Formulary Drug Reviews

Cangrelor

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Each month, subscribers to The Formulary Monograph Service receive 5 to 6 well-documented monographs on drugs that are newly released or are in late phase 3 trials. The monographs are targeted to Pharmacy & Therapeutics Committees. Subscribers also receive monthly 1-page summary monographs on agents that are useful for agendas and pharmacy/nursing in-services. A comprehensive target drug utilization evaluation/medication use evaluation (DUE/MUE) is also provided each month. With a subscription, the monographs are sent in print and are also available on-line. Monographs can be customized to meet the needs of a facility. A drug class review is now published monthly with The Formulary Monograph Service. Through the cooperation of The Formulary, Hospital Pharmacy publishes selected reviews in this column. For more information about The Formulary Monograph Service, call The Formulary at 800-322-4349. The November 2015 monograph topics are evolocumab, dichlorphenamide, necitumumab, cobimetinib, and reslizumab. The Safety MUE is on alirocumab and evolocumab.

Generic Name: Cangrelor
Proprietary Name: Kengreal (The Medicines Company)
Approval Rating: 1S
Therapeutic Class: Aggregation Inhibitors
Similar Drugs: Clopidogrel, Prasugrel, Ticagrelor, Ticlopidine
Sound- or Look-Alike Names: Concerta, Kenalog

INDICATIONS

Cangrelor (AR-C69931MX) is approved as an adjunct to percutaneous coronary intervention (PCI) to reduce the risk of periprocedural myocardial infarction (MI), repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a P2Y₁₂ platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor. Other potential uses are as a bridge therapy for patients receiving oral antiplatelet agents during surgery and for patients who cannot receive oral medications.

CLINICAL PHARMACOLOGY

The P2Y₁₂ receptor is a member of a superfamily of at least 3 purino-receptors, and it is abundantly expressed on human platelets. Inhibition of the platelet adenosine diphosphate (ADP) P2Y₁₂ pathway blocks the activation of platelets by ADP and reduces the incidence of ischemic events in patients with acute coronary syndrome (ACS) and patients undergoing PCI. Other P2Y₁₂ receptor inhibitors (eg, clopidogrel, prasugrel, ticagrelor, ticlopidine) are used to reduce the risk of ischemic events and improve patient outcomes during acute coronary procedures, including PCI.

Cangrelor, a novel nonthienopyridine adenosine triphosphate (ATP) analogue, is an intravenous (IV), potent, rapid-acting, reversible P2Y₁₂ receptor antagonist that inhibits platelet activation and aggregation. Therapeutic doses of cangrelor achieve platelet inhibition greater than 90% to 95%.

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Unlike other P2Y$_{12}$ receptor antagonists (eg, ticlopidine, clopidogrel, ticagrelor, prasugrel), cangrelor is not a prodrug and does not require hepatic activation.$^{11}$ Platelet inhibition begins within 2 minutes following bolus administration of cangrelor.$^{2,11,12}$ Other oral P2Y$_{12}$ receptor antagonists (eg, ticlopidine, clopidogrel, ticagrelor, prasugrel) require several hours before measurable platelet inhibition can be detected.$^{11,12}$ Maximum inhibition of ADP-induced platelet aggregation occurs within 30 minutes of starting the cangrelor infusion.$^{12}$ Following the cessation of cangrelor infusion, platelet function is nearly fully restored within 60 minutes.$^{2,6,8,9,11-13}$

**PHARMACOKINETICS**

Cangrelor is rapidly distributed after administration by IV bolus; peak plasma concentrations are reached within 2 minutes.$^{2}$ Cangrelor is not metabolized by the liver; instead, it is rapidly deactivated in the circulation by dephosphorylation to its primary metabolite, which has negligible antiplatelet activity.$^{2}$ Cangrelor has a plasma half-life of approximately 3 to 6 minutes and a clinical half-life of less than 5 minutes.$^{5,8,12,13}$ Its elimination rate is not influenced by sex, age, renal status, or hepatic function.$^{2}$ Volume of distribution is 3.68 to 3.9 L, plasma clearance is about 43 L/h, and protein binding is 97% to 98%.$^{2,12}$

