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PHARMACOLOGY AND POTENTIAL ROLE OF SELATOGREL, A SUBCUTANEOUS PLATELET $P2Y_{12}$ RECEPTOR ANTAGONIST

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DISCLOSURES

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LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
ADP	Adenosine diphosphare
ALI	Acute limb ischaemia
CABG	Coronary artery bypass grafting
PAD	Peripheral artery disease
PCI	Percutanous coronary intervention
PD	Pharmacodynamic
PK	Pharmacokinetic
PPCI	Primary percutaneous coronary intervention
PR	Platelet reactivity
RCT	Randomised controlled trial
SC	Subcutaneous
STEMI	ST-elevation myocardial infarction
TIA	Transient ischaemic attack

1. INTRODUCTION

Atherothrombosis of the coronary, cerebral or peripheral arteries may lead to acute coronary syndromes (ACS), stroke/transient ischaemic attack (TIA) and acute limb ischaemia (ALI) respectively, contributing to premature mortality and chronic morbidity. The central pathological process in these conditions is platelet activation, usually precipitated by rupture/erosion of an atherosclerotic plaque, with concurrent contact activation of coagulation and release of prothrombotic factors [1].

Whilst platelet activation during thrombosis involves multiple pathways, the platelet $P2Y_{12}$ receptor ('$P2Y_{12}$'), activated by adenosine diphosphate (ADP) that is released from platelets in dense granules, plays a central role in amplifying the response to a range of agonists [1]. $P2Y_{12}$ therefore represents a powerful therapeutic target in arterial thrombosis. Several $P2Y_{12}$ antagonists have now been developed. Orally-administered agents include the thienopyridines clopidogrel and prasugrel that irreversibly inhibit $P2Y_{12}$, and the cyclo-pentyl triazolopyrimidine ticagrelor, which reversibly binds to $P2Y_{12}$ [2]. A parenterally-administered $P2Y_{12}$ antagonist, cangrelor, is also available. Cangrelor is reversibly-binding with rapid onset and offset, but requires intravenous access and a maintenance infusion after an initial bolus reducing its practicability, as well as significant cost implications [3].

The effectiveness of $P2Y_{12}$ antagonists in preventing cardiovascular events in patients with atherothrombosis is well established. Large randomised clinical trials (RCTs) have shown benefits of $P2Y_{12}$ antagonists added to aspirin in ACS [2], or substituted for it in cerebrovascular disease and peripheral arterial disease (PAD) [4]. Furthermore, in ACS, particularly when managed by percutaneous coronary intervention (PCI), the more potent oral $P2Y_{12}$ antagonists ticagrelor, in all ACS, and prasugrel, in the setting of ACS managed by PCI,

offer clinical benefits over clopidogrel [2]. Similarly, intravenous cangrelor reduces ischaemic complications of PCI when compared to oral clopidogrel without increasing severe bleeding [3].

2. DEVELOPMENT AND PHARMACOLOGY OF SELATOGREL

Selatogrel (4-((R)-2-|[6-((S)-3-methoxypyrrolidin-1-yl)-2-phenylpyrimidine-4-carbonyl]amino|-3-phosphonopropionyl)piperazine-1-carboxylic acid butyl ester), known earlier in development as ACT-246475, is a novel $P2Y_{12}$ antagonist for subcutaneous (SC) administration. A selective, potent and reversibly-binding 2-phenyl-pyrimidine-4-carboxamide analogue, it shares a pyrimidine core with ticagrelor and other aspects of its structure with a family of molecules previously investigated as reversible $P2Y_{12}$ antagonists (BX 048, BX 667; Berlex Biosciences) (Figure 1) [5].

In vitro studies characterised selatogrel's basic pharmacology: using Chinese hamster ovary cells expressing $P2Y_{12}$, the concentration required for 50% inhibition was 4.8 nmol/L, and 31 nmol/L using light transmittance aggregometry of human platelet-rich plasma using 3 μmol/L ADP as an agonist [5]. It was determined that the drug was not metabolised by cytochrome P450 enzymes but was a substrate for the hepatic uptake transporters organic-anion-transporting polypeptide 1B1 and 1B3 [6]. In animal studies, the drug led to significantly less bleeding whilst maintaining significant antithrombotic effect compared with clopidogrel or ticagrelor in an experimental rat model of arterial injury. The investigators concluded this suggested a wider therapeutic window than these two existing agents, although no human studies have been powered to assess this. [7, 8].

