

Minipress™ 
Ergo Canada Inc.
Prazosin HCl
Antihypertensive

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Pharmacology: Prazosin causes a decrease in total peripheral resistance. Animal studies suggest that the vasodilator effect of prazosin is related to selective blockade of post-synaptic alpha₁-adrenoceptors. The results of dog forelimb experiments demonstrate that the peripheral vasodilator effect is confined mainly to the level of the resistance vessels (arterioles). Hemodynamic studies have been carried out in man following acute single dose administration and during the course of long-term maintenance therapy. The results confirm that the therapeutic effect is a fall in blood pressure unaccompanied by a clinically significant change in heart rate, renal blood flow and glomerular filtration rate. In patients with hypertension there is little change in cardiac output. In addition, clinical pharmacology studies have shown that prazosin antagonizes the vasopressor effect of i.v. phenylephrine, an alpha₁-agonist.

In man blood pressure is lowered in both the supine and standing positions. The hypotensive effect of prazosin is greater when the patient is standing, and a mild reflex tachycardia can result. Tolerance has not been observed to develop in long-term hypertensive therapy. Rebound elevation of blood pressure does not seem to occur following abrupt cessation of therapy with prazosin.

Following oral administration in normal volunteers and hypertensive patients, plasma concentrations reach a peak at about 3 hours with a plasma half-life of 2 to 3 hours. The drug is highly bound to plasma protein (97%). After chronic administration, no apparent drug accumulation was observed nor were any obvious decreases in plasma concentrations noted. Secondary plasma drug peaks and shoulders suggested probable enterohepatic circulation. Animal studies indicate that prazosin is extensively metabolized, primarily by demethylation and conjugation, and excreted (primarily as glucuronide conjugates) mainly via bile and feces. Similar metabolism and excretion has been documented in human studies.

Most clinical studies indicate that chronic therapy with prazosin has little effect on plasma renin activity. However one report suggests a transient increase in plasma renin activity following the initial dose, as well as attenuated transient increase with subsequent doses. Hypotensive Action: The nature of the hypotensive action of prazosin was studied both by in vitro and in vivo methodology. I.V. administered prazosin in dogs caused prolonged hypotension and reduction in total peripheral resistance. Cardiac output, heart rate, and blood flow in the femoral, renal, and splanchnic vascular beds were increased transiently. Cardiac responses to electrical stimulation of cardioaccelerator nerves were not depressed, nor was there sympathetic ganglion or adrenergic neurone blockade. Although prazosin reversed the epinephrine pressor response in intact animals, vasodilator activity was only slightly diminished when the vessels were deprived of sympathetic tone by ganglionic blockade.

Physiologic and direct radioligand binding data from studies in experimental animals indicates that the hypotensive effect of prazosin ascribed to peripheral vasodilation is achieved primarily by competitive blockade of the vascular postsynaptic alpha₁-adrenergic receptors. As prazosin acts preferentially on postsynaptic alpha₁-adrenergic receptors, the feedback control of neuronal norepinephrine release by presynaptic alpha₂-receptors remains unchanged.

In the dog, the hypotensive effect of prazosin i.v. was reversed by metaraminol and norepinephrine given by i.v. infusion.

Miscellaneous Actions: At doses considerably higher than those required for antihypertensive activity, prazosin has mild CNS depressant activity, decreases heart norepinephrine and adrenal epinephrine in rats, causes diuresis in anesthetized dogs, but fluid retention in conscious dogs and mice and is hyperglycemic in rats.

In clinical studies in which lipid profiles were followed, there were generally no adverse changes noted between pre- and post-treatment lipids levels.

Indications: The treatment of mild to moderate essential hypertension. It is employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive agents as needed for proper patient response. Prazosin may be tried as a sole therapy in those patients in whom treatment with other agents caused adverse effects or is inappropriate.

Contraindications: Known sensitivity to quinazolines.

Warnings: Prazosin may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been associated with a bout of severe tachycardia with heart rates of 120 to 160 beats/minute. The incidence of syncopal episodes is approximately 0.8% when the gradual dose build up described under dosage is followed. The incidence is higher if the initial dose exceeds 0.5 mg. Syncopal episodes have occurred within 30 to 90 minutes of the initial dose of the drug. They have also been reported in association with dosage increases or the introduction of prazosin into the regimen of a patient taking another antihypertensive agent or a diuretic.

