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Cangrelor Tetrasodium

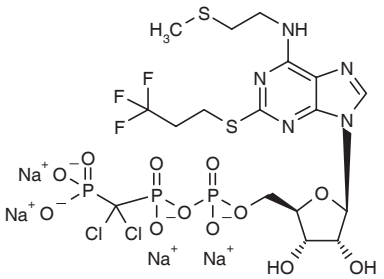
$P2Y_{12}$ Antagonist
Antiplatelet Agent

Rec INNM; USAN

AR-C69931
AR-C69931MX

5'-*O*-[[[Dichloro(phosphono)methyl](hydroxy)phosphoryloxy](hydroxy)phosphoryl]-*N*-[2-(methylsulfanyl)ethyl]-2-(3,3,3-trifluoropropylsulfanyl)adenosine tetrasodium salt

InChI=1/C17H25Cl2F3N5O12P3S2.4Na/c1-43-5-3-23-12-9-13(26-15(25-12)44-4-2-16(20,21)22)27(7-24-9)14-11(29)10(28)8(38-14)6-37-42(35,36)39-41(33,34)17(18,19)40(30,31)32;;;;/h7-8,10-11,14,28-29H,2-6H2,1H3,(H,33,34)(H,35,36)(H,23,25,26)(H2,30,31,32);;;;/q;4*+1/p-4/t8-,10-,11-,14-;;;;/m1..../s1



$C_{17}H_{21}Cl_2F_3N_5Na_4O_{12}P_3S_2$
Mol wt: 864.2881

CAS: 163706-36-3

CAS: 163706-06-7 (free acid)

EN: 259645

Abstract

Cangrelor (AR-C69931MX) is a nonthienopyridine direct-acting $P2Y_{12}$ antagonist under development for the treatment of acute coronary syndrome and as an ultrafast-acting intravenous antithrombotic agent. Cangrelor inhibits platelet aggregation with a rapid onset and offset and does not require metabolism for therapeutic activity. In *ex vivo* samples of blood from patients with acute coronary syndromes, cangrelor reduced platelet-leukocyte interactions, suggesting that the drug may possess additional disease-modifying activity. Phase II studies have shown a good safety profile and a greater inhibitory effect on platelet aggregation compared to clopidogrel. Results of clinical studies indicate that cangrelor may possibly inhibit the potentiation of platelet aggregation associated with heparin. In comparative studies with gpIIb/IIIa receptor antagonists, cangrelor showed similar inhibitory effects on platelet aggregation responses, with a slightly more favorable impact on bleeding time. Cangrelor has shown promising results as an adjunct to fibrinolysis with tissue-type plasminogen activator (t-PA). Ongoing phase III trials will provide more definitive information on clinical efficacy and safety.

Synthesis*

Cangrelor tetrasodium can be prepared by the following method. 2-Mercaptoadenosine (I) is *S*-alkylated with 3,3,3-trifluoropropyl chloride or iodide in the presence of NaH to give the trifluoropropyl sulfide (II). After acylation of (II) with Ac_2O and NaOAc at 80 °C, the resulting peracetylated compound (III) is *N*-alkylated with 2-(methylthio)ethyl iodide and NaH, yielding (IV). Subsequent hydrolysis of (IV) with 0.1 M NaOH in refluxing MeOH furnishes the adenosine derivative (V). The 5'-hydroxyl group of (V) is then phosphorylated employing $POCl_3$ in cold triethyl phosphate to produce the phosphoryl chloride (VI), which is hydrolyzed to the phosphate salt (VII) upon treatment with aqueous ammonium bicarbonate. Activation of the 5'-monophosphate (VII) with carbonyl diimidazole and tributylamine produces the phosphoryl imidazole intermediate (VIII), which after condensation with dichloromethylenebis(phosphonic acid) (IX) is converted to the title tetrasodium salt by treatment with either aqueous $NaHCO_3$ or with NaI in methanol-acetone (1-3). Cangrelor tetrasodium can alternatively be obtained by condensation of acid chloride (VI) with dichloromethylenebis(phosphonic acid) (IX) in the presence of tributylamine, followed by conversion to the target tetrasodium salt with aqueous $NaHCO_3$ (1, 2). Scheme 1.

