PRODUCT MONOGRAPH

Dipyridamole Injection, USP

5 mg/mL

Coronary Vasodilator

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Control No.: 181913
Dipyridamole is a coronary vasodilator in man. The mechanism of vasodilation has not been fully elucidated, but may result from inhibition of uptake of adenosine, an important mediator of coronary vasodilation. The vasodilatory effects of dipyridamole are abolished by administration of the adenosine receptor antagonist theophylline.

How dipyridamole-induced vasodilation leads to abnormalities in thallium distribution (when administered intravenously for myocardial perfusion imaging) and ventricular function is also uncertain, but presumably represents a “steal” phenomenon. In this situation, relatively intact vessels dilate, and sustain enhanced flow, leaving reduced pressure and flow across areas of hemodynamically important coronary vascular constriction.

Following intravenous administration, the distribution half-life in man is about 25 minutes. When plasma levels of drug are followed for up to 60 hours after i.v., plasma levels decline tri-exponentially with half-lives of 5 minutes (i.v. only), 53 minutes and about 10 – 12 hours. The volume of distribution is about 140 litres with about 92 – 99% binding to plasma proteins, primarily alpha1-acid glycoprotein.

**INDICATIONS AND CLINICAL USES**

**Myocardial Perfusion Imaging**
Intravenous dipyridamole can be used to induce pharmacologic vasodilation for myocardial perfusion imaging.

**CONTRAINDICATIONS**
Hypersensitivity to dipyridamole. Intravenous administration of dipyridamole is not recommended in states of shock or collapse.
WARNINGS

Rare serious adverse reactions associated with the administration of intravenous dipyridamole for myocardial imaging have been reported. These have included fatal and non-fatal myocardial infarction, ventricular fibrillation, symptomatic ventricular tachycardia, stroke and transient cerebral ischemia.

Since excessive doses of dipyridamole or intravenous doses given too rapidly can produce peripheral vasodilation, dipyridamole should be used with caution in patients with hypotension, rapidly worsening angina, subvalvular aortic stenosis or hemodynamic instability. In rare cases, such patients may be at risk for developing myocardial ischemia and infarction.

An intravenous bolus of dipyridamole (40 – 50 mg over 4 minutes) can result in chest pain in patients with coronary artery disease. Rarely, hypotension or ventricular arrhythmias occur with a rapid, i.v. bolus. The infusion rate should be monitored to minimize this risk. The symptoms can generally be reversed with an intravenous injection of 50 – 250 mg of aminophylline over several minutes.

Patients with a history or presence of bronchial hyperreactivity may be at risk of developing bronchospasm during the use of intravenous dipyridamole as an adjunct to myocardial perfusion imaging. Although the actual overall incidence of this occurrence is small (~ 0.2%), the clinical information to be gained through the use of intravenous dipyridamole should be weighed against the potential risk to the patient.

PRECAUTIONS

Intravenous dipyridamole as an adjunct to myocardial perfusion imaging should be used with caution in patients with unstable angina, as such patients may be at risk for severe myocardial infarction.

As with exercise-induced stress, the use of intravenous dipyridamole as an adjunct to myocardial perfusion imaging may occasionally precipitate cardiac arrhythmias in patients with severe heart disease. Scanning should therefore be performed with constant monitoring of the patient's ECG. Parenteral aminophylline should be readily available and should be administered as a slow intravenous injection of 50 – 250 mg in the event of occurrences such as chest pain, bronchospasm, severe nausea/vomiting, hypotension, severe headache.

In the case of severe hypotension, the patient should be placed in a supine position with the head tilted down if necessary, before administration of parenteral aminophylline. If 250 mg of aminophylline does not relieve chest pain symptoms within a few minutes, sublingual nitroglycerin may be administered. If chest pain continues despite use of aminophylline and nitroglycerin, the possibility of myocardial infarction should be considered. If the clinical
condition of a patient with an adverse event permits a one minute delay in the administration of parenteral aminophylline, thallium-201 may be injected and allowed to circulate for one minute before the injection of aminophylline. This will allow initial thallium perfusion imaging to be performed before reversal of the pharmacologic effects of dipyridamole on the coronary circulation.

Use in Pregnancy
Reproductive studies have been performed in mice, rats, and rabbits at doses of up to 125 mg/kg and have not revealed evidence of impaired embryonic development attributable to dipyridamole. However, there have not been adequate, well controlled studies in pregnant women and the drug should be used during pregnancy only if the expected benefits outweigh the potential risks.