Following preclinical studies, several human phase I and II trials of selatogrel have now been performed (Table 1). In summary, a standard oral formulation of ACT-281959, a pro-drug of selatogrel, failed to achieve satisfactory reduction in platelet reactivity (PR), even at high doses. An aqueous-organic solution of ACT-281959 achieved a better response but had low palatability limiting dose escalation [9]. Subsequently, a SC-administered preparation of selatogrel was tested in healthy volunteers and its pharmacodynamics (PD) and pharmacokinetics (PK) determined [6, 10]. A dose-dependent potent effect on PR with rapid time to peak effect (30 minutes to 1 hour) and offset (significant by 8 hours, almost total by 24 hours) was demonstrated, with good tolerance and safety. No plasma major metabolites were identified and elimination was largely faecal with a small urinary component. The investigators concluded that inhibitors or inducers of drug-metabolising enzymes are unlikely to affect selatogrel's plasma profile, but could not rule out drug-drug interaction with agents affecting the hepatic uptake transporters organic-anion-transporting polypeptide (OATP) 1B1 and 1B3 as well the efflux transporter multidrug resistance-associated protein 2 (MRP2), of which selatogrel is a substrate. This includes drugs such as cyclosporine, eltrombopag, lapatinib, lopinavir, rifampicin and ritonavir, and patients receiving these drugs were excluded from clinical studies.

Two phase 2 studies of SC selatogrel have now been reported. 345 patients were randomised in a 1:1:1 ratio to receive an SC injection of either selatogrel 8 mg, 16 mg or placebo [11]. Platelet function tests were performed before injection and at serial timepoints up to 24 hours after. Both doses of selatogrel rapidly and powerfully inhibited ADP-induced platelet activation by 30 minutes and with significant inhibition for at ≥ 8 hours, reversing by 24 hours. Whether the injection site was the thigh or abdomen made no difference to the profile of effect.

Significantly, in those patients already receiving maintenance therapy with an oral $P2Y_{12}$ antagonist, including clopidogrel or ticagrelor, selatogrel provided an additive effect. No severe or serious adverse events occurred. There was, however, an increased incidence of mild or moderate dyspnoea in those receiving selatogrel when compared to placebo, not seen in phase I studies. There was some evidence of this being a dose-dependent effect: 5% reported dyspnoea after 8 mg and 9% after 16 mg, compared to no reports after placebo. Certain $P2Y_{12}$ antagonists (ticagrelor and cangrelor) are associated with increased rate of dyspnoea, sharing with selatogrel the property of reversible binding, suggested as a factor in this non-pathogenic phenomenon [3]. No other adverse effects appeared more common following drug rather than placebo, with the possible exception of dizziness, which occurred in 4% and 3% receiving 8 mg and 16 mg respectively, and 1% receiving placebo; and injection site bruising (3% vs. 2% vs. 0%). No significant bleeding occurred in any participant and there were no changes in haemodynamic or electrocardiographic parameters.

A study of 47 patients given selatogrel 8 or 16 mg SC in the early phase of ACS confirmed similar PD/PK findings [12].

3. EXPERT OPINION: POTENTIAL CLINICAL ROLES FOR SELATOGREL

Selatogrel is currently neither commercially-available nor licensed for clinical use. Whilst only phase 2 trials have been conducted at present, the attractive prospect of a rapid-onset parenterally-administered potent and reversible $P2Y_{12}$ antagonist raises the possibility of its use in a number of specific situations, especially, but not limited to, ACS (Figure 2). Outcome-driven phase 3 data would, of course, be needed to make definitive recommendations but potential future roles can be speculated upon.

3.1 Early $P2Y_{12}$ inhibition in ACS

Understanding the natural history of an ACS event can help to identify when $P2Y_{12}$ inhibition might be beneficial. Coronary thrombosis with resulting distal ischaemia +/- infarction is a dynamic process, with thrombus being formed and broken down, the net effect determining the extent of vessel occlusion, a process that can take hours or even days to reach its peak [1]. Even in patients on pre-existing oral antiplatelet therapy, factors such as increased platelet turnover, compliance or reduced absorption may lead to reduced effect, and even small numbers of uninhibited platelets may initiate thrombosis. Whilst in high-risk groups there is evidence that long-term maintenance therapy with $P2Y_{12}$ antagonists can help to prevent thrombotic events [2], this comes at the expense of bleeding risk, limiting the attractiveness of this strategy in the wider population.