The precursor 2-mercaptoadenosine (I) can be obtained as follows. Treatment of adenosine (X) with H_2O_2 and AcOH affords the N^1-oxide (XI), which is further converted to N^1-benzyloxyadenosine perchlorate (XII) according to known methods. Boiling of (XII) with aqueous NaOH effects cleavage of the pyrimidine ring to generate the imidazole carboxamidoxime (XIII), which is then

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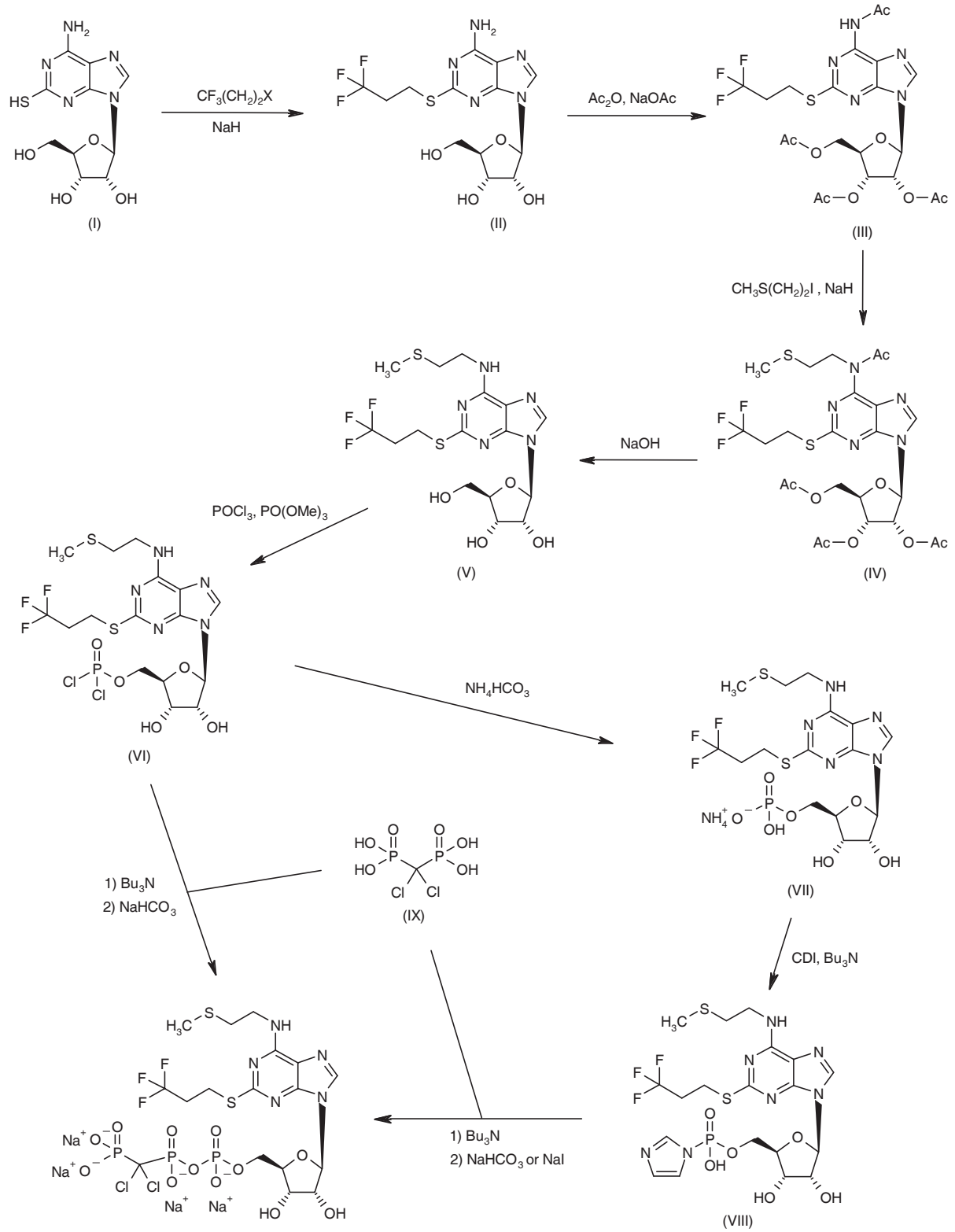
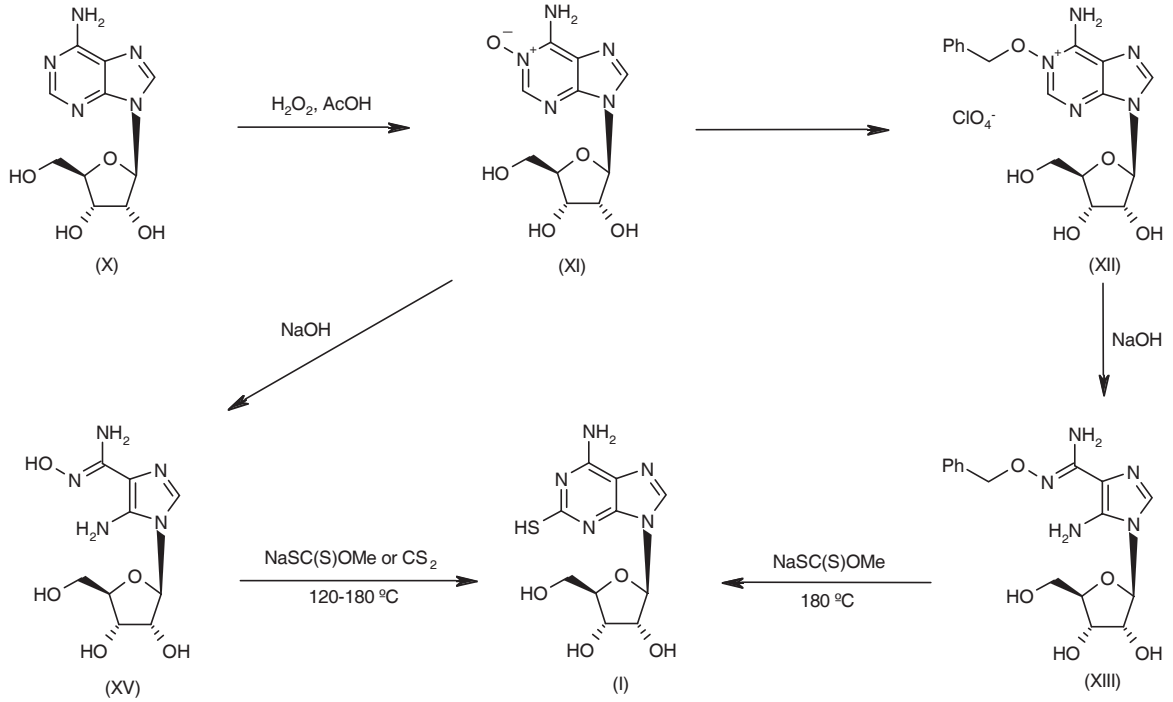
Scheme 1: Synthesis of Cangrelor Tetrasodium