**COMPARATIVE EFFICACY**

**Indication:** Percutaneous Coronary Intervention

**Studies**

**Drug:** Cangrelor vs Placebo

**Reference:** Bhatt DL, et al, 2009 (CHAMPION PLATFORM trial)$^9$

**Study Design:** Randomized, double-blind, placebo-controlled, double-dummy, multicenter study

**Study Funding:** The Medicines Company

**Patients:** 5,301 patients (modified intention-to-treat [ITT] cohort) with at least 1 atherosclerotic lesion eligible for PCI with or without stent implantation, and evidence of either MI without ST-segment elevation or unstable angina were randomized. Median age was 63 years; 70.3% and 72% were male; 75.7% and 75.8% of patients were White, and 17.8% and 17.9% were Asian in the placebo and cangrelor groups, respectively. Approximately 35% and 60% were undergoing PCI for unstable angina and non-ST-segment elevation (NSTEMI) ACS, respectively.

**Intervention:** Patients were randomized (1:1) to receive either cangrelor 30 mcg/kg as a bolus and cangrelor 4 mcg/kg/min as an infusion, or a placebo bolus and infusion for the duration of the PCI procedure, with a minimum infusion duration of 2 hours and a maximum duration of 4 hours. Patients in the cangrelor group received clopidogrel 600 mg after the end of the cangrelor infusion, and patients in the placebo group received clopidogrel 600 mg at the end of the PCI procedure.

**Results**

**Primary Endpoint(s)**

- Composite of death, MI, or ischemia-driven revascularization 48 hours after PCI in modified ITT population (randomized and received at least 1 dose) was 7% for cangrelor and 8% for placebo (odds ratio [OR], 0.87; 95% confidence interval [CI], 0.71 to 1.07; $P = .17$).

**Secondary Endpoint(s)**

- Rate of death at 48 hours was 0.2% for cangrelor and 0.7% for placebo (OR, 0.33; 95% CI, 0.13 to 0.83; $P = .02$).
- MI at 48 hours: No significant difference between groups.
- New Q-wave MI at 48 hours: No significant difference between groups.
- Ischemia-driven revascularization at 48 hours: No significant difference between groups.

**Endpoint(s)**

- Rate of death at day 30 was 1.1% in the cangrelor group and 1.1% in the placebo group.
- Rate of stent thrombosis at 48 hours was 0.2% for cangrelor and 0.6% for placebo (OR, 0.31; 95% CI, 0.11 to 0.85; $P = .02$).
- Rate of stent thrombosis at 30 days was 0.38% for cangrelor and 0.46% for placebo ($P = .65$).

**Comments:** Cangrelor was not superior to placebo in reducing the primary composite endpoint. The Thrombolysis in Myocardial Infarction (TIMI)– and Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)–defined rates of bleeding did not differ between groups. Power set at 85% estimated 6,400 patients would be required to detect a 25% relative reduction in the primary endpoint, assuming occurrence of 7.7% in the placebo group. There was a greater incidence of Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY)–defined minor and major bleeding and GUSTO-defined mild bleeding in cangrelor-treated patients.
Limitations: Trial enrollment was terminated after a second interim analysis, because it was decided that cangrelor was not superior to placebo.

Drug: Cangrelor vs Clopidogrel

Reference: Harrington RA, et al, 2009 (CHAMPION PCI trial)\(^{13}\)

Study Design: Randomized, double-blind, double-dummy, active-control, multicenter, international study

Study Funding: The Medicines Company

Patients: 8,722 patients (modified ITT cohort) with stable angina, unstable angina, ST-segment elevation myocardial infarction (STEMI), or NSTE ACS were scheduled to undergo PCI. Patients were excluded if they had received fibrinolytic agents or glycoprotein IIb/IIIa inhibitors within the previous 12 hours or clopidogrel greater than 75 mg per day in the previous 5 days. Median age was 62 years; 72.2% and 73.9% were male, 81.7% and 82.6% of patients were White, 7.1% and 7% were Asian, and 5.4% and 4.9% were African American in the clopidogrel and cangrelor groups, respectively. Approximately 49%, 25%, and 15% of patients were diagnosed with NSTE ACS, unstable angina, and stable angina, respectively, prior to PCI.