Physicians are therefore advised to limit the initial dose of the drug to 0.5 mg b.i.d. or t.i.d., to subsequently increase the dosage slowly, and to introduce any additional antihypertensive drugs into the patient's regimen with caution.

Patients whose blood pressure is not adequately controlled by high doses of a β -adrenergic blocking agent such as propranolol may develop acute hypotension when prazosin is added. To minimize the incidence of acute hypotension in such patients, the dose of β -adrenergic blocking agent should be reduced before prazosin is administered. A low initial dose of prazosin is also strongly recommended (see Dosage).

If syncope occurs, place the patient in the recumbent position and institute supportive measures. This adverse effect is self-limiting and in most cases does not recur once a steady maintenance level is initiated. Caution patients to avoid situations where injury could result should syncope occur during prazosin therapy, especially in the initial dose adjustment period. Occupational Hazards: More common than loss of consciousness are the symptoms often associated with lowering of blood pressure, namely dizziness and light headedness. Caution the patient about these possible adverse effects and advise what measures to take should they develop.

Pregnancy: Although no teratogenic effects were seen in animal testing, there are no adequate

and well controlled studies which establish the safety of prazosin in pregnant women. Limited uncontrolled use in the management of hypertension in the later stages of pregnancy suggests that prazosin in combination with a beta-blocker can lower blood pressure in pregnant patients. The drug appears to be less effective in patients with proteinuria in whom the addition of i.v. hydralazine was usually required. Accordingly prazosin should be used during pregnancy only if in the opinion of the physician the potential benefit outweighs potential risk to mother and child.

Lactation: Prazosin has been shown to be excreted in small amounts in human milk. Caution should be exercised when prazosin is administered to nursing mothers.

Children: Not recommended for the treatment of children under 12 years of age since safe conditions for its use have not been established in this group.

Precautions: Use in Patients with Moderate to Severe Grades of Renal Impairment: Because some patients with moderate to severe grades of renal impairment have responded to smaller than usual doses of prazosin, it is recommended that therapy be initiated at 0.5 mg daily and that dose increases be instituted cautiously.

Drug Interactions: Prazosin has been administered without any adverse drug interaction in limited clinical experience to date with the following: cardiac glycosides-digitalis and digoxin; hypoglycemics-insulin, chlorpropamide, tolazamide and tolbutamide; tranquilizers and sedatives-chlordiazepoxide, diazepam and phenobarbital; antigout-allopurinol, colchicine and probenecid; antiarrhythmics-procainamide, propranolol (see Warnings), and quinidine; and analgesics, antipyretics and anti-inflammatories-propoxyphene, ASA, indomethacin and phenylbutazone.

Addition of a diuretic or other antihypertensive agent to prazosin has been shown to cause an additive hypotensive effect (see Warnings and Dosage). An exaggerated hypotensive response has also been observed.

Drug/Laboratory Test Interactions: False positive results may occur in screening tests for pheochromocytoma (urinary vanillylmandelic acid [VMA] and methoxyhydroxyphenyl glycol (MHPG) urinary metabolites of norepinephrine in patients who are being treated with prazosin. If an elevated VMA is found, prazosin should be discontinued and the patient retested after a month.

Adverse Effects: The most common reactions associated with prazosin therapy are postural dizziness 11%, nausea 9.5%, drowsiness 8.7%, headache 8.4%, palpitations 6.6%, dry mouth 5.6%, weakness 4.6% and fatigue/malaise 4.5%. In most instances, side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug. The following reactions have also been observed during prazosin administration.

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: syncope (see Warnings), orthostatic hypotension, edema, dyspnea, tachycardia, faintness.

CNS: nervousness, vertigo, depression, paresthesia, hallucinations.

Dermatologic: rash, pruritus, alopecia, lichen planus.

Genitourinary: urinary frequency, incontinence, impotence, priapism.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, nasal congestion.

Hepatic: liver function abnormalities, pancreatitis.

Hematologic: decreased hematocrit/hemoglobin.