Scheme 2: Synthesis of Intermediate (I)



cyclized with sodium methyl xanthate at 180 °C in an autoclave to afford the target mercaptoadenosine (I), along with its *S*-methyl and *S*-benzyl analogues. In a related method, the alkaline cleavage of adenosine *N*-oxide (XI) gives the amidoxime (XV). Cyclization of (XV) with sodium methyl xanthate or with CS_2-MeOH-pyridine under a variety of conditions leads to different mixtures of the target (I) and some related byproducts. Best results have been obtained by treatment of (XV) with CS_2-MeOH-H_2O at 120 °C (4). Scheme 2.

Background

Atherothrombotic complications are the main contributors to mortality in developed countries and platelets play an important role in their pathogenesis (5). Platelets are known to participate in early events leading to the development of atherosclerosis (6, 7) and also in the precipitation of acute ischemic events (8, 9).

Thrombotic complications attributed to platelets almost invariably require prior formation of a mural thrombus. The thrombus itself, or embolized portions, can be responsible for downstream ischemic complications. Several factors are known to participate in the regulation of thrombus formation. Platelet adhesion to the vessel wall increases with shear stress (10). Glycoprotein IIb/IIIa (gpIIb/IIIa) is expressed in an active conformation after platelets become exposed to a damaged arterial surface under flow conditions (11, 12). Both thrombin generated through the activation of the coagulation system and thromboxane A_2 (TxA_2) generated through arachidonic acid metabolism are powerful platelet-activating agents, thus facilitating platelet deposition and the growth of platelet aggregates (13-15). In addition, platelets possess several receptors for adenosine diphosphate (ADP) on their membrane surface and contain ADP in their storage granules, which is released during platelet secretion (16). The release of ADP and other vasoactive substances stored in platelet granules is of critical importance in the regulation of platelet responses (17).

Patients with congenital defects of platelet ADP receptors and those with storage pool deficiency who are selectively deficient in dense granules develop hemorrhagic syndromes, produce smaller aggregates and adhere defectively on damaged vascular surfaces (10, 11). ADP also plays a key role in the development and extension of arterial thrombosis (12, 18) and is partially responsible for cyclic flow variations in stenosed arteries (19). Platelets possess three P2 receptors for adenine nucleotides: $P2Y_1$ and $P2Y_{12}$, which interact with ADP, and $P2X_1$, which interacts with adenosine triphosphate (ATP) (20-22). The transduction of the ADP signal involves both a transient rise in free intracellular Ca^{2+} (23, 24) mediated by the G_q-coupled $P2Y_1$ receptor, and the inhibition of adenylyl cyclase mediated by the G_i-coupled $P2Y_{12}$ receptor (Fig. 1). While activation through the $P2Y_1$

