Pidogrel-AP®

(Clopidogrel + Aspirin)

Highnoon

COMPOSITION

Pidogrel-AP 75mg Tablet: Each tablet contains:
Clopidogrel (as Clopidogrel Bisulphate) 75mg
Aspirin 75mg
Pidogrel-AP 150mg Tablet: Each tablet contains:
Clopidogrel (as Clopidogrel Bisulphate) 75mg
Aspirin 150mg

DESCRIPTION

PIDOGREL-AP is a fixed-dose combination containing clopidogrel and aspirin. Clopidogrel bisulphate is a thienopyridine class inhibitor of P2Y12 ADP platelet receptors. It is platelet purinoreceptor-$P2Y_{12}$ antagonist that acts by inhibiting adenosine diphosphate-mediated platelet aggregation. It is given for the prophylaxis of thromboembolic events as an alternative to aspirin in patients with chronic occlusive peripheral arterial disease.
Aspirin is a salicylate non-steroidal anti-inflammatory drugs (NSAID) and has many properties in common with non-aspirin NSAID. Aspirin and other salicylates have analgesic, anti-inflammatory and anti-pyretic properties. Aspirin also inhibits platelet aggression while non-acetylated salicylates do not.

MECHANISM OF ACTION

Clopidogrel

Clopidogrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets.

Aspirin

Aspirin (acetylsalicylic acid) is an inhibitor of both prostaglandin synthesis and platelet aggregation. Aspirin inhibits platelet aggregation by irreversible inhibition of platelet cyclooxygenase and thus inhibits the generation of thromboxane A2, a powerful inducer of platelet aggregation and vasoconstriction. The differences in activity between aspirin and salicylic acid are thought to be due to the acetyl group on the aspirin molecule. This acetyl group is responsible for the inactivation of cyclo-oxygenase via acetylation.

PHARMACOKINETICS

Clopidogrel

Clopidogrel is rapidly but incompletely absorbed after oral doses, absorption appears to be at least 90%. It is prodrug and extensively metabolized in the liver, mainly to the inactive carboxylic acid derivatives. Metabolism is mediated by cytochrome P450 isoenzymes including CYP3A4 and CYP2B6, CYP1A2,CYP1A1 and CYP2C19. The active metabolite appears to be a thiol derivatives, it has been identified in vitro but appears to be too unstable to the isolated from plasma. Clopidogrel and carboxylic acid derivative are highly protein bound. Clopidogrel and its metabolites are excreted in urine and in feces. About 50% of an oral dose is recovered from the urine and about 46% from the feces.

Aspirin

Aspirin and other salicylates are absorbed rapidly from the gastrointestinal tract when taken orally but absorption after rectal doses is less reliable. Aspirin and other salicylates can also be absorbed through the skin. After oral doses, absorption of non-ionised aspirin occurs in the stomach and intestine. Some aspirin is hydrolysed to salicylate in the gut wall. Once absorbed, aspirin is rapidly converted to salicylate, but during the first 20 minutes after an oral dose aspirin is the main form of the drug in the plasma. Aspirin is 80% to 90% bound to plasma proteins and is widely distributed; its volume of distribution is reported to be 170 mL/kg in adults. Both aspirin and salicylate have pharmacological activity although only aspirin has an anti-platelet effect. Salicylate is extensively bound to plasma proteins and is rapidly distributed to all body parts. Salicylates appears in the breast milk and crosses the placenta. Salicylate is mainly eliminated by hepatic metabolism; the metabolites include salicyluric acid, salicyl phenolic glucuronide, salicylic acyl glucuronide, gentisic acid, and gentisuric acid. The formation of the major metabolites, salicyluric acid and salicyl phenolic glucuronide, is easily saturated and follows Michaelis-Menten kinetics; the other metabolic routes are first-order processes. As a result, steady-state plasma-salicylate concentrations increase disproportionately with dose. After a 325mg aspirin dose elimination is a first-dose process and the plasma-salicylate half-life is about 2 to 3 hours; at high aspirin doses, the half-life increases to 15 to 30 hours. Salicylate is also excreted unchanged in the urine; the amount excreted by this route increases with increasing dose and also depends on urinary pH, about 30% of a dose being excreted in alkaline urine compared with 2% of a dose in acidic urine. Renal excretion involves glomerular filtration, active renal tubular secretion, and passive tubular reabsorption. Salicylate is removed by haemodialysis.