Hypothetically, delivering potent $P2Y_{12}$ inhibition as early as possible during an ACS event may have clinical benefits, likely derived from a reduction in the impact of thrombosis on vessel occlusion and the most dangerous sequelae such as ST-elevation myocardial infarction (STEMI). However, early pre-hospital treatment with oral $P2Y_{12}$ antagonists, for example to those with STEMI, has proved disappointing when compared to in-hospital dosing. One factor potentially reducing benefits of pre-treatment is that absorption of oral $P2Y_{12}$ antagonists in the proximal small intestine is significantly delayed by the presence of opioid drugs, commonly administered in ACS [13]. SC-administered selatogrel, with its rapid onset even during ACS, therefore represents an additional option to be investigated with the possibility of preventing the early thrombotic propagation and hence reducing haemodynamic impact within a coronary artery. The route of administration and the possibility of a pre-filled syringe is likely to be practical for pre-hospital administration by caregivers. Similarly, it is feasible that

patients/carers could be trained to give selatogrel at the onset of a suspected ACS event, minimising delay, perhaps akin to the use of pre-filled adrenaline pen by patients at high-risk of anaphylaxis. Clearly this strategy would require robust investigation in the target population before it could be recommended.

3.2 Use during primary percutaneous coronary intervention

Similarly, whether oral $P2Y_{12}$ antagonists should be given before or after primary PCI (PPCI) for STEMI remains debated. Providing cover with a parenteral antiplatelet agent, such as a glycoprotein IIb/IIIa inhibitor, may reduce the risk of acute ischaemic complications in those treated with opiates [13]. Use of selatogrel to achieve rapid $P2Y_{12}$ inhibition during PPCI, circumventing reduced enteral absorption related to morphine or other factors, might hypothetically reduce the need for additional parenteral antiplatelet agents, e.g. glycoprotein IIb/IIIa inhibitors, with the attendant risk of increased bleeding.

3.3 Peri-procedural bridging of $P2Y_{12}$ inhibition

The risk of bleeding during major operative procedures in patients receiving oral $P2Y_{12}$ antagonists is regarded as unacceptably high, hence these are normally withheld in all but the most emergent cases. This includes patients who are admitted to hospital with ACS and require urgent coronary artery bypass grafting (CABG) shortly after diagnosis, when their thrombotic risk remains high. The timing of discontinuation prior to procedures such as CABG may depend on the agent in question and is sometimes guided by platelet function testing [14]. The effect of ticagrelor, for example, begins to reduce from 1 day after discontinuation but it may take at least 72 hours for most patients to reach a level of PR deemed safe for surgery, longer if receiving clopidogrel or prasugrel [14]. This may lead to a period of vulnerability to further

thrombosis, which is prolonged further in cases of inevitable delay. Speculatively, given the rapid onset and offset in effect of SC selatogrel, it may be possible to provide adequate $P2Y_{12}$ inhibition closer to the point of surgery than with oral drugs, similar to anticoagulation with SC low-molecular- weight heparin to cover a period of vitamin K antagonist discontinuation. Based on phase II data, it seems likely that $P2Y_{12}$-mediated PR would fully recover in most patients by 24 hours after the last dose [15], thus allowing safe surgery sooner after discontinuation. Although the 8 and 16 mg doses tested in phase II showed relatively short periods of therapeutic effect (around 8 hours) meaning multiple injections per day may be needed, data from phase I trials suggests that using a higher dose e.g. 32 mg might prolong effect to around 12 hours per dose whilst still returning to near baseline by 24 hours after discontinuation, hence twice daily administration might be sufficient. Given kinetics may complicate multiple dosing regimens, prospective studies in this patient group would be needed to determine the appropriate doses and intervals, but the emergence of selatogrel is a promising development in this area.