Use in Lactation
Dipyridamole is excreted in human milk. Caution should therefore be used when this drug is administered to nursing mothers.

Use in Children
The safety and effectiveness of dipyridamole have not been established in the pediatric population.

Drug Interactions
The use of oral maintenance xanthines (e.g., theophylline, aminophylline) may abolish the coronary vasodilation produced by intravenous dipyridamole administration. This could lead to false negative imaging results. Xanthine derivatives (e.g., found in coffee, tea) may weaken the effect of dipyridamole.

Caution is necessary when dipyridamole is used concurrently with anticoagulants or thrombolytics as the combined use of such agents may result in an increased risk of hemorrhage.

Dipyridamole may increase the hypotensive effect of blood pressure lowering drugs.

Dipyridamole may counteract the anticholinesterase effect of cholinesterase inhibitors. In patients with myasthenia gravis, readjustment of therapy may be necessary during treatment with dipyridamole.

ADVERSE REACTIONS

Serious adverse events (fatal and non-fatal myocardial infarction, severe ventricular arrhythmias, and serious CNS abnormalities) associated with the intravenous administration of dipyridamole for myocardial imaging are described in WARNINGS.

When intravenous dipyridamole was used as an adjunct to myocardial perfusion imaging in a study of 3911 patients, the following events occurred in greater than 1% of the patients:
<table>
<thead>
<tr>
<th>Event Description</th>
<th>Incidence (%) of Occurrence in 3911 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain/angina pectoris</td>
<td>19.7</td>
</tr>
<tr>
<td>Headache</td>
<td>12.2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11.8</td>
</tr>
<tr>
<td>Electrocardiographic Abnormalities/ST-T changes</td>
<td>7.5</td>
</tr>
<tr>
<td>Electrocardiographic Abnormalities/Extrasystoles</td>
<td>5.2</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.6</td>
</tr>
<tr>
<td>Flushing</td>
<td>3.4</td>
</tr>
<tr>
<td>Electrocardiographic Abnormalities/Tachycardia</td>
<td>3.2</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2.6</td>
</tr>
<tr>
<td>Pain Unspecified</td>
<td>2.6</td>
</tr>
<tr>
<td>Blood Pressure Lability</td>
<td>1.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.5</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Less common events (i.e., occurred in 1% or less of the patients in the study) included, in decreasing order of frequency:

**Cardiovascular System**
Electrocardiographic abnormalities unspecified, arrhythmia unspecified, palpitation, ventricular tachycardia, bradycardia, myocardial infarction, AV block, syncope, orthostatic hypotension, atrial fibrillation, supraventricular tachycardia, ventricular arrhythmia unspecified, heart block unspecified, cardiomyopathy, edema.

**Central and Peripheral Nervous System**
Hypoesthesia, hypertonia, nervousness/anxiety, tremor, abnormal coordination, somnolence, dysphonia, migraine, vertigo.

**Gastrointestinal System**
Dyspepsia, dry mouth, abdominal pain, flatulence, vomiting, eructation, dysphagia, tenesmus, increased appetite.

**Respiratory System**
Pharyngitis, bronchospasm, hyperventilation, rhinitis, coughing, pleural pain.

**Other**
Myalgia, back pain, injection site reaction unspecified, diaphoresis, asthenia, malaise, arthralgia, injection site pain, rigor, earache, tinnitus, vision abnormalities unspecified, dysgeusia, thirst, depersonalization, eye pain, renal pain, perineal pain, breast pain, intermittent claudication, leg cramping.

**SYMPTOMS AND TREATMENT OF OVERDOSEAGE**
Hypotension, if it occurs, is likely to be of short duration but vasopressor substances may be used if necessary. Symptoms such as feeling warm, flushes, sweating, accelerated pulse, restlessness, feeling of weakness and dizziness, and anginal complaints may occur.