INDICATIONS

It is used in;

- Acute Coronary Syndrome (ACS)
  - To reduce the rate of Myocardial Infarction (MI) and stroke in patients with non ST-segment elevation ACS (unstable angina (UA)/ non ST-elevation myocardial infarction [NSTEMI], including patients who are to be managed medically and those who are to be managed with Coronary revascularization. It should be administered in conjunction with Aspirin.
  - To reduce the rate of Myocardial Infarction and stroke in patients with acute ST-elevation Myocardial Infarction (STEMI) who are to be managed medically. It should be administered with Aspirin.
- Recent MI, Stoke or established Peripheral Artery Disease
  - To reduce the rate of MI and stroke in patients with peripheral artery disease or with history of recent Myocardial Infarction (MI) or recent stroke.
- Prevention of atherothrombotic and thromboembolic events in patients with arterial fibrillation and at least one risk factor for a vascular event and whom for Warfarin is unsuitable.
- Prevention of atherothrombotic events in percutaneous coronary intervention patients on already on Clopidogrel.
- Prevention of atherothrombotic events in peripheral artery disease or with 35 days of MI or within six months of Ischemic Stroke.

DOSAGE AND ADMINISTRATION

- In prevention of Ischemic events the recommended dose is one tablet once daily.
- In Acute Coronary Syndrome the loading dose is two tablets and then one tablet daily as maintenance dose.
- In prevention of atherothrombotic and thromboembolic events in patients with arterial fibrillation and at least one risk factor for a vascular event and whom for Warfarin is unsuitable. The dose is 75mg once daily.
- In prevention of atherothrombotic events in percutaneous coronary intervention patients on already on Clopidogrel. The loading dose is 300mg to be taken prior to the procedure, alternatively loading dose is 600mg, higher dose produces a greater and more rapid inhibition of platelet aggregation.
- In prevention of atherothrombotic events in peripheral artery disease or with 35 days of MI or within six months of Ischemic Stroke. The dose is 75mg once daily.

CONTRAINDICATIONS

- Hypersensitivity to clopidogrel.
- Hypersensitivity to aspirin and/or non-steroidal anti-inflammatory agents.
- Recent history or active pathological bleeding such as peptic ulcer or intracranial haemorrhage.
- Severe hepatic impairment.
- Severe renal impairment.
- Gout.
- Children under 16 (except under medical supervision for use for example in juvenile rheumatoid arthritis).
- Third trimester of pregnancy.
- Breast feeding.
- Haemorrhagic diathesis; coagulation disorders such as haemophilia and thrombocytopenia and where there is concurrent anti-coagulant therapy.

ADVERSE EFFECTS

Clopidogrel

The reported adverse events are bleeding including fatal bleeding, thrombotic thrombocytopenic purpura, intracranial hemorrhage, hemorrhagic strokes, intraocular bleeding with significant loss of vision, cerebral or noncerebral bleeding, epistaxis, hematoma, skin reaction, diarrhea, constipation, dizziness, leucopenia, vomiting, nausea, paraesthesia, neutropenia and pruritus.
The additional reported events are agranulocytosis, aplastic anemia/pancytopenia,, acquired hemophilia A, bone marrow disorder, gynaecomastia, colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis, taste altered, gastric/duodenal ulcer, fever, acute liver failure, hepatitis (noninfectious), abnormal liver function test, hypersensitivity reactions, anaphylactoid reactions, serum sickness, insulin autoimmune syndrome, which can lead to severe hypoglycemia, myalgia, arthralgia, arthritis, taste disorders, headache, ageusia, confusion, hallucinations, vertigo, bronchospasm, interstitial pneumonitis, eosinophilic pneumonia, increased creatinine levels, maculopapular, erythematous or exfoliative rash, urticaria, bullous dermatitis, eczema, toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis (AGEP), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), erythema multiforme, lichen planus, generalized pruritus, vasculitis, Kounis syndrome, glomerulonephritis and hypotension.