Intervention: Patients were randomized (1:1) to receive cangrelor (30 mcg/kg as a bolus and 4 mcg/kg/min as an infusion) and placebo capsules, or a placebo bolus and infusion and clopidogrel 600 mg. Treatments were initiated at least 30 minutes before PCI and continued for the duration of the procedure or for 2 hours, whichever was longer. The infusion could continue for 4 hours at the discretion of the investigator. At the end of the infusion, patients in the cangrelor group received clopidogrel 600 mg and patients in the clopidogrel group received placebo capsules.

Results

Primary Endpoint(s)
- Composite of death from any cause, MI, or ischemia-driven revascularization at 48 hours was 7.5% for cangrelor and 7.1% for clopidogrel (OR, 1.05; 95% CI, 0.88 to 1.24; \(P = .59\)).

Secondary Endpoint(s)
- Composite of death or MI at 48 hours and at 30 days; composite of death, MI, or ischemia-driven revascularization at 30 days; stroke at 48 hours; abrupt vessel closure; threatened abrupt vessel closure; need for urgent coronary artery bypass grafting or an unsuccessful procedure during the index PCI; acute stent thrombosis (at 24 hours) and subacute stent thrombosis (at 48 hours); death from any cause at 6 months and at 1 year: No significant differences were observed between groups.

Comments: CHAMPION PCI enrollment was terminated on May 13, 2009, at which point 8,877 of the expected 9,000 patients (98.6%) had been enrolled. At the time of termination, CHAMPION PLATFORM underwent a 70% interim analysis and it was estimated conditional power in CHAMPION PLATFORM was also low; therefore, discontinuation of enrollment into both trials was recommended. Dyspnea was reported in 1% of patients who received cangrelor compared with 0.4% of patients who received clopidogrel (\(P = .001\)). GUSTO-defined mild bleeding occurred in 19.6% and 16.9% of cangrelor and clopidogrel patients, respectively. ACUITY-defined mild bleeding occurred in 17.6% and 15.2% of cangrelor and clopidogrel patients, respectively. Adverse reactions that occurred more often with cangrelor included ecchymosis; oozing at puncture site; and decreased hemoglobin, hematocrit, or both.

Limitations: Enrollment was terminated before power was reached.

Reference: Bhatt DL, et al, 2013 (CHAMPION PHOENIX trial)\(^{8,11}\)

Study Design: Randomized, prospective, double-blind, double-dummy, active-control, multicenter, superiority study

Study Funding: The Medicines Company

Patients: 11,145 patients were enrolled (modified ITT population = 10,942 patients received study drug) with coronary atherosclerosis who required PCI for stable angina (57% in the cangrelor arm and 55.2% in the clopidogrel arm), NSTE ACS (25.4% and 26%), or STEMI (17.6% and 18.8%). Exclusion criteria included pretreatment with platelet inhibitors; prior treatment with P2Y\(_{12}\) inhibitors or abciximab at least 7 days before randomization; or epifibatide, tirofiban, or fibrinolytic therapy at least 12 hours before randomization. Median age was 64 years; 28.5% and 27.3% were female, and 93.8% and 93.7% were White in the cangrelor and clopidogrel groups, respectively.

Intervention: In the cangrelor treatment arm (\(n = 5,472\)), patients received a cangrelor 30 mcg/kg bolus followed by a cangrelor 4 mcg/kg/min infusion.
infusion for at least 2 hours or the duration of the procedure, whichever was longer, and placebo 300 mg (25.7%) or 600 mg (74.3%) prior to PCI. In the clopidogrel treatment arm (n = 5,470), patients received placebo bolus and infusion and clopidogrel 300 mg (25.6%) or 600 mg (74.4%) (clopidogrel dose determined by the site investigator) prior to PCI procedure. At the end of the infusion, patients assigned to the cangrelor infusion received clopidogrel 600 mg, and patients assigned to the placebo infusion received placebo tablets. All patients received matching placebos to maintain blinding. Additionally, all patients received aspirin 75 to 325 mg and clopidogrel 75 mg for 48 hours post procedure (after 48 hours, another P2Y₁₂ inhibitor could be used at the discretion of the investigator). Periprocedural anticoagulants, including bivalirudin, unfractionated heparin, low-molecular-weight heparin (LMWH), or fondaparinux, could also be used at the discretion of the investigator. Glycoprotein IIb/IIIa inhibitors were allowed only as rescue therapy during PCI.

