PRODUCT MONOGRAPH

PrAPRESOLINE®

Hydralazine hydrochloride Injection Mfr. Std.

(hydralazine hydrochloride USP)

20 mg/mL

Antihypertensive Agent

SteriMax Inc.
2770 Portland Drive,
Oakville, ON
L6H 6R4

Date of Revision:
August 15, 2019

Control # 227648

PRODUCT MONOGRAPH

PrAPRESOLINE®

Hydralazine hydrochloride Injection Mfr. Std.

(hydralazine hydrochloride USP)

20 mg/mL

THERAPEUTIC CLASSIFICATION

Antihypertensive Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Although the precise mechanism of action of APRESOLINE (hydralazine hydrochloride USP) 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 APRESOLINE 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:

Distribution:

After intravenous administration of APRESOLINE no first-pass effect occurs; acetylator status therefore has no influence on the plasma levels. In the plasma only small amounts of the free drug can be traced, the bulk circulating in conjugated form, i.e. mainly as pyruvic acid hydrazone. Only the so-called “apparent” hydralazine, i.e. the sum of the free and conjugated hydralazine, can be measured reliably.

Hydralazine becomes bound to plasma proteins (chiefly albumin) to the extent of 88 - 90%. It is rapidly distributed in the body and displays a specific affinity for muscle tissue in the arterial walls. It crosses the placental barrier and also passes into breast milk.

Metabolism:

The pattern of the metabolites depends on the subject's acetylator and presumably hydroxylator status. Urinary excretion of NAc-HPZ (N-acetyl-hydrazine-phthalazinone), the main metabolite from the acetylation pathway, may be used to determine acetylator phenotype. The plasma half-life generally ranges from 2 to 3 hours, but in rapid acetylators it is shorter, averaging 45 minutes. In patients with impaired renal function, the plasma half-life is prolonged to up to 16 hours at a creatinine clearance of < 20 mL/min.

Excretion:

Hydralazine and its metabolites are rapidly excreted by the kidney. 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. Renal elimination may be impaired in patients of advanced age.

INDICATIONS

APRESOLINE (hydralazine hydrochloride Injection Mfr. Std) is indicated for the emergency treatment of severe essential hypertension when the drug cannot be given orally or when there is an urgent need to lower blood pressure (e.g. toxemia of pregnancy or pre-eclampsia).

CONTRAINDICATIONS

1) Hypersensitivity to hydralazine or dihydrazine, or to any of the excipients.

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.

8) Porphyria

WARNINGS

The overall “hyperdynamic” state of the circulation induced by hydralazine may accentuate certain clinical conditions. Hydralazine can cause anginal attacks and ECG changes indicative of myocardial ischemia. Myocardial stimulation may provoke or aggravate angina pectoris, congestive heart failure or myocardial infarction.

Patients with suspected or confirmed coronary artery disease should therefore be given APRESOLINE only under beta-blocker cover or in combination with other suitable sympatholytic agents. It is important that the beta-blocker medication should be commenced a few days before the start of treatment with APRESOLINE.

Patients who have survived a myocardial infarction should not receive APRESOLINE until post-infarction stabilization has been achieved. APRESOLINE should not be used in heart failure.

Cerebrovascular disease:
Like all potent antihypertensives, APRESOLINE should be used with caution in patients suffering from cerebrovascular disease, since it can increase ischemia.

APRESOLINE (hydralazine hydrochloride USP) 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. Rapid acetylators, often respond inadequately even to doses of 100 mg daily. In these patients, the dosage can be raised with only a slightly increased risk of a SLE-like syndrome. 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. Microhaematuria and/or proteinuria, in particular together with positive titres of anti-nuclear factors (ANF), may be initial signs of immune-complex glomerulonephritis associated with the SLE-like syndrome. A positive ANF titre

requires that the physician carefully weighs the implications of the test results against the benefits of continued therapy with APRESOLINE. If overt clinical signs and symptoms develop, the medicine should be withdrawn at once. A complete blood count and ANF titre determination is indicated before and periodically during prolonged therapy with APRESOLINE even if 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 antibodies 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 APRESOLINE.