Aspirin

The reported adverse event are: gastrointestinal disturbances such as dyspepsia, nausea, vomiting, irritation of the gastric mucosa with erosion, ulceration, haematemesis, melaena, increase bleeding tendencies, bleeding time, decrease platelet adhesiveness, thrombocytopenia, granulocytosis, aplastic anaemia, intracranial haemorrhage, existing (haematemesis, melaena) or occult gastrointestinal bleeding, may lead to iron deficiency anaemia (more common at higher doses), Steven-Johnsons syndrome, Lyells syndrome, purpura, erythema nodosum, erythema multiforme, haemorrhagic vasculitis, menorrhagia, hepatotoxicity, dizziness, tinnitus, deafness, sweating, headache, confusion, symptoms of severe intoxication include hyperventilation, fever, restlessness, ketosis and respiratory alkalosis, metabolic acidosis, cardiovascular collapse, respiratory failure, in children drowsiness, metabolic acidosis and hypoglycemia may be seen. In asthma patient; chronic urticarial or chronic rhinitis, exhibit hypersensitivity to aspirin which may provoke reactions including urticaria and other skin eruptions, angioedema, rhinitis and severe, even fatal paroxysmal bronchospasm, dyspnoea, hypersensitivity reactions, allergic oedema, anaphylactic reactions including shock have rarely occurred.

DRUG INTERACTION

Clopidogrel:

- Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of drugs that inhibit the activity of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition.
- Avoid concomitant use of Clopidogrel with omeprazole or esomeprazole. Dexlansoprazole, lansoprazole, and pantoprazole had less effect on the antiplatelet activity of Clopidogrel than did omeprazole or esomeprazole.
- As with other oral P2Y12 inhibitors, coadministration of opioid agonists delay and reduce the absorption of clopidogrel, presumably because of slowed gastric emptying, resulting in reduced exposure to its metabolites. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring coadministration of morphine or other opioid agonists.
- Coadministration of Clopidogrel and NSAIDs increases the risk of gastrointestinal bleeding.
- Although the administration of clopidogrel 75 mg per day did not modify the pharmacokinetics of S-warfarin (a CYP2C9 substrate) or INR in patients receiving long-term warfarin therapy, coadministration of Clopidogrel with warfarin increases the risk of bleeding because of independent effects on hemostasis.
- Since selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) affect platelet activation, the concomitant administration of SSRIs and SNRIs with clopidogrel may increase the risk of bleeding.
- The acyl-β-glucuronide metabolite of clopidogrel is a strong inhibitor of CYP2C8. Clopidogrel can increase the systemic exposure to drugs that are primarily cleared by CYP2C8, thereby needing dose adjustment and appropriate monitoring. Clopidogrel increased repaglinide exposures by 3.9-fold to 5.1-fold. Avoid concomitant use of repaglinide with Clopidogrel. If concomitant use cannot be avoided, initiate repaglinide at 0.5 mg before each meal and do not exceed a total daily dose of 4 mg. Increased frequency of glucose monitoring may be required during concomitant use.

Aspirin

Contraindicated combinations

Methotrexate (used at doses >15 mg/week):
The combined drugs, methotrexate and acetylsalicylic acid, enhance haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by acetylsalicylic acid. Therefore, the concomitant use of methotrexate (at doses >15 mg/week) with Aspirin 75 mg is contraindicated.

Not recommended combinations

Uricosuric agents, e.g. probenecid and sulfinpyrazone. Salicylates reverse the effect of probenecid. The combination should be avoided.