Other: diaphoresis, fever, arthralgia, positive ANA titer.

Single reports of pigmentary mottling and serous retinopathy have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit lamp and funduscopic studies, which included adequate baseline

examinations, no drug related abnormal ophthalmological findings have been reported.

Literature reports exist associating prazosin therapy with a worsening of pre-existing narcolepsy. A causal relationship is uncertain in these cases.

Overdose: Symptoms: A few reports of prazosin overdose have been documented with prazosin. The most frequently observed symptoms of overdose include hypotension and somnolence.

Accidental ingestion of at least 50 mg of prazosin in a 2 year old child resulted in profound drowsiness and depressed reflexes. No decrease in blood pressure was noted. Recovery was uneventful.

Treatment: Should overdosage lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If necessary, vasopressors should be used. If this measure is inadequate, shock should then be treated with volume expanders. Renal function should be monitored and supported as needed. Laboratory data indicate that prazosin is not dialyzable because it is protein bound.

Dosage: Note: When titration is to be undertaken using the tablet formulation it will be necessary to split the 1 mg scored tablet to obtain the 0.5 mg starting dose.

It is recommended that the starting dose of 0.5 mg be given with food, preferably with the evening meal, at least 2 or 3 hours before retiring. The dose should be built up gradually with 0.5 mg being given 2 or 3 times daily for at least 3 days. Unless adverse effects occur and subject to the blood pressure lowering effect, this dose should be increased to 1 mg given 2 or 3 times daily for at least a further 3 days.

Thereafter, as determined by the patient's response to the blood pressure lowering effect, the dose should be increased gradually. Response to prazosin is usually seen within 1 to 14 days if it is to occur at any particular dose. When a response is seen, continue therapy at that dose until the degree of response has reached the optimum before the next dose increment is added. Continue incremental increases until a desired effect is achieved or a maximum daily dose of 20 mg is reached.

The maintenance dose of prazosin may be given as a twice or 3 times daily dosage regimen.

In patients with moderate to severe grades of renal impairment, initiate therapy at 0.5 mg daily and institute dose increases gradually.

Use With Other Drugs: Patients receiving diuretic therapy: The diuretic should be reduced to a maintenance dose level for the particular agent and prazosin initiated at 0.5 mg at bedtime then proceeding to 0.5 mg b.i.d. or t.i.d. After the initial period of observation, gradually increase the prazosin dosage as determined by patient response.

Patients receiving other antihypertensive agents: Because some additive effect is anticipated, reduce the dose of the other agent (e.g. propranolol* or other beta-adrenergic blocking agents*, alpha methyl dopa, reserpine, clonidine*) and initiate prazosin at 0.5 mg h.s. then proceeding to 0.5 mg, 2 or 3 times daily. Make subsequent dosage increase depending upon the patient's response.

* Appropriate precautions should be observed when the dosage of these other antihypertensive agents is reduced.

Patients on Prazosin to whom other antihypertensive agents are added: When adding a diuretic or other antihypertensive agent, reduce the dose of prazosin to 1 or 2 mg 2 or 3 times daily and

carry out retitration.

Supplied: 1 mg: Each orange, scored tablet contains: prazosin HCl equivalent to prazosin 1 mg. Nonmedicinal ingredients: calcium phosphate, cornstarch, FD&C Yellow #6, magnesium stearate/sodium lauryl sulfate and microcrystalline cellulose. Tartrazine-free. Bottles (HDPE) of 100.

2 mg: Each white, round, scored tablet contains: prazosin HCl equivalent to prazosin 2 mg. Nonmedicinal ingredients: calcium phosphate, cornstarch, magnesium stearate/sodium lauryl sulfate and microcrystalline cellulose. Tartrazine-free. Bottles (HDPE) of 100.

5 mg: Each white, diamond, scored tablet contains: prazosin HCl equivalent to prazosin 5 mg. Nonmedicinal ingredients: calcium phosphate, cornstarch, magnesium stearate/sodium lauryl sulfate and microcrystalline cellulose. Tartrazine-free. Bottles (HDPE) of 100.

Store at room temperature between 15 and 30°C.

(Shown in Product Identification Section)