Treatment with APRESOLINE may induce systemic vasculitis, including ANCA (anti-neutrophil cytoplasm antibody)-positive vasculitis, leading to pulmonary renal syndrome which is a combination of diffuse alveolar haemorrhage and rapidly aggressive glomerulonephritis. Patients may present with severe respiratory and/or renal failure and require treatment in an intensive care unit. The syndrome is characterised by a fulminant course if left untreated and may sometimes be fatal.

Usage in Pregnancy (Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on human fetus or neonate without causing malformations. These effects may be reversible.

Hydralazine is known to cross the placenta following intravenous administration and has been associated with fetal distress and fetal cardiac arrhythmia in the last trimester of pregnancy. Teratogenic effects observed in humans included the cleft palate and malformations of facial and cranial bones. In view of the possible teratogenic potential in humans, use of APRESOLINE in pregnancy before the third trimester should be avoided. The medicine should only be given in the third trimester if the expected benefit justifies the potential risk to the fetus.

Animal experiments have shown hydralazine is teratogenic in mice at oral doses equal to or greater than 20 mg/kg/day; a "no effect" dose has not been clearly established. Hydralazine was teratogenic in rabbits where oral doses equal to and greater than 75 mg/kg/day caused phalangeal defects. Hydralazine was not teratogenic in rats at oral doses up to 180 mg/kg/day. Embryolethality was observed in mice at doses equal to or greater than 20 mg/kg/day. Hydralazine was, however, not embryolethal in rats and rabbits at oral doses up to 180 and 60 mg/kg/day, respectively. Delayed ossification was observed in mice and rats at maternotoxic doses greater than 20 and 60 mg/kg/day, respectively, and reduced fetal weight was seen in mice at doses greater than 20 mg/kg/day.

PRECAUTIONS

Postural hypotension may result from APRESOLINE (hydralazine hydrochloride USP), 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 APRESOLINE, 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 APRESOLINE administration. However, as with any antihypertensive agent, APRESOLINE should be used with caution in patients with advanced renal damage.

In patients with renal impairment (creatinine clearance < 30 mL/min or serum creatinine > 2.5 mg/100 mL or 221 µmol/L), serum levels of hydralazine increased as compared to those in patients with normal renal function, therefore the dose or the interval between doses should be adjusted 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 should be adjusted according to the clinical response, in order to avoid accumulation of the "apparent" active substance.

When undergoing surgery, patients treated with Hydralazine may show a fall in blood pressure, in which case one should not use adrenaline to correct the hypotension, since it enhances the cardiac-accelerating effects of hydralazine hydrochloride.

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 or medicine withdrawal 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.

Skin rash and febrile reactions occur rarely, in which case the medicine should be withdrawn.

Tumourigenicity and Mutagenicity

Hydralazine hydrochloride in chronic toxicity studies has been shown to increase the incidence of some tumours 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. Concurrent hepatic and renal insufficiency should be taken into account.

Use in Children

Safety and efficacy of hydralazine hydrochloride has not been established in children. APRESOLINE is not recommended for paediatric use.

Drug Interactions

Concomitant treatment with other vasodilators, calcium antagonists, ACE inhibitors, diuretics, antihypertensives, anaesthetics, tricyclic antidepressants and major tranquilizers, nitrates or drugs exerting central depressant actions (including alcohol), may potentiate the hypotensive effect of APRESOLINE.

Administration of APRESOLINE shortly before or after diazoxide may lead to marked hypotension. When potent antihypertensive drugs, such as diazoxide, are used in combination with APRESOLINE, patients should be continuously observed for several

hours for any excessive fall in blood pressure. MAO inhibitors should be used with caution in patients receiving hydralazine.

Hydralazine hydrochloride may reduce the pressor responses to epinephrine. Concurrent administration of APRESOLINE with beta blockers subject to a strong first pass effect (e.g. propanolol) may increase their bioavailability. Download adjustment of these drugs may be required when they are given concomitantly with hydralazine hydrochloride.