Combinations requiring precautions for use or to be taken into account

- Anticoagulants e.g. coumarin, heparin, warfarin Increased risk of bleeding due to inhibited thrombocyte function, injury of the duodenal mucosa and displacement of oral anticoagulants from their plasma protein binding sites. The bleeding time should be monitored.
- Antidiabetics, e.g. sulphonylureas
  - Salicylics may increase the hypoglycaemic effect of sulphonylureas.
- Anti-platelet agents (e.g clopidogrel, ticlopidine and dipyridamole) and selective serotonin reuptake inhibitors (SSRIs; such as sertraline or paroxetine)
  - Increased risk of gastrointestinal bleeding.
- Diuretics and antihypertensives
  - NSAIDs may decrease the antihypertensive effects of diuretics and other antihypertensive agents. As for other NSAIDs concomitant administration with ACE-inhibitors increases the risk of acute renal insufficiency.
  - Diuretics: Risk of acute renal failure due to the decreased glomerual filtration via decreased renal prostaglandin synthesis, Hydrating the patient and monitoring renal function at the start of the treatment is recommended.
  - Aspirin antagonises the diuretic effect of spironolactone.
- Systemic corticosteroids.
  - The risk of gastrointestinal ulceration and bleeding may be increased when acetylsalicylic acid and corticosteroids are co-administered.
- Digoxin and lithium.
  - Acetylsalicylic acid impairs the renal excretion of digoxin and lithium, resulting in increased plasma concentrations. Monitoring of plasma concentrations of digoxin and lithium is recommended when initiating and terminating treatment with acetylsalicylic acid. Dose adjustment may be necessary.
- Carbonic anhydrase inhibitors (acetazolamide)
  - May result in severe acidosis and increased central nervous system toxicity.
- Methotrexate (used at doses <15 mg/week).
  - The combined drugs, methotrexate and acetylsalicylic acid, may increase haematological toxicity of methotrexate due to decreased renal clearance of methotrexate by acetylsalicylic acid. Weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring should take place in the presence of even mildly impaired renal function, as well, as in elderly.
- Other NSAIDs.
  - Increased risk of ulcerations and gastrointestinal bleeding due to synergistic effects.
- Ibuprofen.
  - Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen.
- Ciclosporin, tacrolimus.
  - Concomitant use of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin and tacrolimus. The renal function should be monitored in case of concomitant use of these agents and acetylsalicylic acid.
- Valproate.
  - Acetylsalicylic acid has been reported to decrease the binding of valproate to serum albumin, thereby increasing its free plasma concentrations at steady state.
- Phenytoin.
  - Salicylate diminishes the binding of phenytoin to plasma albumin. This may lead to decreased total phenytoin levels in plasma, but increased free phenytoin fraction. The unbound concentration, and thereby the therapeutic effect, does not appear to be significantly altered.
- Alcohol.
  - Concomitant administration of alcohol and acetylsalicylic acid increases the risk of gastrointestinal bleeding.
- Antacids will reduce the effect of aspirin. Principle incompatibilities are iron salts, carbonates and alkali hydroxides.
- Metoclopramide potentiates the effect of aspirin.

WARNINGS AND PRECAUTIONS

Clopidogrel:

- *Diminished Antiplatelet Activity in Patients with Impaired CYP2C19Function:* Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is achieved through an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by genetic variations in CYP2C19.The metabolism of clopidogrel can also be impaired by drugs that inhibit CYP2C19, such as omeprazole or esomeprazole. Avoid concomitant use of clopidogrel with omeprazole or esomeprazole because both significantly reduce the antiplatelet activity of clopidogrel.

- *General Risk of Bleeding:* Thienopyridines, including clopidogrel, increase the risk of bleeding. Thienopyridines inhibit platelet aggregation for the lifetime of the platelet (7-10 days). Because the half-life of clopidogrel's active metabolite is short, it may be possible to restore hemostasis by administering exogenous platelets; however, platelet transfusions within 4 hours of the loading dose or 2 hours of the maintenance dose may be less effective.

- *Discontinuation of clopidogrel:* Discontinuation of clopidogrel increases the risk of cardiovascular events. If clopidogrel must be temporarily discontinued (e.g., to treat bleeding or for surgery with a major risk of bleeding), restart it as soon as possible. When possible, interrupt therapy with clopidogrel for five days prior to such surgery. Resume it as soon as hemostasis is achieved.

- *Thrombotic Thrombocytopenic Purpura (TTP):* TTP, sometimes fatal, has been reported following use of clopidogrel, sometimes after a short exposure (<2 weeks). TTP is a serious condition that requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever.

- *Cross-Reactivity among Thienopyridines*: Hypersensitivity including rash, angioedema or hematologic reaction has been reported in patients receiving clopidogrel, including patients with a history of hypersensitivity or hematologic reaction to other thienopyridines.