Results
Primary Endpoint(s)
- Composite of death from any cause, MI, ischemia-driven revascularization, or stent thrombosis in the 48 hours after randomization occurred in 4.7% in the cangrelor group and 5.9% in the clopidogrel group (OR, 0.78; 95% CI, 0.66 to 0.93; P = .005).

Secondary Endpoint(s)
- Incidence of stent thrombosis at 48 hours was 0.8% for cangrelor and 1.4% for clopidogrel (OR, 0.62; 95% CI, 0.43 to 0.9; P = .01).

Endpoint(s)
- Rate of MI at 48 hours was 3.8% for cangrelor and 4.7% for clopidogrel (OR, 0.8; 95% CI, 0.67 to 0.97; P = .02).
- Rate of death or stent thrombosis at 48 hours was 1.1% for cangrelor and 1.6% for clopidogrel (OR, 0.67; 95% CI, 0.48 to 0.94; P = .02).
- The rate of the composite efficacy endpoint was 6% in the cangrelor group and 7% in the clopidogrel group at 30 days (OR, 0.85; 95% CI, 0.73 to 0.99; P = .01).
- GUSTO-defined severe bleeding occurred in 0.16% of the cangrelor group and 0.11% in the clopidogrel group (OR, 1.5; 95% CI, 0.53 to 4.22; P = .44).
- All-cause mortality rate at 48 hours was 0.3% in both groups (hazard ratio [HR], 1; 95% CI, 0.52 to 1.92; P > .999) and death in all 36 patients was from a cardiovascular cause. The mortality incidence at 30 days was 1.1% in the cangrelor group and 1% in the clopidogrel group (HR, 1.09; 95% CI, 0.76 to 1.58; P = .64).
- Results of a prespecified subgroup analysis of patients receiving bivalirudin background therapy were consistent with the entire population; cangrelor reduced the incidence of the primary composite endpoint at 48 hours after randomization. There was also no difference in GUSTO- or TIMI-defined bleeding or in ACUITY-defined major bleeding.
- Intraprocedural stent thrombosis occurred more frequently in the clopidogrel arm (1%) than in the cangrelor group (0.6%) (OR, 0.65; 95% CI, 0.42 to 0.99; P = .04).
- A prespecified subgroup analysis based on age (elderly vs nonelderly) and gender (female) showed similar net benefits in both groups, with no appreciable increase in bleeding.

Comments: CHAMPION PHOENIX is one of the pivotal trials used for drug approval. Projected enrollment was 10,900 patients to allow an 85% power to detect the frequency of the composite primary endpoint at 5.1% in the placebo group and 3.9% in the cangrelor group. Primary event occurred at a greater incidence than used in the sample size and power calculations: 5.9% in the clopidogrel group and 4.7% in the cangrelor group. The difference in the primary composite endpoint was driven by incidence of MI and stent thrombosis. A prespecified pooled analysis of the 3 CHAMPION studies demonstrated that cangrelor was better than the control (clopidogrel or placebo) in decreasing PCI periprocedural thrombotic complications but was associated with an increased incidence of bleeding.

