

NAPAMIDE

Indapamide hemihydrate 2.5 mg tablet

Presentation

Indapamide hemihydrate as:

Circular, pink, biconvex, film-coated tablets of 6.4mm diameter embossed "n" on one side. Tablets contain 2.5 mg Indapamide hemihydrate.

Uses

Actions

Indapamide is an oral antihypertensive agent. The mechanism whereby indapamide exerts its antihypertensive action has not been completely elucidated; both vascular and renal actions have been implicated.

At a dose of 2.5 mg the renal effects of indapamide are minimal and the antihypertensive effect of indapamide has been attributed to a reduction in vascular reactivity to pressor amines. The finding that indapamide retains its antihypertensive activity in functionally anephric patients lends support to the hypothesis.

Chemically indapamide has a sulphonamide group in common with other diuretics but also has an indoline moiety. The N-N bond has similarities to hydralazine that is a direct vasodilator. It does not have a thiazide ring.

In clinical trials daily doses of indapamide between 0.5 mg and 5.0 mg produce dose-related antihypertensive effects. Generally, doses of 2.5 mg and 5.0 mg are indistinguishable but are distinguishable from placebo and doses of 0.5 mg and 1.0 mg.

The effect of indapamide at doses of 2.5 mg daily are approximately equal to those obtained with conventional doses of other anti-hypertensive/diuretics.

The antihypertensive action appears to predominantly involve extra-renal mechanisms including normalisation of vascular hyperreactivity to vasopressor amines and a reduction in peripheral resistance. There is little cardiac: inotropic, chronotropic, output or rhythm effect. The renal site of action of indapamide is the proximal segment of the distal tubule. Indapamide appears to have natriuretic properties (sodium and chloride being excreted in equivalent amounts) with less effect on kaliuresis or uric acid excretion. Only at doses greater than 2.5 mg/day is an appreciable increase in urinary volume observed in man. No significant changes in plasma sodium levels have been observed in clinical studies. Significant hypokalaemia (plasma potassium <3.2 mmols/l) has been reported in some 10% of patients.

Indapamide (2.5 mg daily) does not adversely affect serum triglycerides, LDL cholesterol, the LDL-HDL cholesterol ratio, or glucose tolerance.

Pharmacokinetics

Possibly related to its high lipid solubility, absorption of indapamide from the gastrointestinal tract is rapid (within 0.5 to 1 hour after an oral dose) and complete. Bioavailability of the tablet formulation is 100% and is virtually unchanged with food or antacids. Renal failure, increases plasma concentrations by about 20%. Little is known about the effect of age or impaired hepatic function.

Indapamide is widely distributed throughout the body, with extensive binding to some specific sites. In blood, it is highly bound to red blood cells (80%) and, more specifically, to carbonic acid anhydrase (98%) without having any significant inhibiting activity on this enzyme. Red cell binding has been shown *in-vitro* to be substantially decreased by chlorthalidone and acetazolamide. These latter two agents have greater affinity for the binding site than indapamide. In plasma, it is relatively highly bound to plasma proteins (79%). Peak plasma concentrations are achieved at approximately 3.5 hours. Within plasma indapamide is approximately 76-79% bound to human plasma proteins, however, the specific proteins involved have not been identified. It is also taken up to a significant degree in the vascular compartment, the drug has a relatively low apparent volume of distribution (approximately 60 L) and 40% of the dose is located in the blood one hour after administration.

After a single dose of 2.5 mg, as well as after repeated administration of 2.5 mg daily for 15 days, plasma elimination half life of unchanged indapamide is biphasic with half lives of 14 and 25 hours, indicating that once daily dosing is possible and that no change in kinetics occurs after repeated dosing. Both single and multiple dose data indicate that indapamide's kinetics are linear. Steady state plasma levels are reached within three to four days after starting treatment and the drug does not accumulate in hypertensive patients with various degrees of renal insufficiency. Indapamide is extensively metabolised in the liver. Following radioactivity studies using carbon-14, the main route of elimination is the urine where up to 60-70% of a dose is excreted with 48 hours, but only 5 to 7% of the dose is excreted into the urine as unchanged drug; 20 to 23% of total radioactivity is eliminated into the faeces. Renal clearance of indapamide (as unchanged drug) is approximately 5 mL/minute, representing less than 10% of systemic clearance. This reflects the importance of hepatic clearance. The high lipid solubility of the indoline moiety confers to indapamide its highly localised binding to structures in the cardiovascular system.

