**Animal Models**

A thromboxane A₂/prostaglandin H₂ receptor antagonist (S18886) shows high antithrombotic efficacy in an experimental model of stent-induced thrombosis

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**Summary**

Acute thrombosis is a threat in patients undergoing percutaneous coronary intervention with stent implantation. Our objective was to determine if stent-induced thrombus formation could be inhibited by oral treatment with a thromboxane A₂/prostaglandin H₂ receptor antagonist (TPr; S18886) as an alternative to standard therapy. Pigs were allocated in the following treatment (p.o) groups: I) clopidogrel (CLOP); II) ASA; III) S18886; IV) ASA+CLOP; and V) placebo-control. Damaged vessel was placed in the Badimon chamber containing a stent and perfused at 212/s. Antithrombotic effects were assessed as |

**Keywords**

Thrombosis, thromboxane, aspirin plus clopidogrel, stents

**Introduction**

Despite the efficacy and expanding role of stents in the interventional treatment of coronary artery disease (CAD), the occurrence of acute thrombotic complications is a limiting factor, especially in unplanned stenting (1). Hence, antiplatelet agents are the cornerstone for atherothrombosis prevention in patients undergoing percutaneous coronary intervention (PCI) with stent implantation (2). Over the past years, several antiplatelet agents have been developed to prevent coronary thrombus such as aspirin (ASA), thienopyridine derivatives (clopidogrel and ticlopidine), and glycoprotein IIb/IIIa receptor antagonists. ASA remains the first-line antiplatelet drug with the highest amount of available clinical information (3). ASA exerts its major antithrombotic effect by irreversibly acetylating platelet cyclooxygenase (COX)-1, thereby inhibiting thromboxane A₂ (TXA₂) synthesis (4). In turn, TXA₂ promotes platelet aggregation, vasoconstriction, and proliferation by docking with a membrane-bound receptor, the TX-receptor (TPr) (5). However, ASA only reduces the risk of serious vascular events by about one-quarter in a broad range of high-risk patients (6). Clopidogrel (CLOP), a P2Y₁₂ adenosine-diphosphate (ADP)-receptor antagonist, has shown in clinical trials to produce a significant reduction in secondary cardiovascular, cerebrovascular, and peripheral vascular events both as monotherapy and in combination with ASA (7–10). As such, clopidogrel on top of ASA is currently included as standard care for the prevention of stent thrombosis in patients undergoing PCI and acute coronary syndrome (ACS) (8, 11, 12). Despite the evidence for broad early aggressive clopidogrel use in ACS and the endorsement of the major cardiovascular guideline committees, questions persist in the use of clopidogrel as an antiplatelet agent prior to coronary angiography when indi-
cations for PCI are uncertain (13). In fact, application of clopidogrel before cardiac catheterization leads to potential bleeding complications if angiography reveals that urgent or emergent coronary artery bypass grafting (CABG) is required instead of PCI (14). Thus, in an effort to reduce peri-operative bleeding, the American College of Chest Physicians (ACCP) guidelines recommend withholding clopidogrel until the coronary anatomy is determined (15). On the other hand, previous reports in healthy volunteers and in patients with ACS undergoing coronary stenting (16, 17) have shown that the maximum inhibitory response to clopidogrel loading dose (LD) occurs within a few hours of administration, since clopidogrel requires hepatic metabolism to generate an active metabolite with antiaggregating activity. Taken altogether, these considerations are the rationale for developing alternative, safer, and faster onset of action therapeutic strategies to prevent acute stent thrombosis.

S18886, a specific antagonist of the thromboxane A2/prostaglandin H2 receptor (TPR; Servier, France) (18), is a new molecule currently under clinical development for secondary prevention of atherothrombotic events in patients with cardiovascular disease. S18886, besides its anti-atherogenic properties in animals (19), has previously demonstrated antplatelet efficacy (20–22), improvement of endothelial function (23), and inhibition of TXA2-induced vasoconstriction (24). However, S18886 antithrombotic properties have not been yet formally compared. Thus, in this study, our aim was to assess the efficacy of both antplatelet potential and time-dependency of oral administration of S18886 compared to that of conventional LD with CLOP, ASA, and a combination of CLOP and ASA in a porcine arteriovenous shunt model of in-stent induced thrombosis.

Methods

Experimental model and coronary stents

Experiments were performed in pigs (n=20, ~36 kg), individually caged in a light-, temperature-, and humidity-regulated environment with controlled feeding and free access to water. The investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institute of Health (NIH Publication No. 85–23, revised 1996).