Limitations: Approximately 25% of patients randomized to clopidogrel received clopidogrel 300 mg prior to or during PCI. Previous studies have shown clopidogrel 600 mg given prior to or during PCI reduces the incidence of major cardiac events (composite of death, stroke, MI, or repeat revascularization). The time to administration of clopidogrel relative to PCI was not provided; therefore, it is not possible to determine if the antiplatelet effects of clopidogrel were optimal at the time of procedure.
Indication: Antiplatelet Bridging of Thienopyridine-Treated Patients to Coronary Artery Bypass Grafting Surgery

Studies

Drug: Cangrelor vs Placebo

Reference: Angiolillo DJ, et al, 2012 (BRIDGE trial)\textsuperscript{10}

Study Design: Prospective, randomized, double-blind, placebo-controlled, multicenter study

Study Funding: The Medicines Company, National Institutes of Health – National Center for Advancing Translational Sciences, Clinical and Translational Science Award

Patients: 210 patients who planned to undergo nonemergency coronary artery bypass grafting (CABG) surgery who had received a thienopyridine (at least 500 mg of ticlopidine, 75 mg of clopidogrel, or 10 mg of prasugrel) within 72 hours prior to randomization were enrolled. Median age was 65 and 62 years; 75.5% and 73.3% were male, 87.7% and 93.1% were White, and 5.7% and 5% were African American in the cangrelor and placebo groups, respectively; 99.1% and 92.1% of patients in the cangrelor and placebo groups, respectively, were previously being treated with clopidogrel. In the cangrelor group, 15.1% of patients presented with a STEMI and 32.1% with a non-STEMI; in the placebo group, 11.9% presented with a STEMI and 44.5% with a non-STEMI.

Intervention: In stage 1, patients were assigned to receive cangrelor infusions of 0.5, 0.75, 1, and 1.5 mcg/kg/min until platelet inhibition was greater than 60% in 80% of daily samples or a dose of cangrelor 2 mcg/kg/min was reached. In stage 2, patients were randomized (1:1) to receive a cangrelor infusion of 0.75 mcg/min plus standard of care (\(n = 106\)) or matching placebo infusion plus standard of care (\(n = 101\)). Cangrelor infusion was initiated after discontinuation of thienopyridine therapy and continued for a minimum of 48 hours and a maximum of 7 days. Cangrelor infusion was discontinued 1 to 6 hours before surgery. Aspirin therapy was maintained at a dosing regimen per local practice. The median time from thienopyridine discontinuation to study drug infusion was 29.1 hours in the cangrelor group and 29.5 hours in the placebo group. The median duration of infusion was 2.8 days in the cangrelor group and 3.4 days in the placebo group. The median time from discontinuation of the study drug infusion to surgical incision was 3.2 hours in both groups.

Results

Primary Endpoint(s)

- Stage 1: Maintenance of platelet inhibition above 60% in at least 80% of patient samples was achieved with the 0.75 mcg/kg/min dose (94.4%; 95% CI, 83.9% to 100%).
- Stage 2: Proportion of patients with platelet reactivity of less than 240 P2Y\textsubscript{12} reaction units for all samples assessed during infusion of study drug was 98.8% (95% CI, 96.5% to 100%) with cangrelor and 19% (95% CI, 10.7% to 27.4%; \(P < .001\)) with placebo.

Secondary Endpoint(s)

- Ischemic endpoints occurred in 2.8% and 4% of cangrelor- and placebo-treated patients, respectively.

Comments: The number of patients who underwent CABG surgery was 102 in the cangrelor group and 96 in the placebo group. The ITT efficacy cohort included 93 patients in the cangrelor group and 90 patients in the placebo group. In addition to the intervention, 99.1% and 96% of patients received aspirin, 48.1% and 48.5% received unfractionated heparin, and 35.8% and 42.6% received LMWH as presurgery antithrombotics in the cangrelor and placebo groups, respectively.

Limitations: The study was not powered to assess whether the degree of platelet blockade with cangrelor prior to CABG surgery would reduce the risk of ischemic events compared with placebo. The study also was not designed to assess clinical differences between treatment groups.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

Cangrelor is contraindicated in patients with significant active bleeding or patients with known hypersensitivity (eg, anaphylaxis) to cangrelor or any component of the product (ie, mannitol, sorbitol, sodium hydroxide).\textsuperscript{2}
Warnings and Precautions

Bleeding can occur with drugs that inhibit platelet P2Y\textsubscript{12} function (eg, cangrelor, clopidogrel, prasugrel, ticagrelor). In the CHAMPION PHOENIX trial, bleeding events of all severities were more common with cangrelor than with clopidogrel. The risk of cangrelor-associated bleeding decreases rapidly because there are no antiplatelet effects after 1 hour.