Up to 19 metabolites have been identified although the majority are minor. Hydroxylation of the indoline ring gives rise to the major metabolite. It is thought to be active, however, this remains to be confirmed. 18% of the metabolites in urine appear as conjugates, 14% as conjugates with glucuronic acid and 4% as conjugates with sulphate.

Indications

Management of essential hypertension. It may be tried as a sole therapeutic agent in the treatment of mild to moderate hypertension. Normally Indapamide is used as the initial agent in multiple drug regimes.

Dosage and Administration

Adults. 1 tablet (2.5 mg indapamide) daily to be taken in the morning. The action of Indapamide is progressive and whilst the optimum reduction in blood pressure is usually seen after four weeks, a further small but useful reduction in blood pressure may be observed over the following four to six weeks. A larger dose than 1 tablet (2.5 mg) of Indapamide daily is not recommended as there is little additional antihypertensive effect, whilst the diuretic effect becomes more prominent.

A single daily tablet of Indapamide may effectively be combined with the following antihypertensive agents: beta-blockers, methyldopa, clonidine, prazosin, and ACE inhibitors. Although it is recommended that patients be monitored closely in the initial stages.

Combination with a diuretic agent is not recommended as significant electrolyte disturbances may ensue. Indapamide has a slight but significant carry-over hypotensive effect lasting up to 1 or 2 weeks after the cessation of therapy.

Contraindications

Anuria, progressive and severe oliguria, hepatic coma. Known hypersensitivity to indapamide or to other sulphonamide derivatives.

Warnings and Precautions

Electrolyte changes observed with indapamide become more prominent *at* doses above 2.5 mg/day. The daily maximum recommended dose of indapamide is 2.5 mg administered as one tablet, since doses above 2.5 mg only increase the diuretic effect and electrolyte disturbances consequent to diuresis without any further appreciable antihypertensive effect.

Hypokalaemia and other fluid and electrolyte imbalances:

Hypokalaemia may occur at all doses. (Symptoms of hypokalaemia include weakness, cramps, and cardiac dysrhythmias. Hypokalaemia is a particular hazard in digitalised patients; dangerous or fatal arrhythmias may be precipitated). Although indapamide 2.5 mg daily can be safely administered to hypertensive patients with impaired renal function caution should be observed when the drug is administered to patients with severe renal impairment since the unchanged drug is excreted primarily by the renal route.

Hyperuricaemia may occur during administration of indapamide. Rarely gout has been reported. In general, diuretics should not be given with lithium because they reduce its renal clearance and add a high risk of lithium toxicity. Periodic determinations of serum electrolytes should be performed at appropriate intervals.

Patients receiving indapamide should be monitored for signs and symptoms of fluid or electrolyte imbalance; namely hyponatraemia, hypochloraemia and hypokalaemia. Blood urea, nitrogen and uric acid should also be assessed during therapy. Hypokalaemia will be more common in association with concomitant steroid or ACTH therapy and with inadequate electrolyte intake.

The signs of electrolyte imbalance are dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscle fatigue, hypotension, oliguria, gastrointestinal disturbances such as nausea and vomiting, tachycardia and ECG changes.

Special caution should be used in treating patients with severe hepatic disease to avoid metabolic alkalosis in cases of potassium depletion which may precipitate episodes of hepatic encephalopathy.

The risk of hypokalaemia secondary to diuresis and natriuresis is increased when larger doses are used, when the diuresis is brisk, when severe cirrhosis is present and during concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalaemia. Hypokalaemia can sensitise or exaggerate the response of the heart to the toxic effects of digitalis, such as increased ventricular irritability.

