many are short acting and also possess TP receptor-agonist activity. Thus, the search for more effective and long-acting agents devoid of any TP receptor-agonist activity continues. From these efforts, the 2-aminotetralin derivative and active isomer of the racemate S-18204, terutroban sodium (S-18886), has emerged as a potent and selective antagonist of TP receptors. The orally active agent was shown to inhibit TP agonist-induced platelet aggregation and vasoconstriction, without affecting endothelial and vessel wall prostacyclin production, and it exerted potent antithrombotic effects in animal models. Terutroban was selected for further development as an antithrombotic and antiatherosclerotic agent (1, 3, 6).

Preclinical Pharmacology

The racemate S-18204 exhibited high affinity (K_i = 0.82 nM) for TP receptors in binding assays using human platelet membranes and [^{3}H]-SQ-29548 as a radioligand (7). Terutroban potently inhibited TxA_2 agonist (U-46619)-induced aggregation of human platelets (IC_{50} = 0.23 μM) and U-46619-induced contraction of isolated rabbit saphenous vein (pA_2 = 8.9). Terutroban blocked the contractile effects of PGI_2 and PGD_2 on isolated rabbit saphenous vein segments and the proaggregatory effects of PGD_2 on guinea pig platelets. The agent was effective *in vivo,* where i.v. administration to guinea pigs inhibited U-46619-induced increases in tracheal pressure (ID_{50} = 35 μg/kg) (1, 8).

The antithrombotic efficacy of terutroban was examined and compared to aspirin (5 mg/kg/day) and clopidogrel (3 mg/kg/day) in perfusion studies using plasma from pigs administered the agent (30 and 100 μg/kg/day) and heparin (50 IU/kg bolus plus 50 IU/kg/h) for 3 consecutive

days. Significant and dose-related inhibition of collagen- and ADP-induced platelet aggregation was observed in plasma taken 2 h after treatment with terutroban. Doses of 30 and 100 μg/kg/day produced a mean 25% and 44% inhibition, respectively, of collagen-induced aggregation and 22% and 39% inhibition, respectively, of ADP-induced aggregation; clopidogrel inhibited collagen- and ADP-induced aggregation by a mean of 39% and 56%, respectively. In addition, the higher terutroban dose significantly inhibited platelet deposition under low shear conditions in a manner similar to clopidogrel, and both doses of terutroban significantly inhibited platelet deposition under high shear conditions, the inhibitory effects of the higher dose being similar to the effects observed with clopidogrel. The higher dose of terutroban and clopidogrel also significantly inhibited fibrinogen deposition. Aspirin had no effect on platelet or fibrinogen deposition. No differences from baseline were observed in blood cell count, activated partial thromboplastin time (aPTT), prothrombin time (PT) or thrombin time (TT) in any of the treatment groups (9).

The antithrombotic efficacy of terutroban was examined in a dog model of acute periodic platelet-mediated thrombosis in stenosed coronary arteries with endothelial damage. Treatment with the agent (300 μg/kg by i.v. bolus after thrombosis onset) completely inhibited thrombosis formation in about 5-10 min; i.v. infusion of epinephrine partially restored thrombosis in 3 of 11 terutroban-treated dogs. A slight but significant increase in hematocrit was observed with terutroban treatment, although heart rate, blood pressure, pH, PO_2, PCO_2, platelet count and bleeding time were unaltered. Examination of platelet aggregation *ex vivo* revealed that terutroban significantly attenuated aggregation induced by collagen (90%), collagen + epinephrine (78-98%), ADP + epinephrine (70%) and phorbol 12-myristate 13-acetate (PMA; 28%) (10, 11).

