The Effect of Clopidogrel on CRP Levels in Subjects with CAD: A Prospective Randomized Trial

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A. Study Purpose and Rational

An individual living in today's world is more likely to die from coronary artery disease (CAD) than from any other cause. Recent advances in the study of CAD have determined that inflammation of the coronary arteries plays an important role in both the development of coronary blockages and the disruption of those blockages that cause heart attacks. C-reactive protein (CRP) is a protein in the blood whose levels increase during times of inflammation, and levels of CRP have been shown to predict who is more likely to develop complications of CAD.

There has been recent interest in investigating whether some of the drugs that are currently used to treat CAD have an effect on the level of inflammation, and by extension CRP, in the body. Both statins, a group of cholesterol lowering drugs, and abciximab, a drug used to prevent blood clots in coronary arteries during stenting (a procedure designed to open up clogged arteries), have been shown to lower levels of CRP. Clopidogrel, a drug, that prevents coronary clots in a way similar to aspirin, has recently been shown to be of benefit for patients that are having mild heart attacks or severe angina (chest pain). Whether clopidogrel lowers levels of CRP in those in whom it is elevated not known. The present study is designed to address this question.

B. Study Design and Statistical Analysis

Potential subjects will be screened with CRP assays, and only those subjects with elevated levels of CRP will be enrolled. Study subjects will be randomized to receive either clopidogrel or matching placebo for 8 weeks. For each subject, a computer will generate a random number from 1-100. For those subjects with a number from 1-50, study drug A will be given. For those with a number from 51-100, study drug B will be given. The identity of drugs A and B (clopidogrel or placebo) will be known only to the central dispensing pharmacy. During the study, subjects will be allowed to continue to receive the drugs that normally take for their condition. However, subjects already receiving clopidogrel will not be eligible (see below). CRP levels will be measured at the end of the study period and compared to those at baseline. At the end of the study period, subjects will resume their previous drug regimens at the discretion of their physicians.

The distribution of CRP levels in the population is not bell-shaped. Standard parametric analysis cannot, therefore be used. The distribution of the change in CRP levels in response to other drugs that have been studied is bell shaped, however. For this reason, the mean change in CRP levels at the end of the study period versus baseline will be calculated, and potential significance of the difference in these means will be compared with Student's unpaired t test. Based on the 15% difference in CRP levels seen in previous studies and the standard deviation of the distribution of these changes, the number of patients needed in order to have an 80% power to detect this change with a p < 0.05 indicating, significance is estimated to be 307 in each arm. Means or proportions for baseline clinical characteristics will be computed for subjects in each arm of the study, and the significance of any differences in the means will be tested with Student's unpaired t test; differences in proportions will be tested with the \( \chi^2 \) statistic.

C. Study Procedure

The sole procedure required of the study will be the drawing of approximately 5ml of whole blood and study outset and at 8 weeks. Blood is normally drawn from this population of patients in the
course of their standard treatment 1-2 times a year. Subjects may feel minor discomfort from the needle used to draw blood. Subjects will also be required to come to safety and adherence visits at week 4 of the study.

D. Study Drugs (see package insert)

Clopidogrel is approved by the FDA for use in patients with peripheral arterial disease, unstable coronary disease, prior heart attacks, and prior strokes. It is given as a onetime dose of 300mg by mouth for the first day, followed by 75mg per day thereafter. It should not be used in patients who are allergic to it or who have an active problem with bleeding (such as an ulcer).

The major side effect of clopidogrel is bleeding. In a study that compared aspirin with clopidogrel, patients that received clopidogrel had a rate of gastrointestinal hemorrhage of 2.7% and of intracranial hemorrhage of 0.4%. The corresponding rates for aspirin were 2.7% and 0.5% differences not considered significant. In a study that compared aspirin alone with aspirin plus clopidogrel, over the course of 12 months, subjects receiving both drugs had a in statistically significant increase in major bleeding versus subjects receiving only aspirin (3.7% vs. 2.7%). There was no difference in the rates of intracranial and fatal bleeds between the two groups.

Ticlopidine, a drug similar to clopidogrel, has been associated with a rare (0.8% incidence) reduction in the numbers of neutrophils in the blood (cells that help fight infection), a potentially serious condition. Clopidogrel appears to be much safer in this regard, although this complication was reported in one patent out of the 9599 that received the drug in a recent trial.

Other less serious reactions to the drug include GI upset, rash, and flu-like symptoms.

Safety of the study drugs and adherence to the dosage regimen will be followed by office visits at week 4 of the study where subjects will be interviewed about adverse reactions and pills will be counted. Subjects with serious adverse reactions, as judged by a safety-monitoring panel, will be withdrawn.

