PRODUCT MONOGRAPH

PRASN-HYDRALAZINE

Hydralazine Hydrochloride Tablets, USP

10 mg, 25 mg and 50 mg

Antihypertensive Agent

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DATE OF APPROVAL:
November 1, 2019

Control #: 221556

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THERAPEUTIC CLASSIFICATION

Antihypertensive Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Although the precise mechanism of action of hydralazine hydrochloride is not fully understood, the major effects are on the cardiovascular system. Hydralazine apparently lowers blood pressure by exerting a peripheral vasodilating effect through a direct relaxation of vascular smooth muscle. Hydralazine, by altering cellular calcium metabolism, interferes with the calcium movements within the vascular smooth muscle that are responsible for initiating or maintaining the contractile state.

The peripheral vasodilating effect of hydralazine results in decreased arterial blood pressure (diastolic more than systolic); decreased peripheral vascular resistance; and an increased heart rate, stroke volume, and cardiac output. The vasodilating effect is much greater on arterioles than on veins, and vascular resistance decreases more in the coronary, cerebral, splanchnic and renal circulations than in skin and muscle.

Hydralazine usually increases renin activity in plasma, presumably as a result of increased secretion of renin by the renal juxtaglomerular cells in response to reflex sympathetic discharge. This increase in renin activity leads to the production of angiotensin II, which then causes stimulation of aldosterone and consequent sodium reabsorption and fluid retention.

Sodium retention and excessive sympathetic stimulation of the heart caused by hydralazine may be precluded by co-administration of a thiazide diuretic and a beta-blocker. Beta-adrenergic blocking drugs and hydralazine are complementary in their pharmacologic effects, a beta-adrenergic blocking agent minimizes hydralazine-induced increases in cardiac rate and output, and hydralazine prevents the reflex increase in peripheral resistance induced by beta-blockers.

Pharmacokinetics

Hydralazine is rapidly and fairly completely absorbed after oral administration. In the plasma only small amounts of the free drug can be traced, the bulk circulating in conjugated form, i.e. pyruvic acid hydrazone. Peak serum concentrations are reached within one to two hours after a dose.
Plasma levels of hydralazine vary widely among individuals. Orally administered hydralazine undergoes extensive, saturable first-pass metabolism (systemic availability: 26 - 55%), this first- pass effect being dependent on the individual's acetylator status. In response to the same oral dose, slow-acetylators show higher "apparent" plasma hydralazine levels than rapid acetylators and require lower doses to maintain control of blood pressure.

After intravenous administration of hydralazine no first-pass effect occurs; acetylator status therefore has no influence on the plasma levels.

Hydralazine is widely distributed in the body. The apparent volume of distribution of hydralazine is approximately 50% body weight. Binding to plasma proteins (chiefly albumin) is 85 - 90%.

Hydralazine crosses the placental barrier and is excreted in the breast milk.

The pattern of the metabolites depends on the subject's acetylator and presumably hydroxylator status. The main metabolite, NAc-HPZ (N-acetyl-hydrazine-phthalazinone), was found to be the relevant indicator for the drug-related phenotype.

The plasma half-life generally ranges between 1.7 and 3.0 hours in most subjects, but in rapid acetylators it is shorter, averaging 45 minutes.

Hydralazine and its metabolites are rapidly excreted by the kidney and 80% of the oral dose appears in the urine within 48 hours. The bulk of the hydralazine excreted is in the form of acetylated and hydroxylated metabolites, some of which are conjugated with glucuronic acid; 2 - 14% is excreted as "apparent" hydralazine.

Comparative Bioavailability

A single dose randomized, two-period, two-way crossover bioavailability study comparing ASN-HYDRALAZINE tablets, 50 mg (Ascend Laboratories Limited) to HYDRALAZINE tablets, 50 mg (AA Pharma Incorporated) was conducted under fasting conditions in healthy male adult subjects (n=36). The results are summarized in the following table.

Free Hydralazine (1 × 50 mg of tablets) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.hr/mL)	32.14 43.34 (68.21)	31.46 42.80 (68.65)	102.16	93.34 - 111.81%
AUC_I€ (ng.hr/mL)	33.86 45.31 (67.60)	33.1801 44.76 (68.08)	102.06	93.51 - 111.40%

Free Hydralazine (1 × 50 mg of tablets) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
C_{max} (ng mL)	38.44 63.92 (99.35)	41.95 69.67 (88.26)	91.64	71.25 - 117.86%
T_{max}§ (h)	0.42 (0.33 – 2.50)	0.33 (0.16 – 1.50)		
$T_{½}$€ (h)	3.40 (73.19)	3.19 (67.10)		

* ASN-HYDRALAZINE tablets, 50 mg (Ascend Laboratories Limited)

† HYDRALAZINE tablets, 50 mg (AA Pharma Incorporated) were purchased in Canada.