There is potential for the hypotensive effect of hydralazine to be antagonised when used concomitantly with oestrogens or non-steroidal anti-inflammatory drugs (NSAIDs).

ADVERSE REACTIONS

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug.

The most common adverse reactions are tachycardia, palpitation, anginal symptoms, flushing, headache, dizziness, nasal congestion and gastrointestinal 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. Isolated cases of peripheral neuritis, polyneuritis and paraesthesia have also been reported.

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

(The following frequency estimates are used: frequent > 10%; occasional 1-10%; rare 0.001-1%; isolated cases < 0.001%)

Cardiovascular System

Frequent: Tachycardia, palpitations,

Occasional: flushing, hypotension, anginal symptoms,

Rare: edema, heart failure,

Isolated cases: paradoxical pressor responses.

Central and Peripheral Nervous System

Frequent: Headache,

Rare: dizziness,

Isolated cases: peripheral neuritis evidenced by paresthesia numbness and tingling, polyneuritis, tremor.

Musculo-Skeletal System

Occasional: Arthralgia, joint swelling, myalgia, muscle cramps.

Skin and Appendages

Rare: Rash.

Urogenital System

Rare: Proteinuria, increased plasma creatinine, hematuria sometimes in association with glomerulonephritis,

Isolated cases: acute renal failure, urinary retention, difficulty in micturition.

Gastrointestinal Tract

Occasional: Gastrointestinal disturbances, diarrhea, constipation, nausea, vomiting,

Rare: jaundice, liver enlargement, abnormal liver function sometimes in association with hepatitis,

Isolated cases: paralytic ileus.

Blood

Rare: Anemia, leukopenia, neutropenia, thrombocytopenia with or without purpura,

Isolated cases: hemolytic anemia, leucocytosis, lymphadenopathy, pancytopenia, splenomegaly, agranulocytosis, antinuclear antibodies.

Psychiatric reactions

Rare: Agitation, anorexia, anxiety,

Isolated cases: depression, hallucinations, disorientation, sleep disturbances

Sense Organs

Rare: Increased lacrimation, conjunctivitis, nasal congestion, blurred vision.

Hypersensitivity Reactions

Occasional: SLE-like syndrome (sometimes resulting in a fatal outcome; see **WARNINGS**), chills, eosinophilia,

Rare: hypersensitivity reactions such as pruritus, urticaria, vasculitis, hepatitis.

Respiratory Tract

Rare: Dyspnea, pleural pain.

Miscellaneous

Rare: Fever, weight decrease, malaise,

Isolated cases: exophthalmos, decreased libido, pancreatitis.

Hyperuricemia, hyperglycemia and hypokalemia have been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Signs and Symptoms of Overdosage

Symptoms include hypotension, tachycardia, accompanied by headache, generalized skin flushing, sweating, nausea and dizziness. Also possible are myocardial ischemia with angina pectoris, and cardiac arrhythmia. Further signs may include impairment of consciousness, headache and vomiting, as well as possible tremor, convulsions, oliguria, hypothermia, profound shock and coma.

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

Treatment for Overdosage

There is no known specific antidote. Supportive measures including intravenous fluids are also indicated. If hypotension is present, an attempt should be made to raise the blood pressure without increasing the tachycardia. Adrenaline should not be used to correct the hypotension, since it enhances the cardiac-accelerating effects of hydralazine.

Support of the cardiovascular system is of primary importance. Shock should be treated with plasma expanders. If possible, vasopressors should not be given, but if a vasopressor is required, care should be taken not to precipitate or aggravate cardiac arrhythmia. The ECG should be monitored while the vasopressors are being administered. Tachycardia responds to beta blockers. Digitalization may be necessary, and renal function should be monitored and supported as required. The use of dopamine to elevate systolic blood pressure to 90 mmHg may be considered in an emergency.

No experience has been reported with extracorporeal or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

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

Parenterally

The injection solution should be used immediately after the vial is opened. It should not be added to infusion solutions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Patients should be hospitalized. The parenteral administration of APRESOLINE should always be carried out cautiously and under strict medical supervision.