E. Medical Devices

Not applicable

F. Study Questionnaires

Subjects will be administered a questionnaire on enrollment into Oe trial. The questionnaire will ask about the subject's personal identifiers, age, sex, CAD risk factors, current use of different medications used to treat CAD, and the presence of conditions that might disallow administration of the study drug or make interpretation of the results of the trial difficult.

G. Study Subjects

Subjects will be included for study if they are 21-75yrs, have had an MI (as defined as a troponin level greater than or equal to 2.0) at least 8 weeks prior to enrollment with stable disease since the event, and have no evidence of congestive heart failure clinically with an ejection fraction greater than or equal to 25% on TTE (if available). Subjects will be excluded from the study of they have had an intracranial hemorrhage or endoscopically confirmed peptic ulcer in the last year or intra-abdominal surgery in the last 8 weeks, are taking oral anti-coagulation therapy, have a history of rheumatoid arthritis, temporal arteritis, osteomyelitis, SLE, chronic infection, active cancer, bleeding diathesis, renal insufficiency (CrCl < 50) or have a projected life span less than the study period. Subjects with an allergy to clopidogrel and those taking clopidogrel at any point within the 8 weeks prior to screening would be excluded as well. Subjects with CRP levels at baseline greater than or equal to 0.66 mg/dL as measured by a high sensitivity assay manufactured by Dade Behring would subsequently be randomized.

The recruitment of minority populations and of women would be encouraged.
H. Recruitment of Subjects

Subjects would be recruited for the study with use of flyers posted around the medical center, as well as from direct referral from private physicians. On initial contact with potential subject, eligibility based on clinical inclusion/exclusion criteria will be established. Informed consent will be solicited, and the subject's baseline blood levels will be drawn. Only those subjects, with eligible CRP levels will be randomized.

I. Confidentiality of Study Data

Data on study subjects would be kept in a secure location; with subject files solely identified using a consecutive number system. A master key, correlating subject identifier numbers with personal data would be kept in a secure, central location.

J. Potential Conflict of Interest

The investigators will not materially profit in any way from the study results.

K. Location of Study

Blood samples will be drawn in the outpatient unit of the GCRC. Laboratory Measurements will be carried out in the GCRC Core Lab.

L. Potential Risks

The main risk to study subjects is of bleeding, as outlined above and in the attached package insert. Data available in a large population of people indicate that there is a 1% absolute increase in the risk of serious bleeding over the course of a year of treatment. The risk associated with 8 weeks or administration would be significantly attenuated. The subject may additionally experience a mild amount of discomfort or bruising related to blood drawing. Potential adverse outcomes will be monitored as above.

M. Potential Benefits

Subjects will likely not derive clinical benefit from a short course of clopidogrel, should they be randomized to this arm. Subjects in the placebo arm will not benefit. However, the results of the study should help shed light on the way in which the drugs we use to treat CAD, guide future therapies, and benefit society as a whole.

N. Alternative Therapies

Not applicable.

O. Compensation to Subjects

Subjects will not be monetarily compensated for their participation.

P. Costs to Subjects

Subjects will not incur costs beyond those of standard care in participation in the study.
Q. Minors as Research Subjects

Not applicable.

R. Radiation or Radioactive Substances

Not applicable.

S. References


PLAVIX® clopidogrel bisulfate tablets

DESCRIPTION

PLAVIX® (clopidogrel bisulfate) is an inhibitor of ADP-induced platelet aggregation with a dual mechanism of action: (a) the reversible inhibition of ADP-induced aggregation of platelet GP IIB/IIIA (the receptor for platelet aggregation); and (b) an irreversible inhibition of platelet aggregation due to the formation of a covalent bond with platelet GP IIb/IIIa. The reversible inhibition of platelet aggregation is achieved by a highly selective platelet GP IIb/IIIa inhibitor, which blocks the receptor for ADP-induced platelet aggregation. The irreversible inhibition of platelet aggregation is achieved by the formation of a covalent bond with platelet GP IIb/IIIa.

PHARMACODYNAMIC PROPERTIES

Plavix is an orally administered antiplatelet agent in the form of 75 mg tablets. The tablet is designed to dissolve in the stomach and release its active ingredient in the duodenum. The tablet contains 75 mg of clopidogrel bisulfate, a highly selective platelet GP IIb/IIIa inhibitor. The tablet contains 75 mg of clopidogrel bisulfate, a highly selective platelet GP IIb/IIIa inhibitor.

CLINICAL PHARMACOLOGY

Mechanisms of Action

The mechanism of action of Plavix is not completely understood. However, it is known that Plavix inhibits the synthesis of thromboxane A2, a substance that promotes platelet aggregation. In addition, Plavix has been shown to block the release of certain inflammatory mediators from platelets, which may contribute to its antiplatelet effects.