§ Expressed as the median (range) only.

€ Expressed as the arithmetic mean (CV%) only.

INDICATIONS AND CLINICAL USE

ASN-HYDRALAZINE (hydralazine hydrochloride) is indicated in the treatment of essential hypertension. It is used in conjunction with other antihypertensives such as beta-blockers and diuretics.

CONTRAINDICATIONS

1. Hypersensitivity to hydralazine or other hydrazinophthalazine derivatives.
2. Idiopathic systemic lupus erythematosus (SLE) and related diseases.
3. Severe tachycardia and heart failure with a high cardiac output (e.g. in thyrotoxicosis).
4. Myocardial insufficiency due to mechanical obstruction (e.g. in the presence of aortic or mitral stenosis or constrictive pericarditis).
5. Isolated right-ventricular heart failure due to pulmonary hypertension (cor pulmonale).

6. Acute dissecting aneurysm of the aorta.

7. Coronary artery disease.

WARNINGS

1. Hydralazine may provoke in a few patients a clinical picture simulating systemic lupus erythematosus (SLE) including glomerulonephritis. In its mild form this syndrome is reminiscent of rheumatoid arthritis (arthralgia, sometimes associated with fever and skin rash). When fully developed a syndrome resembling disseminated lupus erythematosus occurs.

   Should this SLE-like syndrome develop, treatment should be discontinued immediately. Symptoms and signs usually regress when the drug is discontinued but residua have been detected many years later. Long-term treatment with adrenocorticosteroids may be necessary.

   The frequency of these untoward effects increases with dosage and duration of exposure to the drug and is higher in slow than in fast acetylators. When treated with the same dosage, slow acetylators have higher serum concentrations than fast acetylators. The lowest effective dosage should therefore be used for maintenance therapy. If 100 mg daily fails to elicit an adequate clinical effect, the patient's acetylator status should be evaluated.

   Slow acetylators and women run a greater risk of developing this SLE-like syndrome. In such cases dosage should be kept below 100 mg daily and the patients carefully

monitored for clinical signs and symptoms suggestive of this syndrome.

Complete blood counts, examination of lupus erythematosus cell preparations, antinuclear antibody titer determinations and urine analysis are indicated before and periodically (e.g. every 6 months) during prolonged therapy with hydralazine even though the patient is asymptomatic. These tests are also indicated if the patient develops arthralgia, fever, chest pain, continued malaise or other unexplained signs or symptoms. If the results of these tests are abnormal, treatment should be discontinued.

Antinuclear antibody may be found in the blood of as many as 50 percent of patients receiving hydralazine who remain asymptomatic. A positive antinuclear antibody titer requires that the physician carefully weigh the implications of the test results against the benefits to be derived from antihypertensive therapy with hydralazine.

Microhematuria and/or proteinuria, in particular together with positive titres of antinuclear antibodies, may be initial signs of immune-complex glomerulonephritis associated with the SLE-like syndrome.

2. The chronotropic and inotropic effects of hydralazine increase myocardial oxygen requirements. It can cause electrocardiographic changes of myocardial ischemia, and in patients with coronary artery disease may precipitate angina pectoris or congestive heart failure. Hydralazine has been implicated in the production of myocardial infarction. ASN-HYDRALAZINE must therefore be used with caution in patients with suspected coronary artery disease. It should be given only in combination with a beta-blocker or other suitable sympatholytic agents. The beta-blocker medication should be commenced a few days before the start of treatment with ASN-HYDRALAZINE.

Patients who have survived a myocardial infarction should not receive ASN- HYDRALAZINE until post-infarction stabilization has been achieved.

The "hyperdynamic" circulation caused by hydralazine may accentuate specific cardiovascular inadequacies (e.g. hydralazine may increase pulmonary artery pressure in patients with mitral valvular disease).

3. Use in Pregnancy

Animal studies indicate that high doses of hydralazine are teratogenic in mice, possibly in rabbits, but not in rats (see TOXICOLOGY). Teratogenic effects observed were cleft palate and malformation of facial and cranial bones. There are no adequate and well-controlled studies in pregnant women. Although clinical experience does not include any positive evidence of adverse effects on the human fetus, hydralazine should be used during pregnancy only if the benefit clearly justifies the potential risk to the fetus.

PRECAUTIONS

Postural hypotension may result from hydralazine, but is less common than with ganglionic blocking agents. The drug should be used with caution in patients with cerebral vascular disease since abrupt decreases in blood pressure should be avoided in these patients.