**DOSAGE AND ADMINISTRATION**

**Myocardial Perfusion Imaging**
The dose of intravenous dipyridamole used as an adjunct to myocardial perfusion imaging should be adjusted according to the weight of the patient. Prior to use, Dipyridamole Injection, USP should be diluted 1:1 with Dextrose Injection, USP 5%. The diluted solution should be used within 6 hours after mixing. The recommended dose is 0.142 mg/kg/min., infused over 4 minutes. A total dose of greater than 60 mg is not recommended for use in any patient. The imaging agent should be injected within 5 minutes following the 4 minute infusion of dipyridamole. Do not mix i.v. dipyridamole with other drugs in the same syringe or infusion container.
PHARMACEUTICAL INFORMATION

**Drug Substance**
**Non-proprietary Name:** Dipyridamole

**Chemical Name(s):** 2,2',2'',2''-[(4,8- Dipiperidinopyrimido[5,4-d] pyrimidine-2,6-diyl)dinitrilo]tetraethanol

**Structural Formula:**

![Structural Formula Image]

**Molecular Formula:** C$_{24}$H$_{40}$N$_8$O$_4$

**Molecular Weight:** 504.6

**Melting Range:** 164 - 168°C

**Description:** A homogeneous yellow crystalline powder, odourless but with a bitter taste. It is soluble in dilute acids, methanol, ethanol and chloroform. In solution, dipyridamole is yellow and shows a strong blue-green fluorescence.

**Composition**
Each mL contains: 5 mg dipyridamole, 50 mg polyethylene glycol 600, 2 mg tartaric acid, hydrochloric acid for pH adjustment, in Water for Injection.
STABILITY AND STORAGE RECOMMENDATIONS

Dipyridamole Injection, USP should be stored at room temperature (15 to 30°C). Protect Dipyridamole Injection from direct light, and avoid freezing.

**Parenteral Products**
Diluted solutions should be used within 6 hours after mixing. For detailed information regarding dilution, see DOSAGE AND ADMINISTRATION.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration and leakage should not be used. Discard unused portions.

AVAILABILITY OF DOSAGE FORMS

Dipyridamole Injection, USP is available as 5 mg/mL in 10 mL single-dose vials as follows:

C601310 10 mL single-dose vials in packages of 10 vials.

PHARMACOLOGY

**Pharmacokinetics**
In animal studies, autoradiography in rats shows the liver with the highest concentrations of dipyridamole, with decreasing quantities in the following tissues: adrenal cortex, kidneys, myocardium, pituitary, skeletal muscle, lungs and blood. Twice as much drug is found in the myocardium as in skeletal muscle. Within the myocardium, the largest portion of dipyridamole is intracellular with the sarcolemma fraction containing up to 50%. On the basis of autoradiography, there are only small amounts of placental transfer. The drug does not cross the blood-brain barrier.

Conjugation of dipyridamole with glucuronic acid is the primary pathway of metabolism. In individuals with surgical drainage of the biliary tract, 95% of an intravenous 25 mg dose can be recovered from the bile within 2 hours. Enterohepatic circulation has been demonstrated in both animals and man.1

**Pharmacodynamics**

Circulatory Effects:
The effects, of endogenous adenosine are potentiated by dipyridamole inhibition of adenosine uptake in erythrocytes and platelets.3 Since adenosine is involved in physiological regulation of coronary blood flow, the coronary vasodilation induced by dipyridamole may be related to the adenosine-sparing effect of this drug.
Intravenous injection of dipyridamole in the dog causes coronary vasodilation.\textsuperscript{2,16} The threshold dose is 0.01 mg/kg with maximal effects reached by 0.2 mg/kg. A fall in systemic blood pressure, due to peripheral vasodilation, can be detected at a dose of 0.5 mg/kg with variable but not major effects on heart rate. The diastolic pressure decrease is larger than that for systolic pressure. The respiratory rate and depth are slightly increased, probably due to stimulation of carotid sinus chemoreceptors. An oral dose of 2.0 mg/kg in the dog increases coronary blood flow by 246\% for 5 hours.\textsuperscript{5}

In the presence of aneroid ring constriction of coronary vessels, chronic administration of dipyridamole in dogs, rabbits and pigs increases the number and diameter of collateral coronary vessels.\textsuperscript{21} The rate of mortality in these animals is decreased compared to non-drug treated controls. Even in the absence of a chronic hypoxic stimulus, chronic dipyridamole treatment produces greater flow across intercoronary vessels in response to acute ligation of a coronary mainstem artery, compared to controls.\textsuperscript{6,16} When blood flow through ischemic areas was measured in experimentally produced infarctions, acute intravenous dipyridamole has produced both increases and decreases, as well as no change in flow.\textsuperscript{2,5,9,10} Intravenous dipyridamole, 10 mg/hr for 6 hours, decreased the size of experimental infarctions in dogs by 76\% compared to saline-treated controls.\textsuperscript{2}