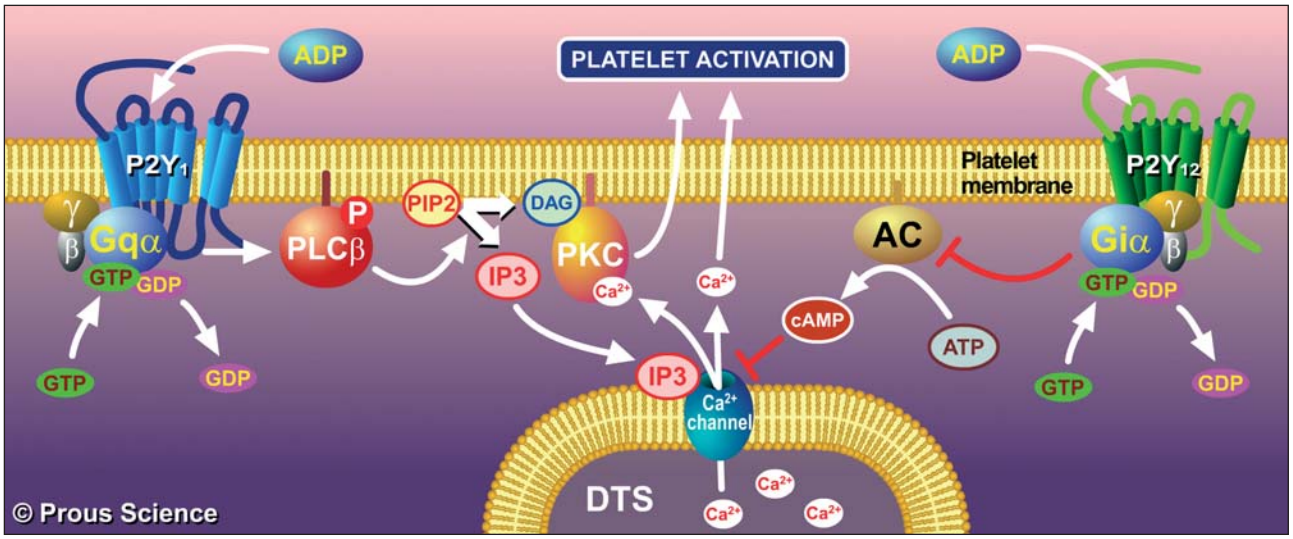


Fig. 1. Signal transduction pathways associated with platelet $P2Y_1$ and $P2Y_{12}$ ADP receptors. ADP binding to a G-protein-coupled P2 receptor induces a conformational change that allows the binding of the G-protein complex, in which the α-subunit becomes activated through the release of bound GDP, which allows a GTP molecule to bind in its place. The $P2Y_1$ receptor is coupled to a q-type G-protein. Activated G_q protein in turn activates phospholipase C β (PLCβ), which cleaves phosphatidylinositol bisphosphate (PIP2) to diacylglycerol (DAG) and inositol triphosphate (IP_3). IP_3 binds to calcium channels in the dense tubular system (DTS) membrane and releases calcium to the cytosol. DAG and calcium activate protein kinase C (PKC) at the surface of the plasma membrane. Increased cytosolic calcium levels and activated PKC are the key elements causing platelet activation. The $P2Y_{12}$ receptor is coupled to an i-type G-protein. Activated G_i protein inactivates adenylyl cyclase (AC). Because active AC dephosphorylates ATP to form cyclic AMP (cAMP), which maintains calcium sequestered internally in the DTS, with inactive AC cellular levels of cAMP drop and calcium can be released to the cytosol.

receptor leads to platelet shape change and rapidly reversible aggregation, activation through the $P2Y_{12}$ receptor causes a slowly progressive and sustained platelet aggregation. In addition, signaling through the $P2Y_{12}$ receptor potentiates platelet dense granule release and TxA_2 generation, stabilizes thrombin-induced aggregate formation, and plays a role in the procoagulant activity of platelets (25, 26). These facts together with its limited distribution make the $P2Y_{12}$ receptor an interesting therapeutic target.

Pharmacological inhibition of the $P2Y_{12}$ receptor with thienopyridine compounds has proven an effective alternative in the regulation of excessive platelet responses. In addition, direct and reversible $P2Y_{12}$ antagonism by new compounds, such as cangrelor, appears to be an interesting alternative when rapid inhibition of platelet aggregation or its quick reversal is required.