3.4 Use in patients with prolonged poor enteral absorption

As well as circumventing poor absorption of oral $P2Y_{12}$ antagonists in morphine-treated ACS patients, selatogrel may potentially find another theoretical niche in patients with longer periods of reduced enteral absorption. Whilst many patients who are 'nil by mouth' e.g. because of swallowing difficulties or reduced consciousness can receive oral $P2Y_{12}$ antagonists via a nasogastric tube or as an orodispersible preparation of ticagrelor, some individuals present challenges when enteral absorption itself is disrupted, most notably those with prolonged periods of critical illness, but also those with chronic conditions such as short bowel syndrome. For specialist use, selatogrel may offer a feasible alternative in those rare cases where a reliable regimen of maintenance therapy with an enterally-active $P2Y_{12}$ antagonist cannot be instigated.

3.5 Use in other thrombotic conditions

As well as ACS, dual antiplatelet therapy with aspirin and a $P2Y_{12}$ antagonist may be of benefit in acute thrombotic stroke or high-risk TIA. For example, recent studies have suggested a reduction in ischaemic complications from acute stroke in those receiving aspirin and clopidogrel vs. aspirin alone, particularly early after the event [16]. Similarly, although a recent study of ticagrelor monotherapy vs. aspirin failed to show a statistically-significant difference in ischaemic events after acute stroke or high-risk TIA, a post-hoc analysis suggested those exposed to both drugs in the peri-infarct period may have improved outcomes compared to a single agent alone, a hypothesis now being tested prospectively in the THALES study (NCT03354429). If $P2Y_{12}$ inhibition is beneficial in acute thrombotic stroke, it is plausible that delivering this as soon as possible after onset of thrombosis may be optimal. The rapid onset of selatogrel, combined with delays in administering oral medication to patients with acute stroke due to concerns regarding safe swallowing, means the novel agent may be a good candidate for further investigation in this setting. Contrary to ACS, it would be difficult, however, to envisage how a patient or pre-hospital caregiver could administer selatogrel in this situation given the need first to exclude intracranial haemorrhage.

Similarly, in cases of ALI due to thrombosis, which may be treated by urgent angioplasty of the peripheral arteries, an oral $P2Y_{12}$ antagonist e.g. clopidogrel is frequently given. Limitations of oral $P2Y_{12}$ antagonists detailed above are potentially relevant in this situation too, hence selatogrel may have a role in improving the speed and reliability of antiplatelet therapy in acute manifestations of PAD.

3.6 Limitations of current evidence

Currently there are no human data to support preclinical work suggesting that selatogrel may have a safer profile compared to other $P2Y_{12}$ antagonists and larger clinical studies are required to assess the safety of selatogrel, including its effect on bleeding rates. Indeed, it is expected that the effects of selatogrel on haemostasis in humans will be consistent with its profile as a $P2Y_{12}$ antagonist, as initially suggested by numerical increase in injection-site bruising.

Cangrelor is known to block the binding of thienopyridine active metabolites to $P2Y_{12}$ [17] and further pharmacodynamic studies of selatogrel are required to investigate any potential negative interaction with clopidogrel and prasugrel in order to guide the switching from selatogrel to oral $P2Y_{12}$ antagonists.

4. CONCLUSIONS

Selatogrel is a novel $P2Y_{12}$ antagonist offering advantages of SC administration, rapid onset/offset and additive effect to maintenance oral therapy. An existing parenterally-administered $P2Y_{12}$ antagonist, cangrelor, is available. It similarly provides rapid, potent and additive antiplatelet effect, and may improve clinical outcomes compared to oral agents in those undergoing PCI [3], but requires intravenous access so is less suited to pre-hospital or repeated administration. Achievement of rapid and reliable $P2Y_{12}$ inhibition in ACS, ALI or acute thrombotic stroke is a logical goal and oral $P2Y_{12}$ antagonists have limitations, as discussed. It should be emphasised that no phase 3 trials have yet been performed, but there is clear rationale for investigating the use of selatogrel to improve clinical outcomes in patients with atherothrombotic conditions.