Apolo coronary 316LVM stainless steel stents (n=50, Ibexhospitex SA, Spain), 18 mm long, with average weight of 16 mg and strut thickness of 0.0045 inches, were pre-expanded on a dilated balloon of a conventional coronary angioplasty balloon catheter to an outer diameter of 2.0 mm prior to deployment in the perfusion chamber.

The number of stent-perfusions examined were eight for each animal (n=4 animals per group; N=32 stents/group). Thus, a total of 50 stents were used for 160 perfusions. Stents were cleaned at the end of each experiment with BTS-450 solution (Beckman Instruments, USA) (25), checked microscopically, and sterilized with ethylene oxide before reutilization.

Experimental design

Radioactive labeling of platelets

After overnight fasting, 43 ml of pig blood was drawn in 7 ml of anticoagulant citrate dextrose solution by femoral venipuncture. Platelets were isolated and labeled with 111In (Amersham Biosciences, UK) as previously described (26), suspended in a final volume of 4 ml of autologous plasma, and reinjected into the pig (ear vein) within 2 hours (h). Labeling efficiency was 93.0 ± 2.0% and the injected activity was 245 ± 10 µCi. Post-mortem 111In-biodistribution indicated a correct platelet distribution with maximal accumulation in blood.

Experimental procedure and extracorporeal perfusion system

Twenty hours after platelet labeling pigs were sedated with an intramuscular injection of 8 mg/kg of Azaperone (Stressnil®, Esteve, Spain), anesthetized by intravascular infusion of pentobarbital sodium solution (10 mg/kg, Braun, Spain), and then intubated and ventilated. Through a neck incision, the common carotid artery and contralateral jugular vein were cannulated. Pigs were then administered intravenous heparin (50 IU/kg bolus; 50 IU/kg/h infusion; Liquemine®, Roche, Switzerland), to avoid clotting inside the catheter system. The catheterized carotid artery was connected by polyethylene tubing to the inlet of the perfusion chamber and the outlet was connected to the catheterized jugular vein through a variable speed peristaltic pump (Masterflex 7518–10, Cole Parmer, USA).

Pig aorta substrates (30 x 10 mm) were mechanically disrupted by peeling off the intimal layer with a thin portion of subjacent media as previously described (27) in order to mimic the in vivo severely injured artery associated with stent implantation. Thereafter, the highly thrombogenic substrate was placed in the perfusion chamber (inner diameter of 2 mm) in a lateral position opposed to the previously placed stent (Fig. 1A) (26, 28). Hence, by pressure of the upper lid of the chamber on the lower core, we obtained a cylindrical channel by which the “stented substrate” was directly exposed to the flowing blood. Concretely, blood was perfused through the chamber at a flow rate of 10 ml/min. This flow was estimated to generate a local shear rate of about 212/s which corresponds to a value encountered in stented coronary arteries (28) as calculated for a Newtonian fluid in the tube flow (29). The chambers were initially flushed with saline (37°C) for 30 seconds (s). Following this, blood from the carotid artery was allowed to perfuse over the “stented vessel” for 5 minutes (min) at the selected rate and returned to the animal through the jugular vein. At the end of the perfusion, and without stasis, the chambers were perfused again with saline for 60 s to remove any non-attached platelets. After each perfusion study both stent and substrate were removed from the chamber and counted in a well-gamma counter (Wizard Wallac, USA) for quantification of deposited platelets. Values were normalized for blood 111In-activity (counts), platelet counts in blood, and area of exposed surface (28).

Tested compounds

Twenty animals were randomized into five groups by treatment (p.o.): I) the vehicle (placebo-control; n=4); II) ASA (Bayer; 5 mg/kg; n=4); III) conventional LD of CLOP (Sanofi-BMS; 10 mg/kg; n=4); IV) S18886 (Institut de Recherches Internationales Servier; 0.3 mg/kg; n=4), a tetrahydroxynaphthalene derivative [C3H3(NO2)2, Na 3-[o-(4-chlorophenylsulfonylamido)-2-methyl-5,6,7,8-tetrahydro-1-naphthyl] propanoid acid, sodium salt]; and V) ASA+CLOP (n=4). All the compounds were administered orally, mixed with the same quantity of commercial chow (30 g) and antplatelet effects were evaluated in two perfusion
series (60 and 180 min post-drug intake) (Fig. 1B). The placebo-control group was given the same amount of chow. Both ASA and CLOP doses were chosen to simulate the standard loading regimen for coronary stenting (30, 31) the S18886 dose (around 10 mg/animal) was selected based on previous human platelet aggregation studies conducted in order to determine the minimum amount of oral S18886 required to yield adequate platelet inhibition (22).