A pronounced lowering of the blood pressure may adversely affect the patient's reactions (e.g. as in driving or operating machinery).

In hypertensive patients with normal kidneys who are treated with hydralazine, there is evidence of increased renal blood flow and a maintenance of glomerular filtration rate. In some instances improved renal function has been noted where control values were below normal prior to hydralazine administration. However, as with any antihypertensive agent, ASN-HYDRALAZINE should be used with caution in patients with advanced renal damage.

In patients with renal impairment, serum levels of hydralazine increased as compared to those in patients with normal renal function, therefore the dose or the dosing interval has to be adapted according to the clinical response, in order to avoid accumulation of the "apparent" active substance.

In patients with hepatic dysfunction, serum levels of hydralazine increased as compared to those in patients with normal hepatic function, therefore the dose or the dosing interval has to be adapted according to the clinical response, in order to avoid accumulation of the "apparent" active substance. Peripheral neuritis, evidenced by paresthesias, numbness and tingling in the extremities has been observed. Published evidence suggests an antipyridoxine effect and the addition of pyridoxine to the regimen if symptoms develop.

Blood dyscrasias consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis and purpura have been reported. Periodic blood counts are advised during therapy. If such abnormalities develop, therapy should be discontinued.

Tumorigenicity and Mutagenicity

Hydralazine hydrochloride in chronic toxicity studies has been shown to increase the incidence of some tumors in aging rodents. A mutagenic potential was observed in some but not all mutagenicity tests (see TOXICOLOGY). The extent to which these findings indicate a risk to man is uncertain. While

long-term clinical observations have not suggested that human cancer is associated with hydralazine use, epidemiologic studies have so far been insufficient to arrive at any conclusion (see TOXICOLOGY).

Lactation

Hydralazine passes into breast milk. Alternatives to hydralazine should be considered in nursing mothers.

Use in the Elderly

The elderly may be more sensitive to the hypotensive effects. In addition the risk of hydralazine-induced hypothermia may be increased in elderly patients.

Use in Children

Although there is some experience with the use of hydralazine hydrochloride in children, controlled clinical trials to establish safety and effectiveness in this age group have not been conducted.

Drug Interactions

Concomitant treatment with other vasodilators, calcium antagonists, ACE inhibitors, diuretics, antihypertensives, tricyclic antidepressants and major tranquilizers, as well as the consumption of alcohol, may potentiate the hypotensive effect of hydralazine.

Administration of hydralazine shortly before or after diazoxide may lead to marked hypotension. When potent antihypertensive drugs, such as diazoxide, are used in combination with ASN-HYDRALAZINE, patients should be continuously observed for several hours for any excessive fall in blood pressure.

Concurrent administration of hydralazine with beta-blockers subject to a strong first-pass effect (e.g.

propranolol) may increase their bioavailability. Downward dosage adjustment of these drugs may be required when they are given concomitantly.

Monoamine oxidase (MAO) inhibitors should be used with caution in patients receiving hydralazine. Hydralazine may reduce the pressor responses to epinephrine.

ADVERSE REACTIONS

The most common adverse reactions are tachycardia, palpitation, anginal symptoms, flushing, headache and gastro-intestinal disturbances. These are more frequent at the start of treatment, especially if the dosage is raised rapidly. However, such reactions generally subside in the further course of treatment or following a reduction of dosage.

The most severe adverse reactions are neuropathy, blood dyscrasias, and an acute rheumatoid state resulting in a syndrome resembling disseminated lupus erythematosus (see WARNINGS and PRECAUTIONS).

Cardiovascular System

Tachycardia, palpitation, flushing, hypotension, anginal symptoms, edema, heart failure, paradoxical pressor responses.

Central and Peripheral Nervous System

Headache, dizziness, peripheral neuritis evidenced by paresthesia, numbness and tingling, polyneuritis, tremor, agitation, anorexia, anxiety, depression, hallucinations, disorientation, sleep disturbances.

Musculo-Skeletal System

Arthralgia, joint swelling, myalgia, muscle cramps.

Skin and Appendages

Rash.

Urogenital System

Proteinuria, increased plasma creatinine, hematuria sometimes in association with glomerulonephritis, acute renal failure, urinary retention, difficulty in micturition.

Gastrointestinal Tract

Gastrointestinal disturbances, diarrhea, constipation, nausea, vomiting, jaundice, liver enlargement, abnormal liver function sometimes in association with hepatitis, paralytic ileus.

Blood

Anemia, leukopenia, neutropenia, thrombocytopenia with or without purpura, hemolytic anemia, leucocytosis, lymphadenopathy, pancytopenia, splenomegaly, agranulocytosis, antinuclear antibodies.