The antiatherosclerotic effects of terutroban were demonstrated in a study using a rabbit model of atherosclerosis and restenosis. Oral treatment at a dose of 5 mg/kg/day for 6 weeks of rabbits with balloon injury to the right iliac arteries and fed a cholesterol-enriched diet for 6 weeks resulted in a decrease in the intima:media ratio in lesions in both the uninjured aorta and injured iliac artery, as well as a decrease in macrophage infiltration and ICAM-1 expression, compared to animals treated with placebo, aspirin (30 mg/kg/day) or a lower dose of terutroban (1 mg/kg/day). In addition, in rabbits with iliac artery lesions subjected to a second balloon injury at week 6, treatment with terutroban (5 mg/kg/day) for 2 weeks reduced the intima:media ratio of restenosing lesions. The smallest lesions in terutroban-treated rabbits correlated with significant reductions in the neointimal area occupied by macrophages and ICAM-1 expression; no effects were observed on the neointimal smooth muscle component. Aspirin had no effect on ICAM-1 expression or smooth muscle. However, it partially inhibited macrophage infiltration. Treatment with terutroban increased lesion stability, possibly by reducing inflammatory processes (12).

Another study in rabbits with established aortic atherosclerosis induced by a high-cholesterol diet (9 months) and double aortic balloon injury further demonstrated the antiatherosclerotic effects of oral terutroban (5 mg/kg/day for 6 months). Magnetic resonance imaging (MRI) revealed that treatment with the agent significantly regressed advanced atherosclerotic plaques, such that reductions in total vessel area and vessel wall area were observed. In addition, immunohistochemical studies showed that terutroban significantly decreased markers for macrophages (RAM-11), apoptotic cells (caspase-3), metalloproteinases (MMP-1) and endothelin-1 (ET-1), while increasing α-actin, a marker for vascular smooth muscle cells. Thus, terutroban arrested atherosclerotic progression, with lesions acquiring a more stable phenotype (13).

Oral terutroban (5 mg/kg/day for 11 weeks starting when animals were 9 weeks old) inhibited atherogenesis in apolipoprotein E-deficient mice; aspirin (30 mg/kg/day) had no effect. Terutroban-treated mice displayed significant reductions in aortic root lesions (0.19 ± 0.01 mm^2 *vs.* 0.21 ± 0.02 mm^2 in controls), serum ICAM-1 (24 ± 2 μg/ml *vs.* 35 ± 3 μg/ml in controls) and serum TxB_2 levels (42 ± 8 ng/ml *vs.* 69 ± 8 ng/ml in controls). Although aspirin had no effect on atherogenesis or adhesion molecule levels, it was more effective in inhibiting serum TxB_2 (17 ± 4 ng/ml), indicating a greater capacity to inhibit platelet TxA_2 synthesis. Neither agent had any affect on body or heart weight or serum cholesterol levels. Studies *in vitro* using cultured human umbilical vein endothelial cells (HUVEC) confirmed that treatment with terutroban prevents U-46619-induced increases in ICAM-1 expression. From these results, it appears that the antiatherogenic effects of terutroban are independent of platelet-derived TxA_2 and possibly occur via inhibition of adhesion molecule expression (14).

Further experiments using apoE knockout mice fed a high-fat diet (92 days) showed that terutroban (5 and 10 mg/kg p.o. for 6 weeks) significantly delayed atherogenesis, whereas the COX-1/COX-2 inhibitor indomethacin (6 mg/l) or a selective tricyclic COX-2 inhibitor were ineffective. Average aortic lesion area was significantly decreased in terutroban-treated animals compared to controls (9.1 ± 0.9% and 6.6 ± 0.8%, respectively, *vs.* 14.1 ± 1%). Combination treatment with terutroban and the COX-2 inhibitor did not enhance the effects of the former agent on lesion area. Lipid peroxidation during atherogenesis was not altered in any treatment group. Although treatment with terutroban significantly delayed disease progression, it did not cause regression of established atherosclerotic disease (15).