Dilutional hyponatraemia may occur in oedematous patients; the appropriate treatment is restriction of water rather than administration of salt, except in rare instances when the hyponatraemia is life threatening. However, in actual salt depletion, appropriate replacement is the treatment of choice.

Any chloride deficit that may occur during treatment is generally mild and usually does not require specific treatment except in extraordinary circumstances as in liver or renal disease.

Orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates, narcotics or concurrent therapy with other antihypertensives.

When Indapamide is given with other non diuretic antihypertensive agents, the effects on blood pressure are additive.

Interaction with Systemic Lupus Erythematosus:

Sulphonamide derivatives have been reported to exacerbate or activate systemic lupus erythematosus. Serious allergic skin reactions (such as Stevens-Johnson syndrome) have also occasionally been reported associated with sulphonamides. These possibilities should be kept in mind with the use of indapamide.

Hyperuricaemia and Gout:

Serum concentrations of uric acid increased by an average of 1.0 mg/100 mL in patients treated with indapamide, and frank gout may be precipitated in certain patients receiving indapamide. Serum concentrations of uric acid should, therefore, be monitored periodically during treatment.

Renal Impairment:

Although indapamide 2.5 mg daily can safely be administered to hypertensive patients with impaired renal function, the treatment should be discontinued if increasing azotaemia and oliguria occur. Studies in functionally anephric patients for one month undergoing chronic haemodialysis have not shown evidence of drug accumulation, despite the fact that indapamide is not dialysable.

If progressive renal impairment is observed in a patient receiving indapamide, withholding or discontinuing diuretic therapy should be considered. Renal function tests should be performed periodically during treatment with indapamide.

Impaired Hepatic Function:

Indapamide, like the thiazides, should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Calcium Excretion:

Calcium excretion is decreased by diuretics pharmacologically related to indapamide. In long-term studies of hypertensive patients, however, serum concentrations of calcium increased only slightly with indapamide.

Prolonged treatment with medicines pharmacologically related to indapamide may in rare instances be associated with hypercalcaemia and hypophosphataemia secondary to physiologic changes in the parathyroid gland, however, the common complications of hyperparathyroidism, such as renal lithiasis, bone resorption and peptic ulcer, have not been seen.

Treatment should be discontinued before tests for parathyroid function are performed. Like the thiazides, indapamide may decrease serum PBI levels without signs of thyroid disturbance.

Use in Pregnancy (Category C):

Thiazides, related diuretics and loop diuretics enter the fetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopenia has been reported with thiazides and related diuretics. Loop diuretics like frusemide and bumetanide are probably also associated with this risk. During the latter part of pregnancy products of this type should only be given on sound indications, and then in the lowest effective dose.

There is no information on the use of indapamide in pregnancy. Whilst animal studies have not suggested any teratogenic effect, indapamide is not recommended for administration to pregnant women unless the expected benefit outweighs the potential risk.

Use in Lactation:

It is not known whether indapamide is excreted in breast milk. It is therefore not recommended that the drug be given to lactating women as the possible effect on the newborn is unknown.

Use in Children:

Safety and effectiveness have not been established.

Toxicity:

The toxicity of indapamide is low.

Effects on Ability to Drive and Use Machines:

Presumed to be safe or unlikely to produce an effect on the ability to drive or use machinery.

Adverse Effects

In general, most adverse effects are mild and transient with the most frequently reported being asthenia, dizziness, headache, fatigue, muscle cramps and gastrointestinal disturbances usually occurring within the first month of treatment. Other adverse reactions have been nonspecific. Cutaneous rash and impotence have been occasionally reported. Serum urate levels may rise slightly but gout has rarely been reported. Percentages shown below indicate the incidence in clinical trials.