Sense Organs

Increased lacrimation, conjunctivitis, nasal congestion, blurred vision.

Hypersensitivity Reactions

SLE-like syndrome (see WARNINGS), chills, eosinophilia, hypersensitivity reactions such as pruritus, urticaria, vasculitis, hepatitis.

Respiratory Tract

Dyspnea, pleural pain.

Miscellaneous

Fever, weight decrease, malaise, exophthalmos, decreased libido, pancreatitis.

Hyperuricemia, hyperglycemia and hypokalemia have been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: Hypotension, tachycardia, headache, generalized skin flushing, sweating, nausea and dizziness. Myocardial ischemia with angina pectoris, cardiac arrhythmia and profound shock can develop.

Further signs may include impairment of consciousness, vomiting, tremor, convulsions, oliguria and hypothermia.

Treatment: There is no known specific antidote.

Evacuate gastric contents by induction of emesis or gastric lavage, taking adequate precautions against aspiration and for protection of the airway. If general conditions permit, administer activated charcoal slurry and possibly an osmotic cathartic. These procedures may have to be omitted or carried out after cardiovascular status has been stabilized, since they might precipitate cardiac arrhythmias or increase the depth of shock.

Support of the cardiovascular system is of primary importance. Shock should be treated with volume expanders without resorting to use of vasopressors. The use of dopamine to elevate systolic blood pressure to 90 mmHg may be considered in an emergency. If a vasopressor drug is required, a type that

is least likely to precipitate or aggravate cardiac arrhythmia should be used, and the ECG should be monitored while it is being administered. Digitalization may be necessary. Renal function must be monitored and supported as required.

No experience has been reported with extracorporeal or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

The dose of ASN-HYDRALAZINE (hydralazine hydrochloride) must always be individualized and adjusted according to the patient's blood pressure response.

Initially, one 10 mg tablet 4 times daily for the first 2 to 4 days. The dose is increased to 25 mg 4 times daily for the remainder of the first week. Dosage is then increased to 50 mg 4 times daily for the second and subsequent weeks of treatment.

For maintenance, adjust dosage to lowest effective levels. The incidence of toxic reactions, particularly the lupus erythematosus syndrome, is highest in the group of patients receiving large doses of hydralazine.

The usual effective maintenance daily dose ranges from 50 to 200 mg. However, the dose should not be increased above 100 mg per day without determining the acetylator phenotype.
After the titration period, some patients may be maintained on a twice daily schedule.
The influence of food on the bioavailability of hydralazine is uncertain. Contradictory results have been obtained.

Note: Geriatric patients may be more sensitive to the effects of the usual adult dose. Response should be monitored and the dosage adjusted accordingly to lowest effective levels.

In patients with renal impairment the dose or the dosing interval should be adapted according to the clinical response, in order to avoid accumulation of the "apparent" active substance.

In patients with hepatic dysfunction the dose or the dosing interval should be adapted according to the clinical response, in order to avoid accumulation of the "apparent" active substance.

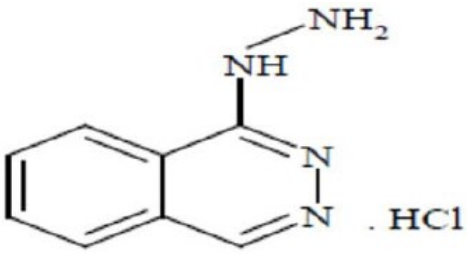
PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: hydralazine hydrochloride

Chemical Name: 1-hydrazinophthalazine monohydrochloride

Structural Formula:



Molecular Formula: $C_8H_8N_4 \bullet HCl$

Molecular Weight: 196.64 g/mol

Description:

Hydralazine hydrochloride is a white to off-white, crystalline powder. Its melting point is between 265.0°C and 275.0°C . It is soluble in water and slightly soluble in alcohol.

Composition

In addition to the active ingredient hydralazine hydrochloride, each 10 mg, 25 mg and 50 mg tablet contains non-medicinal ingredients: colloidal silicon dioxide, lake blend blue (25 mg tablet only), lake pigment (50 mg tablet only), mannitol, microcrystalline cellulose, pigment blend yellow (10 mg tablet only), povidone, sodium starch glycolate, stearic acid micronized.

Stability and Storage Recommendations

Store at room temperature (15°C - 30°C).

AVAILABILITY OF DOSAGE FORMS

ASN-HYDRALAZINE 10 mg: Yellow colored, mottled, round shaped, uncoated tablets, debossed with "A10" on one side and score line on other side. Available in bottles of 100 tablets.