ATP is a competitive antagonist of ADP-induced platelet aggregation (27). This discovery led to the definition of the platelet-specific ADP receptor $P2Y_{12}$ subtype (then named P2T), at which ADP is an agonist and ATP a competitive antagonist (28). ATP is undesirable as a therapeutic agent due to its lack of both specificity and efficacy, and its rapid metabolism to ADP by ectonucleotidases in the blood. Therefore, the search for ATP analogues more resistant to degradation and displaying an increased affinity for the $P2Y_{12}$ receptor began during the 1980s. Manipulation of the chemical structure of ATP resulted in a novel class of pharmacological compounds known as purinoreceptor modulators, with many compounds in the AR-C research and development class (24, 29, 30). AR is a common prefix used in the early development of these ATP analogues and MX represents the tetrasodium salt (31). Addition of substituents in the 2-position of the adenine ring (32, 33) increased the affinity properties, while β,γ-methylene substitutions in the triphosphate part of the molecule increased the stability (34). These analogues provided a starting point for the AstraZeneca R&D Charnwood medicinal chemistry program, which led to the discovery of the potent, selective $P2Y_{12}$ receptor antagonists AR-C66096MX (35), AR-C67085MX (36) and, later, cangrelor tetrasodium (AR-C69931MX) (3). All three compounds potently inhibit ADP-induced aggregation of human washed platelets and show high selectivity for the $P2Y_{12}$ receptor over $P2Y_1$ and $P2X_1$ receptors, which are also present on platelets.

Cangrelor resulted from modifications in the ATP molecule, *i.e.*, replacing the anhydride groups with methylene groups and a halogen to confer higher affinity and a longer half-life, and adding nonpolar moieties and sulfide-linked chains to confer greater antagonist activity. A modification of the AR-C67085 compound at the adenine C2 position with 3,3,3-trifluoropropylthio and *N*6-methylthioethyl groups increased potency by 6 times (24, 29, 30).

Preclinical Pharmacology

Cangrelor acts directly at the $P2Y_{12}$ receptor without the need for conversion in the liver to an active metabo-

lite. Platelets from healthy volunteers treated with cangrelor behaved similarly to platelets from a patient congenitally deficient in the $P2Y_{12}$ receptor when both were exposed to a collagen-coated surface under flow conditions (36). In both cases, platelets formed small, loosely packed aggregates in comparison with normal blood, which formed large, densely packed thrombi. Cangrelor has been used in many studies to characterize the function of the $P2Y_{12}$ receptor (3, 26, 37, 38).

The effects of cangrelor on ADP-induced platelet function have been extensively tested *in vitro* (31). In a turbidimetric assay using human washed platelets, cangrelor inhibited ADP-induced (30 mM) aggregation with an inverse logarithmic concentration causing 50% inhibition (pIC_{50}) of 9.4. In whole blood, the potency of cangrelor depends on the assay type. Using impedance aggregometry in heparinized blood (50% diluted blood in saline), the pIC_{50} was 9.2 with 3 mM ADP. Using citrated blood and the residual platelet count method, the pIC_{50} was 7.6 when aggregation was induced by 20 mM ADP (van Giezen, unpublished data). These differences may relate to the use of different ADP concentrations, the extent of blood dilution and the anticoagulant used. The potency of cangrelor translates well to other species. The pIC_{50} was 9.2 for dog blood and 8.3 for rat blood using impedance aggregometry and heparinized blood.

By inhibiting the $P2Y_{12}$ receptor, cangrelor exerts a marked inhibitory effect on aggregation and a partial inhibition of intracellular Ca^{2+} concentrations, and both these effects are potentiated by prostaglandin E_1 (PGE_1) (39) and prostacyclin (PGI_2) (40), both of which act by stimulating adenylate cyclase to increase levels of cAMP. In addition, cangrelor disrupts the sustained gpIIb/IIIa activation induced by potent platelet agonists such as thrombin, via inhibition of Rap-1b but not protein kinase C (PKC) (41).

Cangrelor reduces thrombin-induced platelet activation (42) and exhibits a synergistic effect with thrombin inhibitors such as melagatran (43). A further interesting effect of cangrelor, not observed with aspirin, is attenuation of the potentiation of platelet aggregation by heparin in human whole blood (44). In studies performed using blood flowing at high shear rates, firm platelet attachment on immobilized von Willebrand factor was inhibited by preincubation of blood with cangrelor, whereas the transient interaction was not influenced (45). In addition, the inhibitory effect of cangrelor on both shear-induced platelet aggregation and adhesion on collagen was enhanced by $P2Y_1$ antagonists (46). Cangrelor was also effective in reducing platelet thrombus formation on atherosclerotic plaque under arterial flow, in contrast to aspirin (47).