**TOXICOLOGY**

Acute Toxicity of Dipyridamole, ASA and their Combination

<table>
<thead>
<tr>
<th>Substance</th>
<th>Species</th>
<th>Route of Administration</th>
<th>LD\textsubscript{50} (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dipyridamole</td>
<td>rat</td>
<td>p.o.</td>
<td>6,000</td>
</tr>
<tr>
<td></td>
<td>rat</td>
<td>i.v.</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>dog</td>
<td>p.o.</td>
<td>400</td>
</tr>
<tr>
<td>acetylsalicylic acid (ASA)</td>
<td>rat</td>
<td>p.o.</td>
<td>1,820</td>
</tr>
<tr>
<td></td>
<td>dog</td>
<td>p.o.</td>
<td>1,000</td>
</tr>
<tr>
<td>dipyridamole/ASA*</td>
<td>mouse (male)</td>
<td>p.o.</td>
<td>3,000 - 5,000</td>
</tr>
<tr>
<td></td>
<td>mouse (female)</td>
<td>p.o.</td>
<td>5,000</td>
</tr>
<tr>
<td></td>
<td>rat (male)</td>
<td>p.o.</td>
<td>5,000</td>
</tr>
<tr>
<td></td>
<td>rat (female)</td>
<td>p.o.</td>
<td>5,000</td>
</tr>
<tr>
<td></td>
<td>mouse (male)</td>
<td>i.p.</td>
<td>910</td>
</tr>
<tr>
<td></td>
<td>mouse (female)</td>
<td>i.p.</td>
<td>1,200</td>
</tr>
<tr>
<td></td>
<td>rat (male)</td>
<td>i.p.</td>
<td>1,050</td>
</tr>
<tr>
<td></td>
<td>rat (female)</td>
<td>i.p.</td>
<td>1,230</td>
</tr>
<tr>
<td></td>
<td>dog</td>
<td>p.o.</td>
<td>875 - 950</td>
</tr>
</tbody>
</table>

*dipyridamole/ASA mixed in a ratio of 1/5, weight/weight

After administration of dipyridamole, signs of toxicity among the survivors were ataxia and depression, while in those that died, prostration and tonic convulsions were also seen. After ASA, lethargy fluctuating with restlessness, bleeding through the nose and respiratory distress occurred. Some animals died in a prostrate position without any preceding agitation.
Symptomatology following administration of the combination dipyridamole/ASA, (1/5), did not differ appreciably from the toxic signs observed with either substance alone.

Subacute intravenous administration of dipyridamole to dogs at levels of 1 and 10 mg/kg/day for 4 weeks did not produce significant signs of toxicity. Oral dipyridamole (20, 40, 60, 80 mg/kg/day) administered for 13 weeks to beagles produced no toxic effect at the low dose but resulted in kidney toxicity with increasing doses. This was manifested by weight loss, increased blood urea and serum creatinine and epithelial nephritis at the high dose. The abnormalities were rapidly reversible upon discontinuation of treatment. When dogs were treated orally for 26 weeks with dipyridamole at doses of 10, 20 and 40 mg/kg/day, only occasional emesis occurred at the high dose level. Hematological, biochemical and urinary analyses were within normal limits. Rats fed dipyridamole in the diet at levels of 25, 75 and 225 mg/kg/day over a period of 27 weeks showed no signs of toxicity.

Treatment of rats for 3 months with the combination dipyridamole/ASA (1/5) at oral doses of 25, 100 and 400 mg/kg resulted in no drug-related toxicity except for a delay in body weight development in the high dose group. In chronic toxicity studies of 6 months duration in rats and dogs, dipyridamole/ASA (1/4) had no toxic effect at doses of 25 and 100 mg/kg in either species. With increasing dose (200 and 400 mg/kg/day), renal and gastrointestinal lesions appeared along with associated biochemical changes. At the high dose in dogs, all animals were dead at 3 months. Control groups of dogs received ASA, 80 and 160 mg/kg/day. The lesions observed were similar to toxic signs in the combination treatment groups except for the nephritis and renal changes seen in the 200 and 400 mg/kg dose groups of dogs.

Two year carcinogenicity studies of dipyridamole in mouse and rat in doses up to 75 mg/kg demonstrated no tumorogenic effect of the drug. The dipyridamole/ASA combination (1/5) also produced no evidence of carcinogenicity in either rats or mice at oral doses up to 450 mg/kg. Mutagenicity assays (cytogenetic, microorganism, dominant lethal and micronucleus tests) of both dipyridamole alone and the dipyridamole/ASA combination (1/15) could not demonstrate any mutagenic potential of these compounds.
SELECTED BIBLIOGRAPHY / REFERENCES


