CLOPIDOGREL

TARGET AUDIENCE: All Canadian health care professionals.

OBJECTIVE:

- To describe the clinical pharmacology and therapeutic application of clopidogrel.
- To discuss drug dosing, duration of therapy, genetic polymorphisms affecting drug metabolism, and potential drug interactions with proton pump inhibitors.

ABBREVIATIONS:

ACS	acute coronary syndrome
ADP	adenosine diphosphate
ASA	acetyl salicylic acid
PCI	percutaneous coronary intervention
TIA	transient ischemic attack

BACKGROUND:

Clopidogrel is an oral thienopyridine adenosine diphosphate (ADP) antiplatelet inhibitor that demonstrated additional cardiovascular protection when added to acetyl salicylic acid (ASA) in patients with acute coronary syndrome (ACS) treated either medically or with percutaneous coronary intervention (PCI).

MECHANISM OF ACTION:

Clopidogrel (Plavix™) is categorized as a thienopyridine, which irreversibly blocks ADP-induced platelet aggregation.

INDICATION:

Clopidogrel is a treatment option for the secondary prevention of atherothrombotic events (myocardial infarction, stroke or vascular death) in patients with atherosclerosis that is manifest clinically by stroke, myocardial infarction (see STEMI or NSTEMI guides) or peripheral artery disease.

Clopidogrel is indicated, in combination with ASA, for the secondary prevention of atherothrombotic events in patients with ACS. Clopidogrel is usually administered for 1 year following an episode of ACS. Clopidogrel, in combination with ASA, is recommended for a minimum of 6 weeks in patients with a bare-metal stent and for a minimum of 12 months in patients with a drug-eluting stent.

Clopidogrel, in combination with ASA, is a treatment option in selected patients with atrial fibrillation who are not suitable for an oral anticoagulant and who require stroke prevention. Clopidogrel is a treatment option in patients who develop an ischemic stroke or transient ischemic attack (TIA) while receiving ASA therapy.

DOSING:

a) Acute coronary syndrome: 300-600 mg loading dose followed by 75 mg daily. A dose of 150 mg daily may be considered for the first week in patients treated by PCI.

b) For all other indications the dose is 75 mg daily.

MONITORING:

It is advisable to obtain a baseline complete blood count, including platelets and hemoglobin, prior to initiating clopidogrel. Ongoing monitoring of coagulation parameters in patients taking clopidogrel is not required.

ADVERSE EFFECTS:

The most common adverse reaction to clopidogrel is an increased rate of bruising and bleeding. Blood disorders such as agranulocytosis, granulocytopenia, aplastic anemia, neutropenia and thrombocytopenia have been reported but are rare events. Gastrointestinal bleeding has been reported. Skin rash has been reported but is a rare event.

PERI-PROCEDURAL MANAGEMENT:

Clopidogrel should be discontinued 5-7 days prior to an invasive procedure associated with an increased bleeding risk. However, caution should be used in discontinuing clopidogrel in patients with coronary stents, and consultation with a specialist is advised. Stent thrombosis can occur when antiplatelet therapy is discontinued prior to 1 year following a drug-eluting stent, and prior to 6 weeks following a bare-metal stent. It is recommended to defer surgery for 6-12 months after drug-eluting stent placement, and to defer surgery for 6 weeks after bare-metal stent placement, rather than performing surgery within these time limits. For patients who require surgery within 6 months of a drug-eluting stent or within 6 weeks of a bare-metal stent, it is recommended to continue dual antiplatelet therapy.

SPECIAL CONSIDERATIONS:

Clopidogrel is a prodrug which is metabolized into the antiplatelet active agent in two steps by the hepatic p450 enzyme system (3A4 and 2C19). Proton pump inhibitors are strong 2C19 inhibitors that can reduce the effect of clopidogrel on platelet aggregation and can increase the risk of

recurrent cardiovascular events. Pantoprazole is not a strong 2C19 inhibitor and should be used whenever a proton pump inhibitor is required.

PEDIATRICS:

There are few studies determining the safety and efficacy of clopidogrel in neonates and children. The PICOLO study in infants with congenital heart disease and a palliative shunt determined the dose of 0.2 mg/kg to provide platelet inhibition.

REFERENCES:

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