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Prasugrel

Updated: July 10, 2014.

OVERVIEW

Introduction

Prasugrel is an inhibitor of platelet aggregation that is used to decrease the risk of myocardial infarction and stroke in patients with acute coronary syndromes. Prasugrel has been linked to mild and transient serum enzyme elevations during therapy and to rare instances of hypersensitivity reactions accompanied by mild liver injury.

Background

Prasugrel (pra' soo grel) is a thienopyridine inhibitor of adenosine diphosphate (ADP) receptors (P2Y12) on platelets, and is used as an anticoagulant to decrease the risk of recurrent coronary thromboses in patients who undergo interventions during an acute coronary syndrome. Activated platelets release ADP which binds to ADP platelet receptors, causing activation of the intracellular glycoprotein IIb/IIIA complex which triggers platelet adherence and aggregation. The aggregation of platelets plays an important role in the growth of atheromatous plaques, which can lead to coronary, cerebral and peripheral arterial occlusions. Prasugrel is an irreversible inhibitor of the P2Y12 receptor and its effects last for the life time of the platelet (7 to 10 days). In clinical trials, prasugrel therapy during acute coronary events (unstable angina and myocardial infarction) was equivalent or slightly better than clopidogrel in decreasing the frequency of recurrence of myocardial infarction and stent thrombosis. Prasugrel was approved for use in the United States in 2009 and has been used in limited numbers of patients for a limited time only. Current indications are reduction of recurrent cardiovascular events in patients with acute coronary syndromes. Prasugrel is available in 5 and 10 mg tablets under the commercial name Effient. The usual oral dose is a loading dose of 60 mg followed by 10 mg daily in combination with aspirin. The most common side effect is bleeding (usually epistaxis); other side effects are not common, but can include headache, dizziness, fatigue, gastrointestinal upset, nausea, arthralgias and rash. Rare, but more severe adverse events include hypersensitivity reactions including anaphylaxis.

Hepatotoxicity

Prasugrel is associated with low rates of serum enzyme elevations during therapy, which are similar to those with clopidogrel. In premarketing studies, no instances of clinically apparent liver injury were reported. Since marketing and release, there has been at least one report of liver injury attributed to prasugrel during a hypersensitivity reaction. The onset was within a few weeks of switching from clopidogrel to prasugrel, and was accompanied by mild-to-moderate ALT and GGT elevations that resolved rapidly once prasugrel was replaced by clopidogrel. The liver injury was overshadowed by features of a hypersensitivity syndrome with fever, eosinophilia and diarrhea, which also reversed rapidly with stopping prasugrel. Autoantibodies were not

reported. There have been no cases of acute jaundice, chronic injury or acute liver failure reported with prasugrel, although such instances have been reported with clopidogrel and ticlopidine.

Mechanism of Injury

The mechanism of prasugrel hepatotoxicity is not known, but is likely to be immunologically mediated and due to hypersensitivity. Prasugrel requires metabolic activation for its antiplatelet effects, which occurs in the liver primarily via the cytochrome P450 system, CYP 3A4 and 2B6. Inhibitors of CYP 3A4 (such as clarithromycin or itraconazole) may result in higher levels of prasugrel and antiplatelet activity, whereas inducers of CYP 3A4 (such as rifampin or phenytoin) may lower levels and result in less of an antiplatelet response.

Outcome and Management

The severity of liver injury associated with prasugrel has been mild and rapidly reversible with stopping therapy. In one instance, switching anticoagulant therapy to clopidogrel was tolerated without recurrence. Rechallenge should be avoided.

Drug Class: Antithrombotic Agents, Antiplatelet Agents

Other Drugs in the Subclass, Antiplatelet Agents: Aspirin, Cangrelor, Clopidogrel, Dipyridamole, Ticagrelor, Ticlopidine, Vorapaxar

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Prasugrel – Effient®

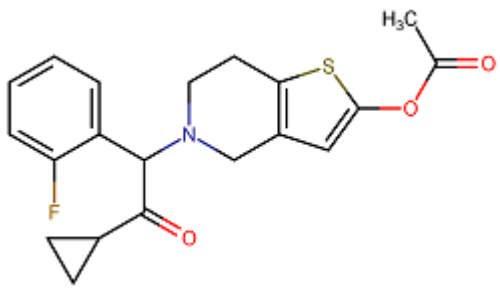
DRUG CLASS

Antithrombotic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Prasugrel	150322-43-3	C20-H20-F-N-O3-S	

ANNOTATED BIBLIOGRAPHY

References updated: 10 July 2014

Zimmerman HJ. Platelet aggregation inhibitors. Drugs used in cardiovascular disease. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 641-3.