Cangrelor is classified as Pregnancy Category C; there are no adequate and well-controlled studies assessing use of cangrelor in pregnant women.

Caution should be observed in women who are breast-feeding; it is unknown whether cangrelor is excreted in human milk.

Safety and effectiveness have not been established in pediatric patients.

ADVERSE REACTIONS

The most common adverse reaction associated with cangrelor is bleeding (see Table 1). An overdose of the bolus or the maintenance infusion does not increase the risk of bleeding. Pooled data from the CHAMPION trials identified 36 patients who received an overdose of cangrelor; 20 received too high a bolus dose and maintenance infusion, 5 received too high a bolus dose, and 11 received too high a maintenance infusion. The incidence of bleeding events in patients receiving an overdose of cangrelor were similar to those in the overall CHAMPION program, and there was no correlation between bleeding and the magnitude of the cangrelor overdose.

The commonly observed adverse reactions that occurred more often in cangrelor-treated patients undergoing PCI or in patients who required bridging from oral antiplatelet agents prior to surgery were ACUITY-defined major and minor bleeding, GUSTO-defined mild bleeding, hematoma of at least 5 cm at puncture site, oozing at puncture site, ecchymosis, epistaxis, decrease in hemoglobin and/or hematocrit level, decreased renal function, agitation, diarrhea, chest pain, and dyspnea. There were no differences in incidence of bleeding events between cangrelor and placebo patients who required bridging from oral antiplatelet medications prior to surgery.

Decreased renal function was observed in clinical trials. Severe renal impairment (creatinine clearance [CrCl] less than 30 mL/min) occurred in 3.2% of cangrelor patients and 1.4% of clopidogrel patients.

Dyspnea also occurred with cangrelor at a rate higher than the control group (1.3% vs 0.4%).

Discontinuation because of an adverse event was low in the CHAMPION PHOENIX study. Therapy discontinuation rate because of a bleeding event was 0.3% in the cangrelor group and 0.1% in the clopidogrel group, while discontinuation rate because of nonbleeding adverse events was 0.6% in the cangrelor group and 0.4% in the clopidogrel group.

Cangrelor does not increase QT in healthy volunteers.

DRUG INTERACTIONS

Cangrelor is not a prodrug and does not require hepatic activation, unlike other oral ADP receptor antagonists; therefore, interactions with drugs that utilize cytochrome P450 metabolism are not expected to inhibit efficacy.

The effect of clopidogrel and prasugrel may be attenuated when given simultaneously with cangrelor. In contrast, the antiplatelet activity of ticagrelor was preserved when given before, during, or after cangrelor. These drugs altered the impact of cangrelor’s effects on platelet activity. Initiation of clopidogrel or prasugrel therapy should occur only after the cangrelor infusion is discontinued.

Coadministration of cangrelor with unfractionated heparin, aspirin, and nitroglycerin in healthy volunteers had no effect on the pharmacokinetics or pharmacodynamics of cangrelor. Coadministration of cangrelor with bivalirudin, LMWH, clopidogrel, prasugrel, or ticagrelor in clinical trials showed no clinically detectable interactions.

RECOMMENDED MONITORING

Monitor patients for signs and symptoms of overt bleeding during the use of cangrelor.

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Table 1. Major bleeding results in the CHAMPION PHOENIX study (non–CABG-related bleeding)

<table>
<thead>
<tr>
<th>CHAMPION PHOENIX</th>
<th>Cangrelor (n = 5,529)</th>
<th>Clopidogrel (n = 5,527)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any GUSTO bleeding</td>
<td>15.5%</td>
<td>10.9%</td>
</tr>
<tr>
<td>Severe/Life-threatening</td>
<td>0.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Mild</td>
<td>14.9%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Any TIMI bleeding</td>
<td>0.8%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Major</td>
<td>0.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Minor</td>
<td>0.6%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Note: CABG = coronary artery bypass grafting; GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries; TIMI = Thrombolysis in Myocardial Infarction.
DOsing