**Light transmittance aggregrometry**
Light transmittance aggregrometry (Menarini) induced by collagen (5 µg/ml), a synthetic thromboxane-endoperoxide analogue (U46619; 1 and 7 µM), and ADP (5 µM), was measured in platelet rich plasma (PRP) as previously described (32) at baseline and both 60 and 180 min post-drug intake.

**Assessment of S18886 plasma concentrations**
Before starting each perfusion series, 5 ml of blood were collected in lithium heparin anticoagulated tubes and immediately placed on ice until centrifuged (10 min, 1,500 g, 4°C). The resulting plasma was aliquoted into polypropylene tubes and stored at −20°C. The S18886 plasma concentration was measured by MDS Pharma Services (Switzerland) with a specific and sensitive high-performance liquid chromatography/tandem mass spectrometry method (LC-MS/MS).

**Bleeding time (BT)**
Saline ear BT was measured in all animals at the end of the experiments (i.e. 4 h after drug intake) according to Mertz (33). Briefly, the marginal edge of the ear was quickly transfixed (standardized incision of 3 mm length through the entire thickness of the ear) with a surgical blade (No.11) and immediately placed into a beaker containing citrated saline solution at 37°C. The time between incision and cessation of bleeding was recorded as BT. Time was recorded as 45 min if bleeding had not spontaneously stopped by this time.

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![Figure 1](https://example.com/figure1.png)

**Figure 1:** Schemes of stent-deployment in chambers (A) and the experimental protocol (B).

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Haematological, coagulation, and biochemical parameters

Blood cells, hematocrit, platelet number, and size distribution were determined before and after each perfusion (System 9000, USA). Levels of PT and aPTT were monitored with an ST4 automated clotter (Diagnostica Stago, France) and the corresponding specific kits according to the manufacturer’s instructions. Serum levels of BUN, creatinine, AST, and ALT were determined by routine analytical chemistry assays before and after drug treatment in all animals.

Immunohistochemical analysis

The stented portion of the perfused pig vessel was fixed in 4% paraformaldehyde, cryoprotected with 2.3 M sucrose and frozen over dry ice in OCT compound (Leica, Germany). Fibrinogen deposition was evaluated in all groups at both time-periods (60 and 180 min post-drug intake). Serially cut of 4 to 5 µm-thick sections were obtained perpendicular to the direction of blood flow using a cryostat (Lung-CM300 Cryostat, Leica, Germany) to evaluate fibrinogen deposition around the stent struts. Cuts were started at 0.5 cm distance from the proximal end of the perfusion chamber to avoid possible flow disturbances at the entrance of the chamber.

Sections were mounted on gelatinized slides for immunohistochemical analysis. As primary antibody we used an anti-fibrinogen antibody.
nogen polyclonal antibody (DAKO A080, Denmark) which we have previously proved efficiency in cross-reacting with pig, whereas as secondary antibody we used rhodamine, TRITC (DAKO R156, Denmark). Results were evaluated with a fluorescence microscope (Vanox AHB3, Olympus, USA) and images were captured by Visilog 5.4 Noesis® program. Controls were run with each set of specimens.

**Statistical analysis**

Results are reported as mean ± SEM. After testing for normal distribution and equality of variances with Levene’s F test, unpaired t-tests was used to compare continuous data between different groups (StatView software; SAS; USA). The correlation between parameters was determined by Pearson’s coefficient of correlation. All probabilities are two-sided with P<0.05 considered statistically significant.

**Results**

**Effects of the antiplatelet drugs on stent-induced thrombus formation**

The effect of the different antiplatelet therapies on stent-induced thrombus formation at 212/s was assessed at two time points (60 min and 180 min post-drug intake) and compared with placebo-control values (Fig. 2).

60 min post-drug intake (Fig. 2A)
The antithrombotic effect of S18886 was already achieved within 1 h after compound-intake, and showed a significant reduction (P<0.05) on platelet deposition (PD) with respect to placebo-control (48% reduction), and monotherapy with either CLOP (40% reduction) or ASA (35% reduction). Combination of ASA+CLOP treatment showed a 58% reduction versus placebo-control (P<0.01); however, interesting enough, it did not show any significant difference on thrombus risk reduction with respect to S18886-treated animals. Neither CLOP nor ASA alone showed any considerable decrease on stent-induced thrombus formation at this time period when compared to placebo-control animals.

180 min post-drug intake (Fig. 2B)

Three hours after drug-intake, when compared to placebo-control group, ASA+CLOP decreased PD by 55%, S18886 by 40%, whereas CLOP alone reduced PD by 28% (P<0.05). Again, no significant differences were detected between S18886 and ASA+CLOP-treated animals and ASA alone exerted no effect.