Terutroban (5 mg/kg/day p.o. for 6 weeks) effectively inhibited diabetes-associated inflammation and enhanced atherogenesis in $apoE^{-/-}$ mice with streptozotocin (STZ)-induced diabetes mellitus. Although it had no effect on diabetes-related increases in serum glucose and cholesterol, it significantly reduced the diabetes-induced increases in aortic lesion area compared to controls. In addition, significant increases in aortic endothelial nitric oxide synthase

(eNOS) expression and significant attenuation of diabetes-induced increases in markers of vascular inflammation and oxidant stress (*e.g.*, VCAM-1, nitrotyrosine and advanced glycation end products [AGEs]) where observed in the aortas of terutroban-treated mice. These observations were confirmed *in vitro*, where exposure of cultured human aortic endothelial cells (HAECs) to terutroban prevented high-glucose-induced decreases in eNOS expression and increases in VCAM-1 expression. Further experiments *in vitro* using aortic rings from diabetic apoE$^{-/-}$ mice showed that exposure to terutroban (1 μM for 30 min) restored the acetylcholine (ACh)-induced endothelium-dependent relaxation that was significantly reduced by diabetes. Thus, terutroban prevented diabetes-related deterioration of endothelial function (16).

Results from two preclinical studies suggest that terutroban may be effective in attenuating diabetic nephropathy. A study using apoE$^{-/-}$ mice with STZ-induced diabetes reported that treatment with the agent (5 mg/kg/day p.o. for 6 weeks) attenuated renal oxidative stress and proteinuria. Terutroban-treated animals exhibited significantly decreased diabetes-related increases in kidney manganese superoxide dismutase (MnSOD) tyrosine-34 nitration and urinary 12-HETE and 8-iso-$PGF_{2\alpha}$. Moreover, significant attenuation of microalbuminuria was observed, as well as amelioration of histological markers of diabetic nephropathy (*i.e.*, TGF-β and extracellular matrix expression in the kidney). Terutroban effectively improved renal morphology and proteinuria and reduced oxidative stress in unilaterally nephrectomized obese Zucker rats. Treatment with doses of 10 and 30 mg/kg/day p.o. 5 days/week for 8 weeks blocked increases in plasma urea, normalized indices of mesangiolysis and reduced glomerulosclerosis (22% and 31%, respectively); the higher dose also partially blocked the increase in advanced oxidation protein products seen in untreated controls. A dose-related reduction in urinary TxB_2 levels was observed in terutroban-treated animals, indicating a decrease in renal TxA_2 production (17, 18).

Results from a study in stroke-prone spontaneously hypertensive rats (SHR-SP) suggested that terutroban may also be effective in preventing cerebrovascular events. SHR-SP fed a high-salt diet and treated with the agent (30 mg/kg/day p.o.) showed a significant delay in the time to appearance of brain lesions (69 ± 10 days *vs.* 38 ± 4 days) and a significant increase in survival (70 ± 10 days *vs.* 42 ± 2 days). Moreover, treatment with terutroban significantly delayed the increase in proteinuria and prevented accumulation of acute-phase proteins and thiobarbituric acid-reactive substance in body fluids. Protective effects were also noted even when the agent was not given until after the appearance of proteinuria (19).

Pharmacokinetics and Metabolism

A multicenter, randomized, double-blind study conducted in 30 patients with peripheral artery disease examined the pharmacokinetics and pharmacodynamics of multiple doses of terutroban (1, 2.5, 5, 10 or 30 mg p.o. for 83 days). Terutroban was well tolerated, with no adverse events reported. The pharmacokinetics after a single dose were linear, with C_{max} (mean: 47-1498 ng/ml) achieved between 30 min and 2 h after dosing; $t_{1/2}$ values ranged from 5.8 to 10 h. No significant accumulation was observed with repeated terutroban dosing. Examination of the effects of terutroban on *ex vivo* U-46619-induced platelet aggregation revealed that plasma drug concentrations were related to the degree of inhibition. Marked inhibition was observed with plasma concentrations > 10 ng/ml, which was concluded to be the minimal effective antiplatelet concentration; this concentration was only maintained with doses of 10 and 30 mg. Maximal inhibition, which was sustained for at least 12 h, was seen within 1 h of oral dosing (20). The results from this and the following studies are summarized in Table I.