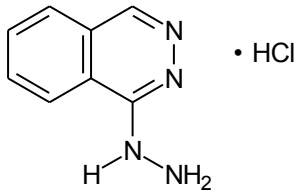
Blood pressure and heart rate should be checked frequently (i.e., every 5 minutes). Blood pressure levels may begin to fall within a few minutes after injection, with an average maximal decrease occurring in 10 to 80 minutes. In cases where there has been increased intracranial pressure, lowering the blood pressure may increase cerebral ischemia. A satisfactory response can be defined as a decrease in diastolic blood pressure to 90 to 100 mmHg.

The initial dose is 5 to 10 mg, administered by slow intravenous injection in order to avoid precipitous decreases in mean arterial pressure with a critical reduction in cerebral or uteroplacental perfusion. Geriatric patients or patients with marked renal damage may require a lower dosage. In hypertensive crises other than pre-eclampsia/eclampsia, usual doses of 20 - 40 mg have been used, repeated as necessary. If it is necessary to repeat the injection, this should be done after an interval of 20 to 30 minutes, throughout which blood pressure and heart rate should be monitored.

Most patients can be transferred to an oral anti-hypertensive within 24 to 48 hours.

PHARMACEUTICAL INFORMATION

Drug Substance



Hydralazine Hydrochloride USP

Molecular Formula: $C_8H_8N_4 \cdot HCl$

Molecular Weight: 196.64

Chemical Name: 1-Hydrazinophthalazine monohydrochloride.

Description: White, odourless, crystalline powder.

Melting Point: 270-280ºC.

Solubility: 1 g dissolves in about 25 mL water and in about 500 mL alcohol. It is very slightly soluble in ether.

pH: 3.5 to 4.2 (2% solution).

Composition

Each mL of sterile solution contains 20 mg of the medicinal ingredient hydralazine hydrochloride USP and the non-medicinal ingredients; propylene glycol, water for injection, and sodium hydroxide and hydrochloric acid for pH adjustment.

Stability and Storage Recommendations

Protect vials from heat (store at 15ºC to 30ºC) and light.

Direct Injection

Administer the solution by slow intravenous injection. For ease of administration the solution may be further diluted with physiological saline.

AVAILABILITY

PrAPRESOLINE® (hydralazine hydrochloride injection Mfr. Std.) 20 mg/mL, 1 mL Solution:

1 mL clear glass vials containing clear to pale yellow sterile solution, available in cartons of 10 vials.

PHARMACOLOGY

APRESOLINE (hydralazine hydrochloride USP) 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 APRESOLINE 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 tumours (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.

Hydralazine was teratogenic in rabbits where oral doses equal to and greater than 75 mg/kg/day caused phalangeal defects.

Genotoxicity: Hydralazine induces gene mutations, chromosomal aberrations and DNA damage in mammalian cells *in vitro*, as well as gene mutations in bacteria, yeast and *Drosophila*. The potential for similar effects *in vivo* has not been adequately reported.

Carcinogenicity

Mice: In a lifetime study in Swiss albino mice, there was a statistically significant increase in the incidence of lung tumours (adenomas and adenocarcinomas) of both male and female mice given hydralazine hydrochloride continuously in their drinking water at a dosage of about 50-200 mg/kg/day; a “no effect” dose has not been established.

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 showed increases in the incidences of hepatic neoplasms in both sexes and of Leydig cell tumours in males. Benign interstitial (Leydig) cell tumours of the testes were also significantly increased in male rats from the high-dose group. The tumours observed are 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.

SELECTED BIBLIOGRAPHY

ABLAD B. A study of the mechanism of the hemodynamic effects of hydralazine in man. Acta Pharmacol Toxicol 1963; 20 (Suppl 1): 1-53.

BRUNNER H, HEDWALL PR, and MEIER M. Influence of adrenergic beta-receptor blockade on the acute cardiovascular effects of hydralazine. Br J Pharmacol 1967; 30: 123-133.