ASN-HYDRALAZINE 25 mg: Blue colored mottled, round shaped, uncoated tablets, debossed with "A25" on one side and plain on other side. Available in bottles of 100 tablets.

ASN-HYDRALAZINE 50 mg:Pink colored mottled, round shaped, uncoated tablets, debossed with "A50" on one side and plain on other side. Available in bottles of 100 tablets.

PHARMACOLOGY

Hydralazine acts directly on peripheral arterioles, where it has a relaxing effect on the smooth muscle of the vessel wall, with a resultant decrease in arteriolar resistance, decreasing arterial blood pressure, diastolic often more than systolic.

Hydralazine exerts no direct actions on the heart. When the drug decreases arterial pressure and thereby

activating the baroreceptors, cardiovascular reflexes result in increased sympathetic discharge. Since hydralazine does not increase venous capacitance or depress cardiac function, sympathetic stimulation increases heart rate, left ventricular velocity, stroke volume and cardiac output.

TOXICOLOGY

Acute Toxicity

Rats: The acute toxicity of hydralazine, as determined intravenously in female white rats is comparatively low: the LD_{50} is 34 mg/kg.

Dogs: Single doses of 20 mg/kg intravenously and 200 mg/kg orally were tolerated. The test animals manifested tachycardia, depression and emesis. Vomiting occurred at doses of 8 and 16 mg/kg and central nervous system stimulation at 32 and 64 mg/kg.

Sub-acute Toxicity

Dogs: Hydralazine in oral doses of 30 mg/kg given 5 days per week for 3 months was well tolerated.

Long-term Toxicity

Mice: Doses of 7.4 mg/day to males and 5.4 mg/day to females administered orally throughout the lifespan resulted in increased incidence of lung tumors (classified as adenomas and adenocarcinomas).

Dogs: Hydralazine was given in oral doses of 1, 3 and 10 mg/kg per day for 6 months. Heinz bodies were detected in the erythrocytes of the high dosage group. Other changes observed included: reversible elevations and depressions of the ST-segment; dose-related tachycardia; dose-related conjunctivitis and in one animal conjunctivitis sicca with pannus formation; in one intermediate dose animal, a small area of subendocardial fibrosis was observed histologically.

Teratogenicity

Mice: Doses of 20, 60, 120 and 150 mg/kg were used. Somnolence and dyspnea, as well as death, at the highest doses indicate that maximum tolerated doses had been exceeded. A dose-related increase in the incidence of cleft palate, agnathia and hypognathia was observed.

Rats: Doses of 20, 60 and 180 mg/kg were used. Maximum tolerated doses were again exceeded, but teratogenic manifestations were not observed, although there was a delay in ossification characterized by unossified calcanei, sternebrae and phalangeal nuclei.

Rabbits: Doses of 10, 30 and 60 mg/kg were used. At the high dose level, some somnolence, as well as one apparent drug-related death, indicated that doses were in the maximum tolerated range. In the 60 mg/kg dose group one out of 84 fetuses showed mandibular aplasia (agnathia inferior). This malformation is considered to be of spontaneous origin, however, a drug related effect cannot be entirely discounted.

Carcinogenicity

Mice: In a lifetime study in Swiss albino mice, there was a statistically significant increase in the incidence of lung tumors (adenomas and adenocarcinomas) of both male and female mice given hydralazine hydrochloride continuously in their drinking water at a dosage of about 250 mg/kg.

Rat: In a 2-year carcinogenicity study of Sprague-Dawley albino rats given hydralazine hydrochloride by gavage at dose levels of 15, 30 and 60 mg/kg/day, microscopic examination of the liver revealed a small but statistically significant increase in benign neoplastic nodules in male and female high-dose rats, and in female rats from the intermediate dose group. Benign interstitial (Leydig) cell tumors of the testes were also significantly increased in male rats from the high-dose group. The tumors observed were common in aged rats and the increased incidence was not observed until 18 months of treatment.

Mutagenicity

Hydralazine was shown to be mutagenic in bacterial systems (Gene Mutation and DNA Repair) and in one of two rat and one rabbit hepatocyte in-vitro DNA repair studies. In the latter study the effect was evident in cells from slow acetylator rabbits but not from fast acetylators. Additional in-vivo and in-vitro studies using lymphoma cells, germinal cells, and fibroblasts from mice, bone marrow cells from Chinese hamsters and fibroblasts from human cell lines did not demonstrate any mutagenic potential for hydralazine.

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25 APO-HYDRALAZINE Product Monograph by Apotex Inc. Control No. 199983; Date of Revision: December 14, 2016.

Last Approved: November 1, 2019