The most severe and common adverse effect is electrolyte imbalance. Electrolyte changes reported include hypokalaemia : serum potassium <3.4 mmol - 25%, serum potassium <3.2 mmol - 10% (Potassium supplementation may be required in up to 25% of cases), hypochloraemia 9.4%; hyponatraemia 3.1%.

Central Nervous System (8.1%). Incidence >1% <3%: asthenia, headache, dizziness, vertigo.

Incidence <1%: drowsiness, sleepiness, insomnia, weakness, lethargy, visual disturbance.

Gastrointestinal (2.6%). Incidence <1%: nausea/anorexia, dryness of mouth, gastralgia, vomiting, diarrhoea, constipation.

Musculoskeletal (1.4%). Incidence >1% <3% muscle cramps.

Incidence <1%: joint pain, back pain, weakness of legs.

Cardiovascular (1%). Incidence < 1%: orthostatic hypotension, tachycardia, ECG changes (non specific ST-T changes, U waves, left ventricular strain).

Urogenital (0.5%). Incidence <1% impotence, modification of libido, polyuria.

Dermatological (0.5%). Incidence <1%: rash, pruritus.

Endocrine (0.2%). Incidence <1%: gout.

Other (0.5%). Incidence <1%: tinnitus, malaise/fainting, sweat.

Laboratory abnormalities. The following values represent the maximum variations from pre-treatment values in occasional patients at some stage during, but not necessarily throughout treatment. Blood uric acid up 8.6%, blood glucose up 6%, BUN up 5.7%, blood creatinine up 3.6%.

Interactions

No interactions have been reported between indapamide and oral hypoglycaemic agents, anticoagulants, uricosurics and anti-inflammatory agents. It is recommended that the drug not be used in combination with a diuretic agent since the combination may produce hypokalaemia and hyperuricaemia.

Indapamide may add to or potentiate the action of other antihypertensive agents. In limited studies of combination therapy of indapamide with other agents compared to the effect of the other agents administered alone there was no notable change in the nature or frequency of adverse reactions associated with the combined therapy.

Diuretics in general should not be given concomitantly with lithium since diuretics reduce the renal clearance of lithium and add a high risk of lithium toxicity. The anti-hypertensive effect of indapamide may be enhanced in the postsympathectomised patient.

Indapamide may decrease arterial responsiveness to noradrenaline but this does not preclude the effectiveness of noradrenaline in therapeutic use. There has been one report of cardiac arrhythmias developing in a 64 year old male hypertensive patient with suspected latent coronary insufficiency after combination of indapamide with disopyramide.

Overdosage

There have been no reports of overdosage. Based on the pharmacological activities of indapamide, overdosage may lead to excessive diuresis with electrolyte depletion. In cirrhotic patients, overdosage might precipitate hepatic coma.

Symptoms of overdose include nausea, vomiting, weakness, gastrointestinal disorders and electrolyte imbalance. In severe instances, depressed respiration and hypotension may develop.

For treatment of overdose, there is no specific antidote. Treatment is symptomatic and supportive. Discontinue drug; induce emesis or perform gastric lavage if treatment begins soon after the overdose occurs; correct dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures.

Pharmaceutical Precautions

Prescription-only Medicine

Shelf life: 2 years

Store below 25°C

Protect from light and moisture. Keep out of reach of children.

Medicine Classification

Prescription Medicine

Package Quantities

100 tablets packed in white high density polyethylene bottles

90 tablets in PVC/PVDC/aluminium blisters

30 tablets in PVC/PVDC/aluminium blisters

Further Information

Indapamide hemihydrate is 4-chloro-N-(2- methyl-indolinyl-1)-3-sulfamoyl-benzamide hemihydrate. It has a molecular formula and weight of $C_{16}H_{16}ClN_3O_3S \cdot 1/2H_2O$ and 374.8 respectively.

Other ingredients of the tablets are: Lactose monohydrate, Maize cornflour, Microcrystalline cellulose, Sodium lauryl sulphate, Magnesium stearate, Opadry pink OY-6925 and Hydroxypropylmethyl cellulose.

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Date of Preparation

January 2011