Potassium excretion is also increased by bumetanide, in a dose-related fashion. Bumetanide may have an additional action in the proximal tubule. Since phosphate reabsorption takes place largely in the proximal tubule, phosphaturia during bumetanide-induced diuresis is indicative of this additional action. This is further supported by the reduction in the renal clearance of bumetanide by probenecid, associated with diminution in the natriuretic response. This proximal tubular action does not seem to be related to an inhibition of carbonic anhydrase. Bumetanide does not appear to have a noticeable action on the distal tubule.

Bumetanide decreases urinary acid excretion and increases serum uric acid. Following a single oral 3 mg dose, an onset of diuresis occurs in 30 to 60 minutes. Peak activity is reached between 1 and 2 hours. At usual doses (1 mg to 2 mg) diuresis is largely complete with 4 hours, with higher doses, the diuretic action lasts for 4 to 6 hours. Diuresis starts within following an intravenous injection and reaches maximum levels within 15 to 30 minutes. The rate of attainment of the peak diuretic action and duration thereof are dose dependent. Since bumetanide is administered orally or parenterally, it is eliminated rapidly in humans, with a half-life of between 1 and 1.5 hours. Plasma protein-binding is in the range of 94% to 96%.

Oral administration of carbon-14 labeled bumetanide to human volunteers revealed that 81% of the administered radioactivity was excreted in the urine, 45% of it as unchanged drug. Urinary and biliary metabolites identified in this study were formed by oxidation of the N-butyl side chain. Biliary excretion of bumetanide amounted to only 2% of the administered dose.

Pediatric Pharmacology: Elimination of bumetanide appears to be considerably slower in neonatal patients compared with adults, possibly because of immature renal and hepatic metabolism. Oral administration of this drug is not practical. Small pharmacokinetic studies of intravenous bumetanide in preterm and full term neonates with respiratory disorders have reported an apparent half-life of approximately 6 hours with a range up to 15 hours and a serum clearance ranging from 0.2 to 1.1 mL/min/kg. In a population of neonates receiving bumetanide for volume overload, mean serum concentrations were 2.17 ± 0.4 mL/kg in patients less than 2 months of age and 3.8 ± 0.9 mL/kg in patients aged 2 to 6 months. Mean serum half-life of bumetanide was 2.5 hours and 1.5 hours in patients aged less than 2 months and those aged 2 to 6 months, respectively. Elimination half-life decreased considerably during the first month of life, from a mean of approximately 6 hours at birth to approximatley 2.4 hours, respectively. Bumetanide administration should be given by the intramuscular or intravenous route. Successful treatment with bumetanide following instances of allergic reactions to furosemide suggests some lack of cross-sensitivity.

CONTRAINDICATIONS

Bumetanide is contraindicated in anuria. Although bumetanide can be used to induce diuresis in renal insufficiency, any marked increase in blood urea nitrogen or creatinine, or the development of oliguria during therapy of patients with progressive renal disease, is an indication for discontinuation of treatment with bumetanide. Bumetanide is also contraindicated in patients with hepatic coma or in states of severe electrolyte depletion until the condition is improved or corrected. Bumetanide is contraindicated in patients hypersensitive to this drug.

WARNINGS

Volume and electrolyte depletion: The dose of bumetanide should be adjusted to the patient’s needs. Excessive doses or too frequent administration may cause elevation in blood pressure, dehydration, reduction in blood volume and circulatory collapse with the possibility of vascular thrombosis and embolism, particularly in elderly patients.

Hypokalemia: Hypokalemia can occur as a consequence of bumetanide administration. Prevention of hypokalemia requires particular attention in the following conditions: patients receiving diabetics and diuretics for congestive heart failure, hepatic cirrhosis and ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, certain diuretic states, or other states where hypokalemia is thought to represent particular added risks to the patient, i.e., history of ventricular arrhythmias.

In patients with hepatic cirrhosis and ascites, sudden alterations of electrolyte balance may precipitate hepatic encephalopathy and coma. Treatment in such patients is best initiated in the hospital with small doses and careful monitoring of the patient’s clinical status and electrolyte balance. Supplemental potassium and or spinorabolone may prevent hypokalemia and metabolic alkalosis in these patients. It should be noted that potassium supplementation has been shown to produce otolucency. In these test animals bumetanide was 5 to 6 times more potent than furosemide and, since the diuretic potency of bumetanide is about 40 to 60 times that of furosemide, it is anticipated that bumetanide, like furosemide may lead to hyperuricemia. However, this increase in diuretic effect. Urine flow rate peaked during the first hour after drug administration in 80% of patients and by 3 hours in all patients. The mode of action has been determined through various clearances studies in both human and animal experimental models. In a group of ten geriatric subjects the dose of bumetanide was 1 mg and the volume of distribution was found to be about 1 L/kg. The volume of distribution at steady state for bumetanide is approximately 40 L/kg, equivalent to 40 mg furosemide. The major site of bumetanide action is the ascending limb of the loop of Henle.