Clinical Studies

A multicenter, randomized, double-blind, controlled study (TAIPAD Study) in 435 patients with peripheral artery disease compared the efficacy of terutroban (1, 2.5, 5, 10 or 30 mg p.o. for 12 weeks) with aspirin (75 mg) in inhibiting *ex vivo* platelet aggregation induced by U-46619 (7 μM), arachidonic acid (AA; 1 mM), collagen (2 μg/ml) and ADP (5 μM). Terutroban dose-dependently inhibited platelet aggregation, with marked effects seen against U-46619- and AA-induced aggregation and moderate effects observed against collagen- and ADP-induced aggregation. Similar results were obtained with aspirin. Over 80% inhibition of U-46619- and AA-induced aggregation was observed at doses of 5 mg/day and above. No increase in bleeding events was observed with terutroban as compared to aspirin (21).

Single doses of terutroban (10 mg p.o.) were shown to improve endothelial function in a randomized, double-blind, placebo-controlled trial in 20 patients with stable coronary artery disease (CAD) on daily aspirin therapy (100 mg/day). No serious adverse events were reported and no clinically significant changes in biochemical, hematological, cardiovascular or coagulation parameters were seen with treatment. Terutroban, but not placebo, increased brachial artery flow-mediated vasodilatation. It had no effect on baseline forearm blood flow (FBF) measured using venous occlusion plethysmography. However, vasodilator responses to brachial artery infusion of ACh were significantly enhanced after terutroban compared to placebo, such that FBF increased from 2.5 ± 1.14% to 3.84 ± 1.8%; vasodilatation in response to norepinephrine and sodium nitroprusside was unaffected by treatment (22, 23).

Treatment with terutroban (2.5, 5 or 10 mg p.o.) for 15 days was shown to provide long-term improvements in endothelial dysfunction in a randomized, double-blind, placebo-controlled trial conducted in 48 patients with severe carotid artery atherosclerosis receiving aspirin (300 mg/day). Endothelial function and platelet aggregation were examined before treatment and 1 h after admin-

Table I: Clinical studies of terutroban sodium (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Peripheral artery disease	Randomized Double-blind Multicenter	Terutroban, 1 mg p.o. o.d. x 12 wks (n=7) Terutroban, 2.5 mg p.o. o.d. x 12 wks (n=6) Terutroban, 5 mg p.o. o.d. x 12 wks (n=5) Terutroban, 10 mg p.o. o.d. x 12 wks (n=6) Terutroban, 30 mg p.o. o.d. x 12 wks (n=6)	30	Terutroban demonstrated antiplatelet efficacy and an excellent safety profile in Caucasian patients with peripheral artery disease	20
Peripheral artery disease	Randomized Double-blind	Terutroban, 1 mg p.o. o.d. x 12 wks Terutroban, 2.5 mg p.o. o.d. x 12 wks Terutroban, 5 mg p.o. o.d. x 12 wks Terutroban, 10 mg p.o. o.d. x 12 wks Terutroban, 30 mg p.o. o.d. x 12 wks Aspirin, 75 mg x 12 wks	435	Terutroban and aspirin were safe and equieffective in inhibiting platelet aggregation in patients with peripheral artery disease	21
Coronary artery disease	Randomized Double-blind	Terutroban, 10 mg p.o. + Aspirin, 100 mg/d (n=12) Placebo + Aspirin, 100 mg/d(n=8)	20	A single oral dose of terutroban was well tolerated and increased flow-mediated vasodilatation in the brachial arteries of patients with coronary artery disease. The drug also enhanced the increase in forearm blood flow induced by acetylcholine administration, but had no effect on the forearm blood flow response to either sodium nitroprusside or norepinephrine	22
Atherosclerosis	Randomized Double-blind	Terutroban, 2.5 mg/d + Aspirin, 300 mg/d x 14 d Terutroban, 5 mg/d + Aspirin, 300 mg/d x 14 d Terutroban, 10 mg/d + Aspirin, 300 mg/d x 14 d Placebo + Aspirin, 300 mg/d x 14 d	48	Terutroban improved endothelial function in patients with atherosclerosis after the first dose, and improvement was sustained through day 14 with repeated administration	24, 25