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TABLES

Table 1 Human studies reported to date of the pharmacodynamics, pharmacokinetics and safety of selatogrel

Study	Study phase	n	Population	Study treatment/design	Key pharmacodynamic findings	Key pharmacokinetic findings	Key safety findings
Baldoni et al. 2014 [9]	I	49	Non-smoking healthy males, 18 to 45 years old, BMI 18 to 32 kg/m^2.	Part I (n=40): oral dose escalation of ACT-281959 (di-ester pro-drug of selatogrel, doses up to 1000 mg) or placebo, dbRCT. Part II (n=9): crossover of single oral doses of selatogrel and two formulations of ACT-281959, open-label RCT.	Part I: Although modest effects on PA and PRU were observed, all doses of oral ACT-281959 tested failed to achieve 50% IPA. Part II: An aqueous-organic oral solution of 70 mg ACT-281959 achieved mean >50% IPA, reverting to baseline by 12-24 hours. PD of other oral preparations of ACT-281959 or selatogrel not assessed.	Part I: Plasma selatogrel concentration peaked at 4 to 6 hours post-dose. None of the doses of ACT-281959 tested achieved mean peak selatogrel levels >IC_{50}. Part II: Of the formulations tested, only the aqueous-organic oral solution of ACT-281959 achieved peak selatogrel levels >IC_{50}, peaking at 2 hours post-dose and ~undetectable by 8 hours.	No clinically relevant effects on laboratory parameters, ECG, physical examination, vital signs. Headache was most common AE, but occurred at similar rates between active drug and placebo. No bleeding events or dyspnoea.
Juif et al 2019 [10]	I	48	Healthy male subjects aged between 19 and 45 years, BMI 18 to 31 kg/m^2.	Randomised to single SC dose of selatogrel 1, 2, 4, 8, 16 or 32 mg, or placebo, dbRCT.	Dose-dependent reduction in PRU, lowest at 30 minutes, duration of effect dependent on dose, reverted to baseline at all doses tested by around 24 hours.	Dose-dependent plasma levels of selatogrel, peaking at 30 minutes post-injection, undetectable by 8 to 12 hours. Plasma concentration of selatogrel correlated with inhibition of PA. Half-life of effect 1.3 to 9.2 hours depending on dose.	No clinically relevant effects on laboratory parameters, ECG, physical examination, vital signs. AEs infrequent and not dose-dependent. No bleeding events or dyspnoea.
Ufer et al. 2019 [6]	I	6	Healthy males, 45 to 63 years old, mean BMI 25.0 kg/m^2.	Single SC dose of 16 mg [^{14}C]-radiolabelled selatogrel.	Not assessed	Time to maximum plasma selatogrel ~45 minutes, plasma half-life 4.7 hours. Geometric mean total recovery of [^{14}C]-radioactivity was 94.9% of which (92.5% in faeces, 2.4% in urine). No major metabolites isolated from plasma. M21 (by gluconuridation) was most abundant metabolite in urine and A1 (by mono-oxidation) in faeces.	No serious adverse events or clinically relevant change of laboratory, vital sign or ECG data. 2/6 had vasovagal presyncope after injection and 1/6 insomnia. No reported bleeding or dyspnoea.
Storey et al. 2019 [11]	II	345	Patients receiving background oral antiplatelet therapy for stable CAD or MI > 3 months prior to enrolment.	Single dose of selatogrel SC 8 mg vs 16 mg vs placebo, 1:1 randomisation to thigh or abdomen injection site, dbRCT.	8 mg and 16 mg achieved significant inhibition of ADP-induced PA and reduction in PRU achieved by 30 mins post-dose, sustained for at least 8 hours and returning to near baseline by 24 hours.	Dose-dependent peak in plasma selatogrel at 30 minutes post-dose, falling in a logarithmic fashion to near-zero at 24 hours.	Dyspnoea in 5% of 8 mg group, 9% of 16 mg group, 0% on placebo. Mild in all but one case (moderate). Injection/venepuncture site bruising, no major bleeding
Sinnaeve et al. 2019 [12]	II	47	Males or post-menopausal females, age 18 to 85 years, diagnosis of acute type 1 MI with symptom onset between 30 mins and 6 hours before enrolment.	Randomised 1:1 to a single SC dose of selatogrel 8 mg or 16 mg.	Mean PRU below pre-defined response threshold after 15 minutes, 91% (8 mg) and 95% (16 mg) were responders at 30 minutes. Effect persisted for at least 60 minutes.	Plasma selatogrel peaked at 1 hour post-dose, had reduced at 8 hours.	Most frequent treatment-emergent AE = ventricular tachycardia (8 mg: n=4, 16 mg: n=3). 1 case of mild dyspnoea (16 mg). 1 case of mild radial access bleeding (8 mg).