The recommended dosage of cangrelor is 30 mcg/kg IV bolus (less than 1 minute) diluted with sodium chloride 0.9% injection or dextrose 5% injection, followed immediately by a 4 mcg/kg/min IV infusion using a dedicated IV line. The IV bolus should be completely administered prior to the start of the PCI procedure and continued for at least 2 hours or for the duration of the PCI, whichever is longer. An oral P2Y\textsubscript{12} receptor antagonist (ie, clopidogrel, ticagrelor, or prasugrel) should be started after discontinuation of the cangrelor infusion to maintain platelet inhibition.\textsuperscript{2,8,9,11,13} If clopidogrel is used, administer at a dose of 600 mg immediately after discontinuation of cangrelor; it should not be administered prior to discontinuation of cangrelor. If prasugrel is used, administer at a dose of 60 mg immediately after discontinuation of cangrelor; it should not be administered prior to discontinuation of cangrelor. If ticagrelor is used, administer at a dose of 180 mg at any time during the cangrelor infusion or immediately after cangrelor discontinuation.\textsuperscript{2}

The antiplatelet regimen used in clinical studies evaluating bridging of thienopyridine-treated patients to CABG surgery was cangrelor 0.75 mcg/min as an infusion initiated after discontinuation of thienopyridine therapy and continued for up to 1 to 6 hours before surgery.\textsuperscript{10}

No dosage adjustment is required for patients with any type of renal impairment. Cangrelor is not metabolized by the liver; no dosage adjustment is necessary in patients with liver impairment.\textsuperscript{2}

PRODUCT AVAILABILITY

Cangrelor was approved on June 22, 2015.\textsuperscript{1} It is available as a lyophilized powder for reconstitution (50 mg) in single-use vials.\textsuperscript{2}

The lyophilized powder should be stored at controlled room temperature (20°C to 25°C [68°F to 77°F]), with excursions permitted between 15°C and 30°C (59°F and 86°F).\textsuperscript{2}

Once reconstituted, the diluted solution should be used immediately. The solution can be stored for up to 12 hours in dextrose 5% injection and 24 hours in sodium chloride 0.9% at room temperature.\textsuperscript{2}

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for cangrelor.\textsuperscript{1}

CONCLUSION

Cangrelor is a potent intravenous ADP receptor antagonist characterized by rapid onset and quick reversible effects. The approved indication for cangrelor is very limited compared to other approved P2Y\textsubscript{12} inhibitors. Cangrelor, when used as an adjunct to PCI, is given as an IV bolus and immediately followed by an infusion for 2 hours or until the procedure is completed, whichever is longer. In the CHAMPION PHOENIX trial, cangrelor was superior to a loading dose of clopidogrel 300 or 600 mg; however, it was not superior to a loading dose of clopidogrel 600 mg or a placebo comparator in 2 separate clinical trials assessing outcomes up to 48 hours after PCI. Cangrelor was shown to be a feasible management strategy in patients waiting for cardiac surgery who require platelet P2Y\textsubscript{12} inhibition and have not received another P2Y\textsubscript{12} inhibitor or glycoprotein IIb/IIIa inhibitor. Bleeding was more common in patients who received cangrelor compared with clopidogrel or placebo.

REFERENCES


Continuing Education Case Study Quiz

Goal—The goal of this activity is to educate pharmacists about the use of cangrelor in the treatment of patients undergoing percutaneous coronary intervention.

Objectives—At the completion of this activity, the reader will be able to:
1. Describe the pharmacology and pharmacokinetics of cangrelor.
2. Discuss the risks associated with the use of cangrelor.
3. Discuss the potential benefit of cangrelor for an individual patient.
4. Apply the information on the use of cangrelor to a case study.

Key Words—cangrelor, chronic heart failure, new drugs

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1. Cangrelor is US Food and Drug Administration (FDA)—approved as an adjunct to percutaneous coronary intervention (PCI) in patients:
   A. Receiving a glycoprotein IIb/IIIa inhibitor.
   B. Already treated with a P2Y12 platelet inhibitor.
   C. Already treated with a P2Y12 platelet inhibitor and receiving a glycoprotein IIb/IIIa inhibitor.
   D. Not already treated with a P2Y12 platelet inhibitor and not receiving a glycoprotein IIb/IIIa inhibitor.