istration of the first and last doses. All patients displayed impaired flow-mediated vasodilatation (FMD < 4.1%) measured in the distal brachial artery during a hyperemia test at baseline. A significant improvement in FMD was observed with all terutroban doses on the first day of dosing as compared to placebo; this improvement was sustained throughout the treatment period. Moreover, complete inhibition of *ex vivo* U-46619-induced platelet aggregation was observed at 2 h postdosing at all dose levels (24, 25).

Terutroban is currently undergoing phase III development for the prevention of cerebrovascular and cardiovascular events of ischemic origin (PERFORM [Prevention of cerebrovascular and cardiovascular Events of ischaemic origin with teRutroban in patients with a history of ischaemic strOke or tRansient ischaeMic attack] study).

Source

Institut de Recherches Servier (FR).

References

1. Cimetière, B., Dubuffet, T., Muller, O. et al. *Synthesis and biological evaluation of new tetrahydronaphthalene derivatives as thromboxane receptor antagonists*. Bioorg Med Chem Lett 1998, 8(11): 1375-80.

2. Lavielle, G., Dubuffet, T., Muller, O., Laubie, M., Verbeuren, T., Simonet, S., Descombes, J.-J. (ADIR et Cie.). *1,2,3,4-Tetrahydronaphthalene, chroman and thiochroman derivatives as antithrombotic agents*. CA 2118102, EP 0648741, FR 2711139, JP 1995188155.

3. Cimetière, B., Thomas, C., Landras, C., Verbeuren, T.J., Lavielle, G. *Synthesis of S-18886, a new potent TP-receptor antagonist, via an optically active 2-aminotetraline*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst ORGN-287.

4. Kinsella, B.T. *Thromboxane A_2 signalling in humans: A 'Tail' of two receptors*. Biochem Soc Trans 2001, 29: 641-54.

5. Narumiya, S., FitzGerald, G.A. *Genetic and pharmacological analysis of prostanoid receptor function*. J Clin Invest 2001, 108: 25-30.

6. Cimetière, B., Dubuffet, T., Muller, O. et al. *Synthesis and biological evaluation of new tetrahydronaphtalene derivatives as thromboxane A_2 receptor antagonists and combined antagonists/synthase inhibitors*. 210th ACS Natl Meet (Aug 20-24, Chicago) 1995, Abst MEDI-062.

7. Verbeuren, T.J., Verbeuren, T.J., Simonet, S., Descombes, J.-J., Vallez, M.-O., Laubie, M., Lavielle, G. *S-18204: A new powerful TxA_2-receptor antagonist with a long duration of action*. Thromb Haemost 1995, 73(6): Abst 1630.

8. Verbeuren, T.J., Descombes, J.J., Simonet, S., Dubuffet, T., Lavielle, G. *The TP-receptor antagonist S 18886 unmasks vascular relaxation and potentiates the anti-platelet action of PGD_2*. Thromb Haemost 1997, Suppl.: Abst PS-2826.

9. Osende, J.I., Shimbo, D., Fuster, V., Dubar, M., Badimon, J.J. *Antithrombotic effects of S 18886, a novel orally active thromboxane A_2 receptor antagonist*. J Thromb Haemost 2004, 2(3): 492-8.

10. Maalej, N., Osman, H.E., Shanmuganayagam,D., Shebuski, R.J., Folts, J.D. *Antithrombotic properties of the thromboxane A_2/prostaglandin H_2 receptor antagonist S18886 on prevention of platelet-dependent cyclic flow reductions in dogs*. J Cardiovasc Pharmacol 2005, 45(5): 389-95.