^{14}C, carbon-14; AE, adverse event; BMI, body mass index; dbRCT, double-blinded randomised controlled trial; CAD, coronary artery disease; ECG, electrocardiogram; IC_{50}, inhibitory concentration required for 50% inhibition; IPA, inhibition of platelet aggregation; MI, myocardial infarction; PA, platelet aggregation; PD, pharmacodynamic; PRU, platelet reactivity units (VerifyNow® $P2Y_{12}$ test) ; RCT, randomised controlled trial; SC, subcutaneous.

FIGURES

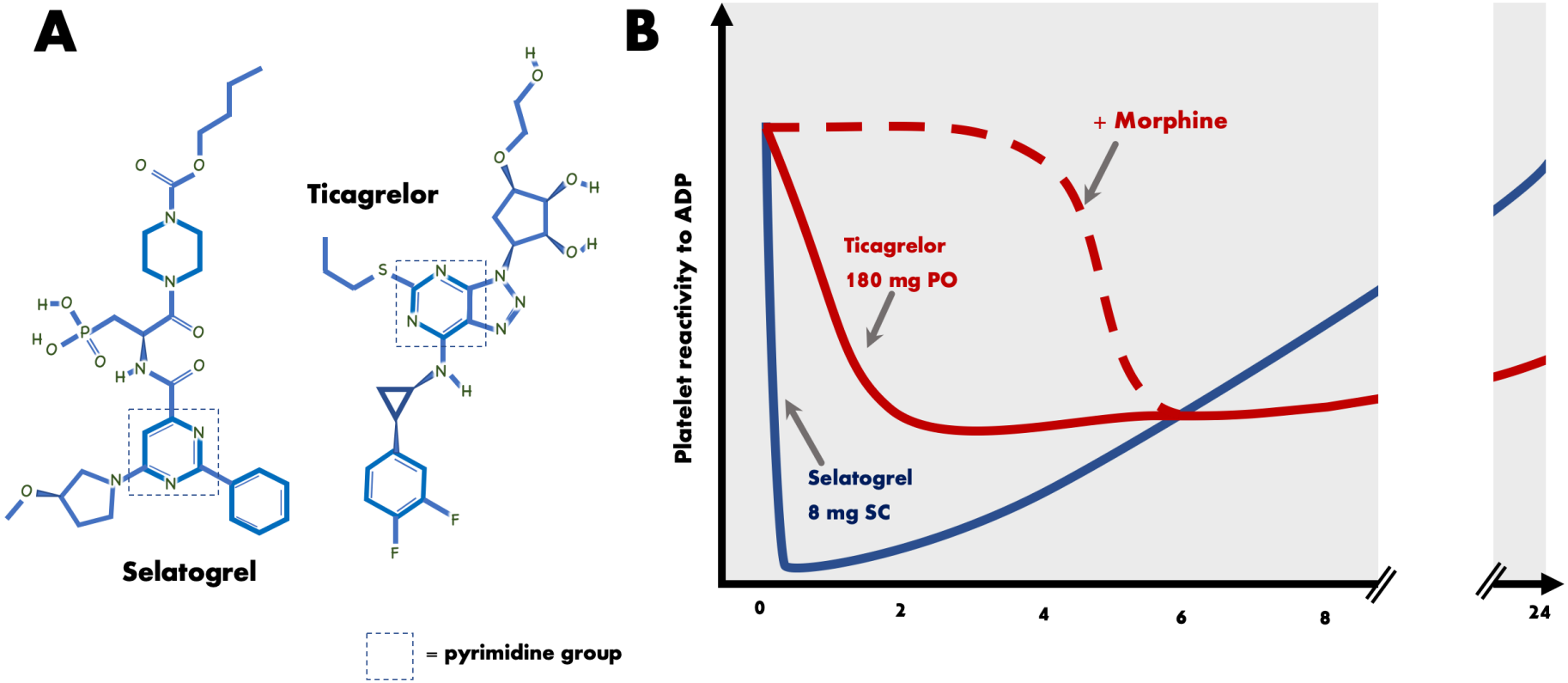

Figure 1 (A) Molecular structure of the novel reversibly-binding $P2Y_{12}$ antagonist selatogrel, shown for comparison alongside the oral $P2Y_{12}$ antagonist ticagrelor. (B) Illustrative figure demonstrating the temporal profile of a single subcutaneous dose of selatogrel's effect on platelet reactivity, compared with an oral loading dose of ticagrelor with (solid line) and without (dotted line) concurrent morphine exposure. ADP, adenosine diphosphate; SC, subcutaneous; PO, per orum.

