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Dipyridamole

Updated: January 4, 2018.

OVERVIEW

Introduction

Dipyridamole is a vasodilator and inhibitor of platelet aggregation that is used to decrease the risk of thromboembolic complications and recurrence of stroke in patients known to have atherosclerotic cerebrovascular disease. Dipyridamole is associated with a low rate of serum enzyme elevations during treatment, but has not been linked to instances of clinically apparent acute liver injury.

Background

Dipyridamole (dye' pir id' a mole) is a pyrimidine analogue that is used as an antiplatelet agent to decrease the risk of thromboembolic complications in patients at high risk, such as with a prosthetic heart value, with hypercoagulable states and with a history of arterial thromboses (heart attack, stroke). Dipyridamole is usually given in combination with other anticoagulants or antiplatelet agents such as warfarin or aspirin. Dipyridamole was approved for use in the United States in 1961 as an adjunct to coumarin anticoagulants in prevention of thromboembolic complications of cardiac valve replacements. Dipyridamole is available in tablets of 25, 50 and 75 mg in generic forms and under the trade name Persantine. It is also available in fixed combinations with aspirin under the name Aggrenox as prophylaxis to reduce the risk of stroke in patients with previous history of ischemic stroke or transient ischemic attacks. The typical recommended dose varies by indication, but for adults is generally 150 to 400 mg daily in divided doses. Dipyridamole is also available as a solution for injection for use as an alternative to exercise in thallium myocardial perfusion imaging ("dipyridamole stress test"). Dipyridamole is generally well tolerated, but side effects can include headache, dizziness, flushing, chest pain, gastrointestinal upset, nausea, diarrhea, rash and pruritus.

Hepatotoxicity

Dipyridamole has been associated with a low rate of serum enzyme elevations during therapy, but in large clinical trials the frequency of liver enzyme abnormalities was similar with dipyridamole therapy as with placebo. Cases of clinically apparent acute liver injury from dipyridamole have not been published although hepatitis is listed as a potential side effect in the product label. The clinical features of the liver injury linked to dipyridamole have not been described.

Likelihood score: E* (unproven but suspected cause of clinically apparent liver injury).

Drug Class: Antithrombotic Agents, Antiplatelet Agents

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

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Dipyridamole – Generic, Persantine®

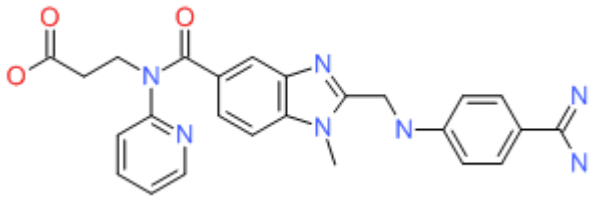
DRUG CLASS

Antithrombotic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Dipyridamole	211914-51-1	C25-H25-N7-O3	

ANNOTATED BIBLIOGRAPHY

References updated: 04 January 2018

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; mentions that there are no published cases of hepatic injury associated with dipyridamole).

De Marzio DH, Navarro VJ. Hepatotoxicity of cardiovascular and antidiabetic drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 519-40.

(Review of hepatotoxicity of cardiovascular agents including antiplatelet drugs; dipyridamole is not discussed).

Weitz JI. Antiplatelet drugs. 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. 868-72.

(Textbook of pharmacology and therapeutics).

Picano E; PISA (Persantin In Stable Angina) study group. Dipyridamole in chronic stable angina pectoris; a randomized, double blind, placebo-controlled, parallel group study. Eur Heart J 2001; 22: 1785-93. PubMed PMID: 11549300.

(Among 400 patients with stable angina treated with dipyridamole vs placebo, headache [25% vs 6%], diarrhea [14% vs 6.5%], and nausea [5.6% vs 1.5%] were more frequent among dipyridamole treated patients; no mention of liver adverse events or ALT levels).

Humphreys DM, Street J, Schumacher H, Bertrand-Hardy JM, Palluk R. Dipyridamole may be used safely in patients with ischaemic heart disease. Int J Clin Pract 2002; 56: 121-7. PubMed PMID: 11926699.