(Textbook of hepatotoxicity published in 1999; ticlopidine, but not clopidogrel or prasugrel is discussed).

De Marzio DH, Navarro VJ. Hepatotoxicity of cardiovascular and antidiabetic drugs: antihypertensives. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, p. 528.

(Review of hepatotoxicity of antiplatelet drugs mentions that prasugrel is a recently approved inhibitor of platelet aggregation and has yet to be linked to cases of clinically apparent liver injury).

Weitz JI. Blood coagulation and anticoagulant, fibrinolytic, and antiplatelet drugs. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 849-76.

(Textbook of pharmacology and therapeutics).

Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, et al.; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007; 357: 2001-15. PubMed PMID: 17982182.

(Controlled trial comparing prasugrel to clopidogrel in 13,608 patients with acute coronary syndromes with planned intervention found similar rates of efficacy, but higher rates of major bleeding with prasugrel [2.4% vs 1.8%]; no mention of ALT elevations or hepatotoxicity).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network(DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, none were attributed to antiplatelet agents).

Scott DM, Norwood RM, Parra D. P2Y12 inhibitors in cardiovascular disease: focus on prasugrel. Ann Pharmacother 2009; 43: 64-76. PubMed PMID: 19050170.

(Review of efficacy and safety of prasugrel in comparison to other antiplatelet agents; mentions that: "..elevated liver function tests could occur with prasugrel treatment").

Prasugrel (Effient) vs. clopidogrel (Plavix). Med Lett Drugs Ther 2009; 51 (1320): 69-70. PubMed PMID: 19738549.

(Concise review of pharmacology, efficacy and safety of prasugrel in relation to clopidogrel, mentions the main adverse events is bleeding which is more common with prasugrel; no mention of hepatotoxicity or ALT elevations).

Mohammad RA, Goldberg T, Dorsch MP, Cheng JW. Antiplatelet therapy after placement of a drug-eluting stent: a review of efficacy and safety studies. Clin Ther 2010; 32: 2265-81. PubMed PMID: 21353100.

(Systematic review of studies of antiplatelet therapy after coronary stenting discussed bleeding complications only, no mention of ALT elevations or hepatotoxicity).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none were due to antiplatelet medications).

Antithrombotic drugs. Treat Guidel Med Lett 2011; 9 (110): 61-6. PubMed PMID: 21941228.

(Guidelines on the use of antiplatelet drugs, including aspirin, clopidogrel, prasugrel, ticagrelor and ticlopidine, mentions that prasugrel appears to be more effective than clopidogrel, but has a greater risk of bleeding; no mention of hepatotoxicity or ALT elevations).

Roe MT, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG, Cornel JH, et al.; TRILOGY ACS Investigators. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. N Engl J Med 2012; 367: 1297-309. PubMed PMID: 22920930.

(Among 7243 patients with unstable angina or myocardial infarction treated with prasugrel or clopidogrel for up to 30 months, both efficacy and safety were similar between the two groups; no mention of ALT elevations or hepatotoxicity).

Fernández-Ruiz M, Carbonell-Porras A, García-Reyne A, López-Medrano F. Management of a hypersensitivity reaction to thienopyridines: prasugrel-induced fever and hepatitis resolved after switching to clopidogrel. Rev Esp Cardiol 2012; 65: 773-4. PubMed PMID: 22377199.

(40 year old woman developed fever, eosinophilia, diarrhea and liver enzyme elevations starting a few weeks after switching from clopidogrel to prasugrel [peak ALT 155 U/L, GGT 723 U/L, 10% eosinophils], resolving rapidly upon switching back).

Serebruany VL, Kipshidze N, Pershukov IV, Kuliczkowski W, Carnes J, Atar D. Fatal sepsis and systemic inflammatory response syndrome after off-label prasugrel: a case report. Am J Ther 2014; 21 (6): e229-33. PubMed PMID: 23665886.

(65 year old man developed hypersensitivity reaction with high fever, confusion and rash 6 days after switching from clopidogrel to prasugrel, with subsequent multiorgan failure and death from sepsis by 16 days; few details given).