The effect of cangrelor was also tested in studies performed to evaluate the relative importance of the platelet ADP receptors $P2Y_1$ and $P2Y_{12}$ in the procoagulant activity of platelets. The $P2Y_{12}$ receptor is involved in thrombin generation and in thrombin-induced exposure of phosphatidylserine on platelets (48). Exposure to cangrelor delayed clotting induced by a collagen-related peptide, although it did not affect fibrinolysis or the elastic properties of the clot (49).

Apart from the inhibitory effect on the cohesive, adhesive and procoagulant properties of platelets, cangrelor has been shown to interfere with dense and α-granule secretion induced by either collagen or thrombin receptor-activating peptide (TRAP) (50). These effects were observed both in the presence of cangrelor alone and in combination with gpIIb/IIIa antagonists.

Data obtained from studies in animal models show that reversible antagonism of $P2Y_{12}$ receptors with cangrelor results in high levels of platelet aggregation inhibition, with prevention of both arterial thrombosis and reocclusion after thrombolytic therapy (51).

The effect of cangrelor in a canine model of arterial thrombosis, consisting of electrically damaged, partially stenosed dog carotid artery (52), was also assessed. Either placebo or cangrelor (4.0 μg/kg/min for 6 h) was administered as an i.v. infusion beginning 15 min before the induction of vessel wall injury. While each of 5 control animals developed occlusive thrombi within 3 h after induction of vessel wall injury, in 5 of 6 cangrelor-treated animals the carotid artery blood flow was maintained for the duration of the protocol. *Ex vivo* ADP-induced platelet aggregation was inhibited at the first measurement time point 75 min after the start of drug infusion and remained inhibited during drug administration. Bleeding time values were increased in the drug-treated group. Values for both *ex vivo* platelet aggregation and bleeding times returned to control values shortly after discontinuation of cangrelor. Therefore, cangrelor antagonizes the *ex vivo* and *in vivo* aggregatory effects of ADP, and displays a rapid onset and offset of action, with the ability to prevent occlusive arterial thrombus formation.

In a model of mechanically damaged rabbit mesenteric artery (53), anesthetized rabbits were treated with cangrelor (3 μg/kg/min i.v.) or clopidogrel (25 mg/kg p.o.). The efficacy of these treatments was monitored *ex vivo* by measuring aggregation and thrombin generation in blood samples. Mesenteric arterioles were mechanically injured; thrombus growth and subsequent embolus formation were visualized by real-time intravital microscopy. Cangrelor and clopidogrel significantly reduced the total duration of embolization (52% and 36%, respectively), and fewer and smaller emboli were produced. The size of the initial thrombus was significantly reduced, but its stability was unaffected, suggesting that plug formation was still effective.

The effect of cangrelor in conjunction with thrombolytic therapy on the prevention of platelet aggregation and thrombus formation was assessed in a canine coronary electrolytic injury model of thrombosis (54). t-PA (1 mg/kg in phase I, 0.5 mg/kg in phase II in the cangrelor group, and 1 mg/kg in the placebo group in phase I and II) was administered 30 min after thrombus formation; either saline or cangrelor (4 μg/kg/min) was given to all animals i.v. 10 min before t-PA administration for a total of 2 h. All animals received heparin (80 U/kg) as an i.v. bolus followed by a continuous infusion of 17 U/kg/min. Myocar-

dial tissue perfusion was evaluated by use of the colored microsphere technique and real-time myocardial contrast echocardiography. The incidence of reocclusion and cyclic flow variations was significantly decreased in the cangrelor group ($p < 0.05$). Myocardial tissue flow with cangrelor treatment improved significantly at 20 and 120 min after reflow, whereas tissue flow with placebo remained at a level similar to that during occlusion. The adjunctive administration of cangrelor blocked ADP-induced platelet aggregation and recruitment and prevented platelet-mediated thrombosis, resulting in prolongation of reperfusion time and a decrease in reocclusion and cyclic flow variations. Myocardial tissue perfusion was significantly improved in the $P2Y_{12}$ antagonist group.

As mentioned previously, significant expression of $P2Y_{12}$ has also been detected in the brain, where it is apparently confined to glial cells (20, 55). Studies performed in the PC-12 cell line, ontogenetically related to sympathetic neurons, showed that cangrelor attenuates the P2Y receptor-mediated control of neuronal Ca^{2+} channels (56).

Although cangrelor does not appear to have significant affinity for other P2 receptors at concentrations > 30 mM, a recent publication described cangrelor as a potent noncompetitive antagonist for the $P2Y_{13}$ receptor (57). The latter finding could not be reproduced in a subsequent, more extensive pharmacological characterization of the $P2Y_{13}$ receptor (Greasley, unpublished data). Interestingly, the $P2Y_{13}$ receptor is a regulator of hepatic high-density lipoprotein (HDL) endocytosis, and cangrelor has been demonstrated to stimulate $P2Y_{13}$ receptor-mediated cholesterol catabolism by the liver (58), conferring a potential atheroprotective effect.