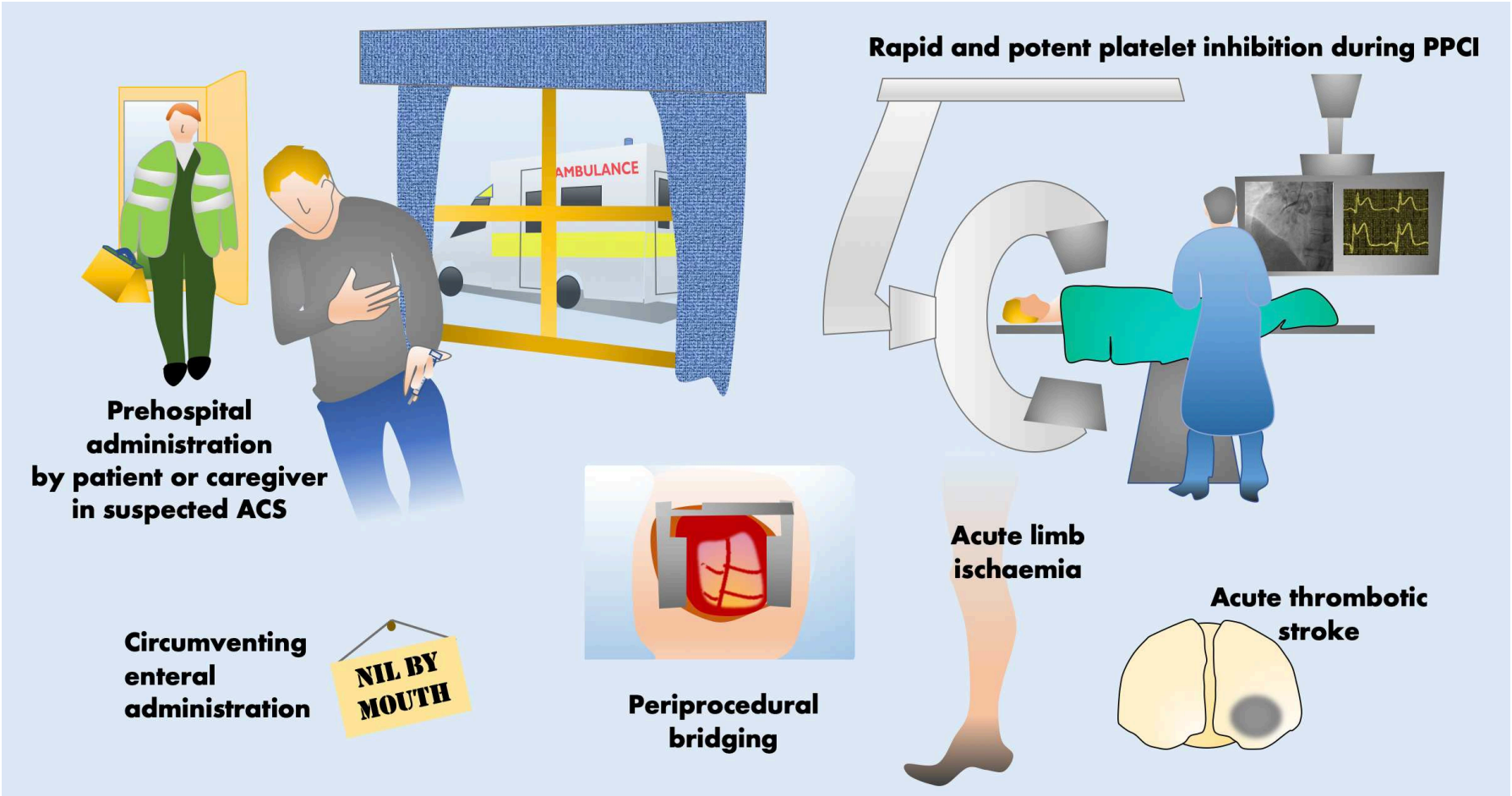

Figure 2 Potential clinical roles for selatogrel, a novel subcutaneous $P2Y_{12}$ antagonist. ACS, acute coronary syndrome; PPCI, primary percutaneous coronary intervention.