**Plasma S18886 concentrations**

Mean plasma levels of S18886-treated animals were 95 ± 9 ng/ml and 70 ± 12 ng/ml at min 60 and 180, respectively. Pearson’s correlation analysis was performed to assess whether platelet deposition on the “stented substrate” was significantly correlated with S18886 plasma concentrations. A regression analysis showed a significant inverse correlation between platelet deposition and plasma levels of S18886 at both shear rate conditions (212/s: r²=0.344, P=0.016; 424/s: r²=0.425, P=0.0061).

**Effects on LTA**

When compared to non-treated values, collagen (5 µg/ml)-induced LTA was markedly reduced by both S18886 and ASA treatment by around 60%, and combination of ASA+CLOP by ~80% 60 min after drug intake. Such inhibitory effect was sustained throughout the experiment (P<0.05; Fig. 3A). In contrast, CLOP did not exert any significant inhibitory effect. As shown in Figure 3B, platelets from S18886-treated animals did not aggregate when challenged by U46619 (97% reduction; P<0.0001). Finally, ADP-triggered LTA-aggregation was time-dependently inhibited by CLOP (alone or in addition to ASA) with a reduction...
of about 50% at min 60 (P<0.001) and 68% at min 180 (P<0.0001) (Fig. 3C). As expected, both ASA and S18886 did not modify ADP-induced platelet aggregation.

Immunohistochemical analysis

Immunohistochemical staining of fibrin(ogen) deposition was performed on the perfused substrates obtained from the placebo-control group and the treated animals at both periods (60 min: Fig. 4; and 180 min: Fig. 5). Both 60 and 180 min after drug intake fibrin(ogen) deposition followed the pattern already observed in platelet deposition; indeed, fibrin(ogen) deposition was markedly decreased in the S18886- and ASA+CLOP-treated animals in comparison with placebo-control, ASA-, and CLOP-treated animals.

BT

CLOP alone or combined with ASA treatment produced a significant prolongation in BT in all animals (>45 min) in comparison with placebo-control (14 ± 1 min), ASA- (20 ± 2 min), and S18886-treated animals (25 ± 7 min) (Fig. 6; P<0.0005). Prolongation of BT induced by S18886 did not reach statistical significance and in these animals and, unlike in CLOP-treated animals, we could not observe any oozing from surgical wound or hemorrhagic complications.

Biochemical, coagulation, and haematological parameters

As shown in Table 1, both hematological and coagulation parameters did not differ significantly between the different treatment groups and they were within the normal pig range. In all animal groups aPTT mean ratio was within the normal range for low level of anticoagulation (mean aPTT ratio: 1.5–2.5 with heparin 50 U/kg). Biochemical parameters in both treated groups were always within the physiological values (data not shown).

Discussion

The porcine ex-vivo arteriovenous shunt model using the Badimon perfusion chamber with stent deployment reflects certain important in-vivo characteristics of stent thrombosis and it is a useful tool for evaluating the efficacy of antiplatelet therapies before moving towards in-vivo animal studies (saving ethical concerns with excessive animal use) or conducting expensive clinical trials. Moreover, it has been widely accepted and successfully adapted to characterize the events resulting in acute stent thrombosis (31). In this study we report that oral treatment with a TPr antagonist (18) induces an effective, fast and steady decrease in stent-induced thrombosis similar to that observed with standard therapy of ASA plus a LD of CLOP but without substantial prolongation of bleeding time. Interestingly, these potent antiplatelet effects were not observed 1 h after oral monotherapy with ASA or CLOP.

Coronary artery stent placement for abrupt or threatened artery occlusion due to plaque rupture or arterial dissection after PCI has been a valuable treatment in maintaining lumen patency and reducing the need for urgent CABG (34). Although modern stent design, accumulated operator experience, and the use of the antiplatelet agents (i.e. CLOP and ASA) have improved clinical outcomes, acute stent thrombosis still occurs in 0.5–1.5% PCI cases, especially in small vessels (2, 35). Indeed, in patients who have undergone PCI, persistent platelet activation accompanied by thrombin generation and subsequent fibrin-induced clot stabilization occurs. Thus, acute thrombosis is triggered within minutes to hours after the stenting procedure (12), supporting the need for a rapid antithrombotic effect. Despite the common practice of CLOP loading on top of ASA for coronary stenting, the dosage, the time dependence, and degree of platelet inhibition after this therapy remains variable (36, 37). Our translational study shows that S18886 alone produces similar inhibitory effects than dual administration of ASA plus loading-dose CLOP on stent-induced thrombotic complications within 1 h. However, no effect was observed after single oral intake of a conventional LD of CLOP.