Cangrelor appears to possess a more powerful inhibitory action than the thienopyridine-derived agent clopidogrel, with additional effects in preventing platelet leukocyte interactions and an inhibitory action on procoagulant activity. In comparison with clopidogrel, cangrelor appears to exert a greater inhibitory action on ADP-, TRAP- or collagen-induced platelet aggregation. In conclusion, a substantially greater $P2Y_{12}$ receptor blockade can be achieved with cangrelor (59). Cangrelor also exhibited a more intense inhibitory action than clopidogrel *ex vivo* on TRAP-induced platelet activation and on the procoagulant response of platelets, as evaluated by annexin V binding.

Interactions of platelets with leukocytes and the formation of heterotypic aggregates are considered to play an important role in the pathophysiology of ischemic heart disease. Storey *et al*. (60) compared the effects of clopidogrel and aspirin on ADP-induced platelet-leukocyte conjugate formation and P-selectin expression in healthy volunteers and in patients with ischemic heart disease. Both clopidogrel and cangrelor suppressed ADP-induced platelet aggregation, P-selectin expression and platelet-leukocyte conjugate formation, whereas aspirin had no inhibitory effect.

Behan *et al*. (61) investigated the effects of clopidogrel and cangrelor on TRAP-induced platelet aggregation, procoagulant activity and microparticle formation in a reduced number of patients with acute coronary syndromes. Measurements were performed in platelet-rich plasma using aggregometry and flow cytometry (n=12). Studies with clopidogrel were performed *ex vivo* using blood from patients treated with a 300-mg loading dose plus 75 mg/day. Results were compared with those of cangrelor (400 nmol/l) added to blood samples *in vitro*. Clopidogrel significantly inhibited TRAP-induced aggregation, procoagulant activity (annexin V binding) and microparticle production (all $p < 0.05$). At the concentration tested, cangrelor appeared to be more effective than clopidogrel at inhibiting the ADP component of platelet responses.

Pharmacokinetics and Metabolism

As previously commented, cangrelor does not require metabolic conversion to exert its inhibitory action on the $P2Y_{12}$ receptor (3, 26, 37, 38). This feature, together with the presence of a triphosphate chain in the compound, results in a short half-life *in vivo*, making cangrelor an ideal antiplatelet agent for i.v. use.

Available pharmacokinetic studies (62) have shown that cangrelor has a short half-life of about 2.6 min and a plasma clearance of 50 l/h (3, 30, 63).

The tissue distribution of cangrelor was investigated in rats by whole-body autoradiography and qualitative tissue distribution studies (64). The physicochemical properties of cangrelor limit its volume of distribution and confine it to the plasma compartment. After infusion of [^{3}H]-cangrelor to male rats, high concentrations of radioactivity were observed at early times in highly vascular organs such as heart, lungs, liver and spleen. Radioactivity decreased rapidly and substantially, and was distributed to the liver, kidney and gut, the organs of elimination. Little or no radioactivity was found in the central nervous system.

Safety

The potential for undesirable effects on hemostasis was examined using a model of cyclic flow reductions in the femoral artery of anesthetized male beagle dogs (3). *Ex vivo* ADP-induced platelet aggregation and tongue bleeding time were measured in response to increasing drug doses. Dose-response relationships showed a favorable (98-fold) safety ratio between the desired antithrombotic action and the prolongation of bleeding time. In consequence, the full inhibition of platelet aggregation needed to produce an antithrombotic effect was achieved at doses that prolonged bleeding time by < 2-fold. This substantial separation of the two effects was in marked contrast to the pharmacological behavior of other antiplatelet agents of the gpIIb/IIIa antagonist class.

Clinical Studies

In an open multicenter study, the safety and efficacy of cangrelor were investigated in a limited number of

patients (n=39) with acute coronary syndromes (65). Cangrelor was administered i.v. over 3 h at stepped dose increments to reach a plateau of 2 μg/kg/min for 21 or 69 h, or 4 μg/kg/min for up to 69 h. Modifications of platelet aggregation, bleeding time and plasma concentrations of cangrelor were assessed. Inhibition of platelet aggregation exceeded 90% after 24 h and progressively increased with dose and duration of administration. Steady-state inhibition of ADP-induced platelet aggregation was achieved within 30 min of infusion of cangrelor at doses up to 4 μg/kg/min and 60% of baseline platelet aggregation was re-established in 70% of volunteers within 1 h of termination of infusion. Bleeding times were prolonged after cangrelor in parallel with time of administration and dose. The plasma half-life of cangrelor was < 9 min in 90% of the patients. Cangrelor was well tolerated, although it was associated with a greater incidence of trivial bleeding symptoms (56%). There were no deaths at 30 days and no serious adverse events could be attributed to the drug. Cangrelor therefore appears to be a potent, short-acting platelet ADP receptor antagonist suitable for further studies as an antithrombotic agent.