11. Folts, J.D., Osman, H., Shanmuganayagam, D. *A novel thromboxane A_2 receptor antagonist, S18886, inhibits experimental in vivo acute platelet-mediated coronary artery thrombosis and ex vivo platelet aggretation*. Exp Biol 2004 (April 17-21, Washington, D.C.) 2004, Abst 430.27.

12. Worth, N.F., Berry, C.L., Thomas, A.C., Campbell, J.H. *S18886, a selective TP receptor antagonist, inhibits development of atherosclerosis in rabbits*. Atherosclerosis 2005, 183(1): 65-73.

13. Viles-Gonzalez, J.F., Fuster, V., Corti, R. et al. *Atherosclerosis regression and TP receptor inhibition: Effect of S18886 on plaque size and composition – A magnetic resonance imaging study*. Eur Heart J 2005, 26(15): 1557-61.

14. Cayatte, A.J., Du, Y., Oliver-Krasinski, J., Lavielle, G., Verbeuren, T.J., Cohen, R.A. *The thromboxane receptor antagonist S18886 but not aspirin inhibits atherogenesis in apo E-deficient mice. Evidence that eicosanoids other than thromboxane contribute to atherosclerosis*. Arterioscler Thromb Vasc Biol 2000, 20(7): 1724-8.

15. Egan, K.M., Wang, M., Lucitt, M.B., Zukas, A.M., Puré, E., Lawson, J.A., FitzGerald, G.A. *Cyclooxygenases, thromboxane, and atherosclerosis. Plaque destabilization by cyclooxygenase-2 inhibition combined with thromboxane receptor antagonism*. Circulation 2005, 111(3): 334-42.

16. Zuccollo, A., Shi, C., Mastroianni, R. et al. *The thromboxane A_2 receptor antagonist S18886 prevents enhanced atherogenesis caused by diabetes mellitus*. Circulation 2005, 112(19): 3001-8.

17. Xu, S., Jiang, B., Maitland, K.A. et al. *The thromboxane receptor antagonist S18886 attenuates renal oxidant stress and proteinuria in diabetic apolipoprotein E-deficient mice*. Diabetes 2006, 55(1): 110-9.

18. Sebekova, K., Eifert, T., Tyralla, K., Amann, K., Heidland, A. *Beneficial effects of the specific TP receptor antagonist S18886 on development of diabetic nephropathy and oxidative status in the model of uninephrectomized obese Zucker rats*. J Am Soc Nephrol 2003, 14: Abst SA-PO414.

19. Nobili, E., Gianella, A., Gelosa, P. et al. *Effect of S 18886, a thromboxane A_2 receptor antagonist, on the occurrence of spontaneous brain damage in stroke-prone rats*. Cerebrovasc Dis [15th Eur Stroke Conf (May 16-19, Brussels) 2006] 2006, 21(Suppl. 4): 52.

20. Gaussem, P., Reny, J.-L., Thalamas, C. et al. *The specific thromboxane receptor antagonist S18886: Pharmacokinetic and pharmacodynamic studies*. J Thromb Haemost 2005, 3(7): 1437-45.

21. Fiessinger, J.N., on behalf of the TAIPAD Study Group. *S 18886, a new specific TP-receptor antagonist, is safe and as effective as aspirin in inhibiting platelet aggregation in patients with peripheral arterial disease*. Eur Heart J 2004, 25(Suppl.): Abst P573.

22. Belhassen, L., Pelle, G., Dubois-Rande, J.-L., Adnot, S. *Improved endothelial function by the thromboxane A_2 receptor antagonist S 18886 in patients with coronary artery disease treated with aspirin*. J Am Coll Cardiol 2003, 41(7): 1198-204.

23. Belhassen, L., Pelle, G., Sediame, S., Dubois-Rande, J.-L., Adnot, S. *Improvement of endothelial function by the selective TP-receptor antagonist S18886 in patients with coronary artery disease (CAD) treated with aspirin*. Circulation 2000, 102(Suppl.): Abst 263.