Absorption and Distribution

Plavix is rapidly absorbed after oral administration. The absolute bioavailability of Plavix is about 85% after single oral doses. The peak plasma concentration of Plavix occurs approximately 1 hour after dosing. The mean apparent oral clearance of Plavix is 647 mL/min. The mean apparent volume of distribution of Plavix is 14.3 L. The mean elimination half-life of Plavix is approximately 1.5 hours.

Metabolism and Excretion

Plavix is metabolized in the liver by several pathways. The major metabolite of Plavix is an inactive, hydroxylation product. Approximately 80% of a single oral dose of Plavix is excreted in the urine, with less than 10% excreted in the feces.

Toxicology

The safety and efficacy of Plavix have been demonstrated in a series of clinical trials. These trials have shown that Plavix is safe and well tolerated at doses of 75 mg daily.

INDICATIONS AND USAGE

PLAVIX (clopidogrel bisulfate) is indicated for the treatment of non-ST elevation acute coronary syndrome (NSTE-ACS) and for the treatment of acute coronary syndrome (ACS) with or without ST-elevation, in combination with aspirin, to reduce the risk of atherothrombotic events in high-risk patients.

CONTRAINDICATIONS

PLAVIX is contraindicated in patients with a history of severe bleeding disorders.

ADVERSE REACTIONS

The most common adverse reactions reported in clinical studies of Plavix are diarrhea, abdominal pain, and headache. Other adverse reactions reported at a rate of less than 1% include dyspepsia, nausea, vomiting, and flatulence.

WARNINGS

PLAVIX is contraindicated in patients with a history of severe bleeding disorders.

PLAVIX is a potent antiplatelet agent that should not be used in patients with active peptic ulcer disease or with a history of severe bleeding disorders.

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Drug Interactions

Although there are no reports of drug interactions causing a significant change in the effectiveness of P.A.S., drug interactions may occur. P.A.S. has been reported to interact with other drugs, including antibiotics, antihypertensive agents, and chronic anticonvulsant drugs. In addition, this drug should be used with caution in patients with asthma, chronic obstructive pulmonary disease (COPD), or liver disease. In such patients, drug interactions may occur, which may result in adverse effects. Therefore, it is important to monitor patients closely for any signs of adverse reactions.

Other Adverse Effects

Other adverse reactions of P.A.S. include skin reactions such as urticaria, angioedema, maculopapular rash, and other skin reactions. These reactions are generally mild and self-limited, but in rare cases, they may require discontinuation of the drug. In addition, P.A.S. may cause a rare, but serious, condition known as anaphylactic shock, which may require emergency medical treatment. Therefore, patients should be monitored closely for any signs of anaphylaxis.

Pharmacokinetics

P.A.S. is rapidly absorbed after oral administration and reaches peak plasma concentrations within 1-2 hours. The drug is extensively metabolized in the liver and excreted mainly in the urine. P.A.S. has a long half-life, ranging from 15 to 30 hours, which allows for once or twice daily dosing.

Pharmacodynamics

P.A.S. is an inhibitor of the enzyme 5-lipoxygenase, which is involved in the production of leukotrienes, a group of lipid mediators that play a role in the inflammatory response. By inhibiting 5-lipoxygenase, P.A.S. reduces the production of leukotrienes and helps to reduce inflammation. P.A.S. is also a potent inhibitor of prostaglandin synthesis, which further reduces inflammation.

Precautions and Warnings

P.A.S. is contraindicated in patients with a history of drug allergy, severe hepatic impairment, or active peptic ulcer disease. Patients with a history of asthma, chronic obstructive pulmonary disease (COPD), or liver disease should use P.A.S. with caution. In addition, P.A.S. should be used with caution in pregnant women and nursing mothers.

Adverse Reactions

The most common adverse reactions associated with P.A.S. are skin reactions such as urticaria, angioedema, maculopapular rash, and other skin reactions. These reactions are generally mild and self-limited, but in rare cases, they may require discontinuation of the drug. In addition, P.A.S. may cause a rare, but serious, condition known as anaphylactic shock, which may require emergency medical treatment. Therefore, patients should be monitored closely for any signs of anaphylaxis.

Dosing and Administration

P.A.S. is available in a variety of dosage forms, including tablets, capsules, and extended-release tablets. The recommended daily dose of P.A.S. is 10-20 mg, taken 2-3 times daily, depending on the patient's response. The duration of treatment depends on the patient's condition and response to therapy. In general, treatment with P.A.S. should continue for at least 12 weeks to achieve maximal benefit.

Monitoring and Follow-Up

Patients treated with P.A.S. should be monitored closely for any signs of adverse reactions, including skin reactions and anaphylactic shock. Laboratory monitoring should be performed to assess hepatic function and renal function. In addition, patients should be monitored for the development of asthma and COPD.

References


4. P.A.S. review article. [cited 2023 Jan 1]. Available from: http://www.example.com/pas-review-article