Jacobsson (66) assessed the safety profile, tolerability and plasma concentrations at steady state of i.v. cangrelor in patients with unstable angina pectoris or non-Q wave myocardial infarction (MI). In this multicenter, double-blind, randomized, placebo-controlled phase II trial, patients were randomized to a 72-h infusion of cangrelor or placebo as adjunctive therapy to aspirin and low-molecular-weight heparin (LMWH). The drug was well tolerated hemodynamically and there were no significant changes in other laboratory values between groups. Plasma concentrations of cangrelor were within the expected range, there were no signs of accumulation and interindividual variability in clearance was low. No serious bleeding events were seen during treatment. The incidence of 1 or more episodes of minor bleeding was slightly higher in patients receiving cangrelor compared with those receiving placebo (38% *vs.* 26%).

Another multicenter, randomized, controlled phase II study evaluated the initial safety and pharmacodynamics of cangrelor in 399 patients undergoing percutaneous coronary intervention (PCI) (67). The first part of the study included 200 patients who were randomized to either placebo or infusion of 1, 2 or 4 μg/kg/min cangrelor in addition to aspirin and heparin beginning before PCI. In the second part of the study, 199 patients were randomized to receive either cangrelor (4 μg/kg/min) or the gpIIb/IIIa receptor antagonist abciximab before PCI. Combined major and minor bleeding occurred in 13% of those receiving cangrelor and 8% of those randomized to placebo during part 1 and in 7% receiving cangrelor compared with 10% randomized to abciximab in part 2; differences never reached the level of statistical significance. The incidence of adverse cardiac events was similar in those receiving cangrelor and those receiving abciximab during part 2 (7.6% *vs.* 5.3%). The mean inhibition of *ex vivo* platelet aggregation in response to ADP at steady state was 100% for both the cangrelor 4 μg/kg/min and abciximab groups. After termination of infusion, platelet aggregation returned to baseline more rapidly with cangrelor than with abciximab. A tendency towards more prolonged bleeding times was observed for abciximab compared with cangrelor.

In a recent study, Greenbaum *et al*. (68) evaluated the safety and coronary artery patency following administration of cangrelor as an adjunct to alteplase (recombinant t-PA). The study was performed in 92 patients with acute MI who received aspirin, heparin and an i.v. infusion of either cangrelor alone, full-dose t-PA alone or one of three doses of cangrelor along with half-dose t-PA. The combination of cangrelor and half-dose t-PA resulted in similar 60-min patency as full-dose t-PA alone and greater patency than with cangrelor alone. The percentage of patients achieving > 70% S-T segment resolution at 60 min tended to be greater with combination therapy than with either cangrelor or t-PA alone (28% *vs.* 13% and 14%, respectively). Bleeding and adverse clinical events were similar for all the study groups. The overall results of the study support the potential of cangrelor as an adjunct to fibrinolysis as a promising therapeutic approach for the treatment of acute MI.

Since many candidates for treatment with cangrelor will often have received previous treatment with thienopyridine-related antiplatelet agents, a recent study by Steinhubl *et al*. (69) evaluated the concurrent effects of cangrelor and clopidogrel administration in a reduced number of patients. Ten healthy volunteers received a 600-mg oral loading dose of clopidogrel and then underwent serial platelet function monitoring for 6 h. Two weeks later, these same individuals received a 600-mg clopidogrel loading dose simultaneously with an i.v. bolus of 30 μg/kg followed by a 2-h infusion of 4 μg/kg/min cangrelor. A separate group of 10 volunteers received a 600-mg clopidogrel loading dose after administration of a cangrelor bolus and a 1-h infusion. Cangrelor and clopidogrel alone achieved the expected levels of platelet inhibition. However, the sustained platelet inhibition anticipated for clopidogrel treatment did not occur when cangrelor was initiated simultaneously. No such effect was found when clopidogrel was started upon completion of the cangrelor infusion. The study concluded that for optimal achievement of sustained platelet $P2Y_{12}$ inhibition in patients treated with cangrelor, clopidogrel administration should be started when the cangrelor infusion is terminated.

Cangrelor is currently undergoing phase III trials in patients requiring PCI (70, 71).

Source

The Medicines Co. (US).

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