(Review of cardiac adverse events during therapy with dipyridamole indicates no evidence of increased risk).

Babaoglu MO, Karadag O, Saikawa Y, Altundag K, Elkiran T, Yasar U, Bozkurt A. Hepatotoxicity due to a possible interaction between cytosine arabinoside and dipyridamole: a case report. Eur J Clin Pharmacol 2004; 60: 455-6. PubMed PMID: 15232664.

(52 year old man with acute myeloblastic leukemia in relapse received an induction regimen while also on dipyridamole and developed jaundice with little change in serum enzyme levels, dying a few days later of septicemia; authors suggested a drug-drug interaction between dipyridamole and cytosine arabinoside).

ESPRIT Study Group, Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. Lancet 2006; 367 (9523): 1665-73. PubMed PMID: 16714187.

(Among 2739 patients treated with dipyridamole/aspirin or aspirin alone after mild stroke or transient ischemic attack, headache was major reason for discontinuation of dipyridamole; no mention of liver adverse events).

Sacco RL, Diener HC, Yusuf S, Cotton D, Ounpuu S, Lawton WA, Palesch Y, et al.; PRoFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. N Engl J Med 2008; 359: 1238-51. PubMed PMID: 18753638.

(Controlled trial of dipyridamole/aspirin vs clopidogrel in 20,332 patients with history of stroke followed for an average of 2.5 years; hepatobiliary adverse events occurred in 0.8% on dipyridamole/aspirin vs 0.9% on clopidogrel, but did not account for any of the early discontinuations or deaths).

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 from 2004 to 2008, none were attributed to antiplatelet agents).

Previtera AM, Pagani R. Agranulocytosis and hepatic toxicity with ticlopidine therapy: a case report. J Med Case Reports 2010; 4: 269. PubMed PMID: 20704700.

(70 year old woman developed agranulocytosis [neutrophils 100/L] 4 weeks after starting ticlopidine, with abnormal liver tests [bilirubin normal, ALT 560 U/L, Alk P 821 U/L, GGT 449 U/L], resolving within 4 weeks of stopping [and switching to dipyridamole and aspirin]).

Bath PM, Cotton D, Martin RH, Palesch Y, Yusuf S, Sacco R, Diener HC, et al.; PRoFESS Study Group. Effect of combined aspirin and extended-release dipyridamole versus clopidogrel on functional outcome and recurrence in acute, mild ischemic stroke: PRoFESS subgroup analysis. Stroke 2010; 41: 732-8. PubMed PMID: 20181679.

(Among 1360 patients treated with either clopidogrel or dipyridamole/aspirin with 72 hours of a stroke, serious adverse events were low and similar between the two groups; no mention of hepatic adverse events).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, no cases were attributed to dipyridamole).

Sun Q, Chang S, Lu S, Zhang Y, Chang Y. The efficacy and safety of 3 types of interventions for stroke prevention in patients with cardiovascular and cerebrovascular diseases: a network meta-analysis. Clin Ther 2017; 39: 1291-312.e8. PubMed PMID: 28606562.

(Metaanalysis of the efficacy and safety of drugs for stroke prevention including dipyridamole; does not mention ALT elevations or hepatotoxicity).

Bath PM, Woodhouse LJ, Appleton JP, Beridze M, Christensen H, Dineen RA, Duley L, et al.; TARDIS Investigators. Antiplatelet therapy with aspirin, clopidogrel, and dipyridamole versus clopidogrel alone or aspirin and dipyridamole in patients with acute cerebral ischaemia (TARDIS): a randomised, open-label, phase 3 superiority trial. Lancet 2017 Dec 20. pii:S0140-6736(17)32849-0. [Epub ahead of print] PubMed PMID: 29274727.

(Among 3096 patients with recent ischemic stroke or transient ischemic attack treated with aspirin, clopidogrel and dipyridamole together or clopidogrel alone or dispyridamole with aspirin, the incidence of recurrent stroke at 90 days was similar in all groups, but bleeding adverse events were more common with the combination of all 3 drugs; no mention of ALT elevations or hepatotoxicity).