Recent human data have also shown that oral doses of 10 mg S18886 achieved plasma concentrations around 100 ng/ml which suffice to render a powerful antiplatelet effect within 1 h and was maintained for at least 12 h (22). This human study (22) was carried out under ex-vivo conditions and antiplatelet effects of S18886 were analyzed against a single agonist. In contrast, our ex-vivo study analyzes platelet function in flow conditions that mimic a “stented arterial vessel” and compares it to that of currently used antiplatelet therapies further supporting S18886 antithrombotic properties. Interestingly, plasma levels in our study were a little lower than 100 ng/ml.

As mentioned above, several studies have suggested that greater LD may reduce the time to achieve optimal inhibition (16). However, divergent results have also been published (38, 39). Moreover, larger trials with adequate statistical power are warranted to confirm these findings. Nevertheless, although a higher LD of CLOP has been demonstrated to improve clinical outcomes and therefore may shorten the time interval necessary for effective pre-treatment, bleeding risk may also be elevated, hence, many clinicians withhold CLOP administration until coronary anatomy is defined. In this porcine model, S18886 besides

![Figure 6: Bar graph of bleeding time in all animal groups. Time was recorded as 45 min if bleeding had not spontaneously stopped by this time. ASA: aspirin; CLOP: clopidogrel. * P<0.0005 versus placebo-control, ASA-, and S18886-treated animals (n= 4 animals per group).](image-url)
its rapid antiplatelet effect also induced little prolongation of bleeding time when compared to CLOP either alone or combined with ASA. In this regard, the potential advantage of S18886 over CLOP + ASA could include a lower risk of adverse hemorrhagic events especially if major surgery is required (14).

When compared to ASA, S18886 has demonstrated to induce a superior platelet and fibrinogen inhibitory profile (20). Yet, S18886 may also have other specific pharmacological advantages over ASA such as the blockade of deleterious prostaglandin-endoperoxides (e.g. PGH2) discharged upon endothelial dysfunction and subsequent prostacyclin inactivation (40), inhibition of the deleterious effects due to extraplatelet sources of TXA2 biosynthesis (possibly driven by COX-2 or isoprostanes) (41), and the potential to antagonize the effects of TXA2 on TPR present on other cells (e.g. monocytes and vascular cells). Indeed, all these effects are markedly increased in patients with CAD and after PCI (42). Besides, S18886 preserves the beneficial COX-1 endothelial production of prostacyclin leading to enhanced platelet inhibition and vasodilatation (22). Conversely, in terms of platelet aggregation, our results showed that ASA alone induced a rapid inhibition on collagen-induced LTA aggregation. However, taking into account that collagen is a weak agonist, animals were healthy, and blood sample was collected in citrate, reduction of TXA2 synthesis by ASA may have been sufficient to inhibit platelet activation.

Finally, fibrinogen deposition followed the pattern already observed in platelet deposition. Since platelet aggregates facilitate thrombin generation by providing a phospholipid surface on which coagulation reactions occur efficiently, the reduction on fibrin deposition is probably explained by a decrease in the platelet mass available for thrombin formation as a result of the inhibition of platelet aggregation.

In conclusion, administration of S18886 (a TPR antagonist) before coronary stenting may provide antithrombotic efficacy similar to dual therapy of ASA plus CLOP while not interfering with hemostasis, thus presenting a more favourable safety profile. Furthermore, a growing number of reports suggest a substantial interindividual variability in patient’s response to CLOP (“clopidogrel resistance”) (37, 43), which raises questions on whether PCI patients should have their platelet function measured before embarking on such procedures and underscores the need for further research in new antithrombotic strategies. Because S18886 has previously shown to exert effects on the progression of atherosclerosis (19) and to improve endothelium-dependent vasodilation (23), altogether these findings in experimental models seem to suggest that in addition to its antithrombotic profile, blockade of the TP-receptor pathway may be of additional benefit to prevent atherothrombotic diseases.

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Table 1: Follow-up of the hematological and coagulation parameters. Values are expressed as mean ± SEM. Between brackets normal pig values. Red blood cells (RBC); platelets (PLT); hematocrit (HCT); activated partial tromboplastin time (aPTT); prothrombin time (PT); Aspirin (ASA; 5 mg/kg); clopidogrel (CLOP; 10 mg/kg); S18886 (0.3 mg/kg).

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<td>ASA + CLOP</td>
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<td>4.4 ± 0.1</td>
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<td></td>
<td>ASA + CLOP</td>
<td>440 ± 10</td>
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<td>ASA + CLOP</td>
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