COOPER I. Maintenance treatment of moderate hypertension with BID hydralazine. Curr Ther Res 1976; 20 (4) Section 2: 579-588.

FINNERTY FA Jr. Relationship of extracellular fluid volume to the development of drug resistance in the hypertensive patient. Am Heart J 1971; 81: 563-565.

FREIS ED, ROSE JC, HIGGINS TF, FINNERTY FA, KELLEY RT and PARTENOPE EA. The hemodynamic effects of hypotensive drugs in man I.V. 1-hydrazinophthalazine. Circulation 1953; 8: 199-204.

FREIS ED. Hydralazine in hypertension. Am Heart J 1964; 67: 133-134.

GREENBLATT DJ and KOCH-WESER J. Clinical pharmacokinetics. N Engl J Med 1975; 293: 702-705, 964-970.

LANSBURY J and ROGERS FB. The hydralazine syndrome. Bull Rheum Dis 1955; 5: 85-86.

LESSER JM, ISRAILI ZH, DAVIS DC and DAYTON PG. Metabolism and disposition of hydralazine-^{14}C in man and dog. Drug Metab Dispos 1974; 2: 351-360.

MOORE-JONES D and PERRY HM Jr. Radiographic localization of hydralazine-1-^{14}C in arterial walls. Proc Soc Exp Biol Med 1966; 122: 576-579.

O'MALLEY K, SEGAL JL, ISRAILI ZH, BOLES M, MCNAY JL and DAYTON PG. Duration of hydralazine action in hypertension. Clin Pharmacol Ther 1975; 18: 581-586.

PERRY HM Jr, TAN EM, CARMODY S and SAKAMOTO A. Relationship of acetyl transferase activity to antinuclear antibodies and toxic symptoms in hypertensive patients treated with hydralazine. J Lab Clin Med 1970; 76: 114-125.

PERRY HM Jr. Late toxicity to hydralazine resembling systemic lupus erythematosus or rheumatoid arthritis. Am J Med 1973; 54: 58-72.

PETTINGER WA and KEETON K. Altered renin release and propranolol potentiation of vasodilatory drug hypotension. J Clin Invest 1975; 55: 236-243.

RASKIN NH and FISHMAN RA. Pyridoxine-deficiency neuropathy due to hydralazine. N Engl J Med 1965; 273: 1182-1185.

REIDENBERG MM, DRAYER D, DEMARCO AL and BELLO CT. Hydralazine elimination in man. Clin Pharmacol Ther 1973; 14: 970-977.

ROWE GG, HUSTON JH, MAXWELL GM, CROSLEY AP Jr and CRUMPTON CW. Hemodynamic effects of 1-hydrazinophthalzine in patients with arterial hypertension. J Clin Invest 1955; 34: 115-120.

SEGAL JL. Hypertensive emergencies. Practical approach to treatment. Postgrad Med 1980; 68(2): 107-125.

STUNKARD A, WERTHEIMER L and REDISCH W. Studies on hydralazine: evidence for a peripheral site of action. J Clin Invest 1954; 33: 1047-1053.

TALSETH T. Studies on hydralazine. II. Elimination rate and steady-state concentration in patients with impaired renal function. Eu J Clin Pharmacol 1976; 10: 311-317.

VEDA H, YAGI S and KANEKO Y. Hydralazine and plasma resin activity. Arch Intern Med 1968; 122: 387-391.

WALKER HA, WILSON S, ATKINS EC, GARRETT HE and RICHARDSON AP. Effect of 1-hydrazinophthalazine (C-5968) and related compounds on cardiovascular system of dogs. J Pharmacol Exp Ther 1951; 101: 368-378.

WILKINSON EL, BACKMAN H and HECHT HH. Cardiovascular and renal adjustments to a hypotensive agent (1-hydrazinophthalazine: CIBA Ba-5968, Apresoline). J Clin Invest 1952; 31: 872-879.

ZACEST R and KOCH-WESER J. Relation of hydralazine plasma concentration to dosage and hypotensive action. Clin Pharmacol Ther 1972; 13: 420-425.