2. As an adjunct to PCI, cangrelor has been shown to reduce the risk of:
   A. Bleeding.
   B. Death within 30 days.
   C. Myocardial infarction (MI) within 30 days.
   D. Stent thrombosis.
3. Cangrelor is best described as a:
A. P2Y_{12} receptor antagonist.
B. Glycoprotein IIb/IIIa inhibitor.
C. Factor Xa inhibitor.
D. Direct thrombin inhibitor.

4. Upon initiation of a cangrelor infusion, maximum inhibition of platelet aggregation occurs within:
A. 2 minutes.
B. 5 minutes.
C. 30 minutes.
D. 60 minutes.

5. Following discontinuation of cangrelor, platelet function is nearly fully restored within:
A. 2 minutes.
B. 5 minutes.
C. 30 minutes.
D. 60 minutes.

6. Which of the following statements best describes the elimination of cangrelor?
A. Cangrelor is eliminated renally as unchanged drug.
B. Cangrelor is deactivated in the circulation by dephosphorylation.
C. Cangrelor is metabolized via cytochrome P450 to the active component, which is renally eliminated.
D. Cangrelor is activated in the circulation by dephosphorylation, and the active metabolite is hepatically eliminated.

7. Which of the following is a contraindication to use of cangrelor?
A. Concomitant administration of aspirin
B. Concomitant administration of heparin
C. Hypersensitivity to clopidogrel
D. Significant active bleeding

8. Cangrelor is in Pregnancy Category:
A. A.
B. B.
C. C.
D. X.

9. Cangrelor, when used as an adjunct to PCI, has a potential drug-drug interaction with which of the following medications if given simultaneously?
A. Bivalirudin
B. Clopidogrel
C. Enoxaparin
D. Pantoprazole

Case History
J.S. is a 66-year-old male patient with no known drug allergies. He has type 2 diabetes mellitus, hypertension, and hypercholesterolemia. His current medications include metformin, lisinopril, atorvastatin, and aspirin. He is currently in the emergency department diagnosed with non-ST-elevation MI. The cardiologist has ordered cangrelor for administration prior to PCI.

10. What is the recommended initial dose of cangrelor for J.S.?
A. 4 mcg/kg IV bolus
B. 30 mcg/kg IV bolus
C. 4 mcg/kg/min IV infusion
D. 30 mcg/kg/min IV infusion

11. What is the recommended follow-up dose of cangrelor for J.S.?
A. 4 mcg/kg IV bolus
B. 30 mcg/kg IV bolus
C. 4 mcg/kg/min IV infusion
D. 30 mcg/kg/min IV infusion

12. For how long should cangrelor therapy be continued in J.S.?
A. Only a bolus dose is required.
B. At least 2 hours or for the duration of the PCI, whichever is longer
C. Until hospital discharge
D. At least 1 year

13. Which of the following regimens is recommended for J.S. following PCI?
A. Aspirin, restarted 5 to 10 days after cangrelor discontinuation
B. Clopidogrel 600 mg daily, starting immediately after cangrelor discontinuation
C. Clopidogrel 600 mg administered immediately after cangrelor discontinuation, followed by 75 mg daily
D. Clopidogrel 600 mg starting during the infusion or immediately after cangrelor discontinuation, followed by 75 mg daily

14. The most common side effect associated with cangrelor is:
A. Agitation.
B. Bleeding.
C. Decreased renal function.
D. Dyspnea.
15. J.S. has a longstanding history of type 2 diabetes mellitus and hypertension that has impacted his renal function. Which of the following statements is correct with regard to the use of cangrelor in patients with renal impairment?

A. Cangrelor use is not recommended in patients with severe renal impairment.
B. No cangrelor dose adjustment is required for patients with renal impairment.
C. The cangrelor dose should be reduced by half, as cangrelor elimination is reduced in renal impairment.
D. The dose should be increased, as cangrelor dephosphorylation is increased in renal impairment.