24. Belhassen, L., Pelle, G., Dubois Rande, J.L., Adnot, S. *S 18886 improves endothelial function on a long term basis in atherosclerotic patients*.12th World Cong Heart Dis (July 16-19, Vancouver) 2005, Abst 263.

25. Belhassen, L. *The TP receptor antagonist S 18886 improves endothelial dysfunction on a long-term basis in atherosclerotic patients*. Eur Heart J 2004, 25(Suppl.): Abst P603.

Additional References

Viles-Gonzalez, J.F., Valdiviezo, C., Teitelbaum, E. et al. *The selective thromboxane A_2 receptor (TP) antagonist S18886 has antiatherosclerotic and plaque-stabilizing effects in the rabbit: Follow-up with serial high-resolution magnetic resonance imaging*. Circulation [Am Heart Assoc Sci Sess (Nov 7-10, New Orleans) 2004] 2004, 110(17, Suppl. 3): Abst 428.

Zuccollo, A., Xu, S., Jiang, B. et al. *The TP receptor antagonist S18886, but not aspirin decreases renal 12-lipoxygenase expression, 12-HETE production, and oxidant stress in diabetic Apo-E deficient mice*. 65th Annu Meet Sci Sess Am Diabetes Assoc (ADA) (June 10-14, San Diego) 2005, Abst 828-P.

Xu, S., Maitland, K.A., Jiang, B. et al. *The TP receptor antagonist, S18886, but not aspirin, attenuates renal oxidative stress and proteinuria in diabetic Apo E-deficient mice*. 64th Annu Meet Sci Sess Am Diabetes Asssoc (ADA) (June 4-8, Orlando) 2004, Abst 53-OR.

Cayatte, A.J., Du, Y., Oliver-Krasinski, J., Lavielle, G., Verbeuren, T.J., Cohne, R.A. *The new thromboxane receptor antagonist, S18886, but not aspirin inhibits atherogenesis in Apo E deficient mice*. FASEB J 2000, 14(8): Abst 1278.

Cohen, R.A., Xu, S., Maitland, K., Cayatte, A.J., Lavielle, G., Verbeuren, T.J. *The TP receptor antagonist, S18886, prevents the enhancement of atherogenesis by diabetes mellitus in apolipoprotein E deficient mice*. Circulation 2001, 104(17, Suppl. 2): Abst 566.

Cayatte, A.J., Du, Y., Yaghoubi, M., Oliver-Krasinski, J., Lavielle, G., Verbeuren, T.J., Cohen, F.A. *The thromboxane A_2 receptor antagonist, S18886, decreases atherosclerotic lesions and serum intracellular adhesion molecule-1 in the Apo E knockout mouse*. Circulation 1998, 98(17, Suppl.): Abst 590.

Egan, K.M., Pratico, D., Powell-Braxton, L., FitzGerald, G.A. *Cyclooxygenase dependent and independent ligation of the thromboxane receptor accelerates atherogenesis*. Circulation 2001, 104(17, Suppl. 2): Abst 309.

Zuccollo, A., Maitland, K., Mastroiani, R. et al. *The TP receptor antagonist S18886, but not aspirin decreases atherogenesis in diabetic apolipoprotein E-deficient mice*. 64th Annu Meet Sci Sess Am Diabetes Assoc (ADA) (June 4-8, Orlando) 2004, Abst 641-P.

Shi, C., Zang, M., Lavielle, G:, Verbeuren, T.J., Cohen, R.A. *The thromboxane receptor antagonist, S18886, decreases VCAM-1 and increases endothelial nitric oxide synthase expression in human aortic endothelial cells exposed to elevated glucose*. 64th Annu Meet Sci Sess Am Diabetes Assoc (ADA) (June 4-8, Orlando) 2004, Abst 757-P.