Aspirin:

- Administer with caution in the presence of allergic disease, renal or hepatic impairment and dehydration. Liver tests should be performed regularly in patients presenting slight or moderate hepatic insufficiency.
- There is a possible association between Aspirin and Reye's Syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver, and can be fatal. For this reason aspirin should not be given to children under 16 years unless specifically indicated (e.g. for Kawasaki's disease).
- There is an increased risk of haemorrhage particularly during or after operative procedures (even in cases of minor procedures, e.g. tooth extraction). Use with caution before surgery, including tooth extraction. Temporary discontinuation of treatment may be necessary.
- Not recommended during menorrhagia where it may increase menstrual bleeding.
- Use with caution in cases of hypertension and when patients have a past history of gastric or duodenal ulcer or haemorrhagic episodes or are undergoing therapy with anticoagulants.
- Patients should report any unusual bleeding symptoms to their physician. If gastrointestinal bleeding or ulceration occurs the treatment should be withdrawn.
- Acetylsalicylic acid may promote bronchospasm and asthma attacks or other hypersensitivity reactions. Risk factors are existing asthma, hay fever, nasal polyps or chronic respiratory diseases. The same applies for patients who also show allergic reaction to other substances (e.g. with skin reactions, itching or urticaria).
- Serious skin reactions, including Steven-Johnsons syndrome, have rarely been reported in association with the use of acetylsalicylic acid. Aspirin 75 mg should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
- Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including acetylsalicylic acid especially gastrointestinal bleeding and perforation which may be fatal. Where prolonged therapy is required, patients should be reviewed regularly.
- Concomitant treatment with Aspirin and other drugs that alter haemostasis (i.e. anticoagulants such as warfarin, thrombolytic and antiplatelet agents, anti-inflammatory drugs and selective serotonin reuptake inhibitors) is not recommended, unless strictly indicated, because they may enhance the risk of haemorrhage. If the combination cannot be avoided, close observation for signs of bleeding is recommended.
- Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration, such as oral corticosteroids, selective serotonin-reuptake inhibitors and deferasirox.
- Acetylsalicylic acid in low doses reduces uric acid excretion. Due to this fact, patients who tend to have reduced uric acid excretion may experience gout attacks.
- The risk of hypoglycaemic effect with sulfonylureas and insulins may be potentiated with Aspirin 75 mg taken at over dosage.

USED IN SPECIAL POPULATION

Pregnancy and lactation

Pregnancy: No clinical data on exposed pregnancies with Pidogrel AP are available, and no adequate data are available for clopidogrel alone. Animal studies have demonstrated a teratogenic effect arising from Aspirin. It is preferable not to use Pidogrel AP during the first two trimesters of pregnancy unless the clinical condition of the woman requires treatment. Contraindicated during the third trimester of pregnancy.
Lactation: Since Aspirin is known to be excreted in human breast milk and studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk, nursing is not recommended if treatment with Pidogrel AP is required.

OVERDOSAGE

Platelet inhibition by clopidogrel is irreversible and will last for the life of the platelet. Overdose following clopidogrel administration may result in bleeding complications. Symptoms of acute toxicity were vomiting, prostration, difficult breathing, and gastrointestinal hemorrhage in animals. Based on biological plausibility, platelet transfusion may restore clotting ability.

Aspirin

Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5 mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning.
Symptoms: Common features of salicylate poisoning include vomiting, dehydration, tinnitus, vertigo, deafness, sweating, warm extremities with bounding pulses, increased respiratory rate and hyperventilation. Some degree of acid-base disturbance is present in most cases.
A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults and children over the age of 4 years. In children aged 4 years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Acidosis may increase salicylate transfer across the blood brain barrier.
Uncommon features of salicylate poisoning include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopaenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema.
Central nervous system features including confusion, disorientation, coma and convulsions, are less common in adults than in children.

DOSAGE AND INSTRUCTIONS

To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION

1. Pidogrel-AP 75mg Tablets: Alu. Alu. Blister Pack of 1 x 10's.

2. Pidogrel-AP 150mg Tablets: Alu. Alu. Blister Pack of 1 x 10's.

پیڈوگرل۔اے پی®

(کلوپیڈوگرل+اسپرین)

خوراک و ہدایات:

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
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