The mode of action has been determined through various clearance studies in both human and experimental animals. Bumetanide inhibits sodium reabsorption in the ascending limb of the loop of Henle, as shown by marked reduction of free-water clearance (CH2O) during hydration and tubular free-water reabsorption (TH2O) during dehydration. Reabsorption of chloride in the ascending limb is also blocked by bumetanide, and bumetanide is somewhat more chloruretic than natriuretic.
Patients under treatment should be observed regularly for possible occurrence of blood dyscrasias, liver damage or idiosyncratic reactions, which have been reported occasionally in foreign marketing experience. An 18-month study showed an occurrence of blood dyscrasias, liver damage or idiosyncratic reactions, which have been reported occasionally in foreign marketing experience. The relationship of these occurrences to bumetanide use is not certain.

Drug Interactions:

Dogs: With ototoxic potential (see WARNINGS): Especially in the presence of impaired renal function, the use of parenterally administered bumetanide in patients to whom aminoglycoside antibiotics are also being given should be avoided, except in life-threatening conditions.

Dugs with nephrotoxic potential: There has been no experience with the concurrent use of bumetanide with drugs known to have a nephrotic potential. Therefore, the simultaneous administration of these drugs should be avoided.

Lithium: Lithium should generally not be given with diuretics (such as bumetanide) because they reduce its renal clearance and add a high risk of lithium toxicity. In rats, lithium chloride-induced growth retardation with propranolol reduces both the natriuresis and hyperreninemia produced by bumetanide. This antagonistic effect of propranolol on bumetanide natriuresis is not due to a direct action on sodium excretion but is probably secondary to its inhibitory effect on renal tubular secretion of bumetanide. Thus, propranolol should not be administered concomitantly with bumetanide.

Indomethacin: Indomethacin blunts the increases in urine volume and sodium excretion seen during bumetanide treatment and inhibits the bumetanide-induced increase in plasma renin activity. Concurrent therapy with bumetanide is thus not recommended.

Hyperkalemic: Bumetanide may potentiate the effect of various antihypertensive drugs, necessitating a reduction in the dosage of these drugs.

Cardiovascular: Interaction studies in humans have shown no effect on digoxin blood levels.

Anticoagulants: Interaction studies in humans have shown bumetanide to have no effect on warfarin metabolism or on plasminogen activator.

Carbohydrogenesis, Mutagenesis, Impairment of Fertility: Bumetanide was devoid of mutagenic activity in various strains of Salmonella typhimurium when tested in the presence or absence of an in vitro metabolic activation system. An 18-month study showed an increase in the urinary adenosine of male and female rats at oral doses of 60 mg/kg/day (2000 times the maximum human therapeutic dose). In rabbits, an increase in the urinary adenosine of male and female rabbits was observed at oral doses of 20 mg/kg/day (500 times the maximum human therapeutic dose). No lethality was observed at 1000 times the human therapeutic dose. The sensitivity of the rabbit to bumetanide paralleled the marked pharmacologic and toxicologic effects of the drug in this species.

Bumetanide was not teratogenic in the hamster at an oral dose of 0.5 mg/kg/day (17 times the maximum human therapeutic dose). Bumetanide was not teratogenic when given intravenously to mice and rats at doses up to 140 times the maximum human therapeutic dose. There is no adequate and well-controlled studies in pregnant women. A small investigational experience in the United States and marketing experience in other countries to date have not indicated any evidence of adverse effects on the fetus, nor has there been any evidence of a teratogenic or embryocidal effect. In the rabbit, the embryo-fetal weights increased at oral doses of 0.3 mg/kg/day; however, no such adverse effects were observed at the dose of 0.03 mg/kg/day. The sensitivity of the rabbit to bumetanide parallels the marked pharmacologic and toxicologic effects of the drug in this species.

In vitro studies using pooled sera from critically ill neonates have shown patient response. In vitro studies using pooled sera from critically ill neonates have shown patient response.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Bumetanide is neither teratogenic nor embryocidal in mice when given in doses up to 10 times the maximum human therapeutic dose. In one study, moderate growth retardation and increased incidence of ossification of sternebrae were observed in rats at oral doses of 100 mg/kg/day, 3400 times the maximum human therapeutic dose. These effects were associated with maternal weight reductions noted during dosing. No such adverse effects were observed at 30 mg/kg/day (1000 times the maximum human therapeutic dose). No lethality was observed at 1000 times the human therapeutic dose. The sensitivity of the rabbit to bumetanide paralleled the marked pharmacologic and toxicologic effects of the drug in this species. This sensitivty of the rabbit to bumetanide paralleled the marked pharmacologic and toxicologic effects of the drug in this species.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. When renal function is greatly decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

The most frequent clinical adverse reactions considered probably or possibly related to bumetanide are muscle cramps (seen in 1.1% of treated patients), dizziness (1.1%), hypotension (0.8%), headache (0.8%), nausea (0.8%), and anorexia (0.6%). One or more of these adverse reactions have been reported in approximately 41% of patients treated with bumetanide. Serious skin reactions (i.e., Stevens-Johnson syndrome, toxic epidermal necrolysis) have been reported in association with bumetanide use.

Less frequent clinical adverse reactions to bumetanide are impaired hearing (0.5%), pruritus (0.4%), electrocardiogram changes (0.4%), weakness (0.2%), hypoglycemia (0.2%), abdominal pain (0.2%), arthritic pain (0.2%), musculoskeletal pain (0.2%), rash (0.2%) and vomiting (0.2%). One or more of these adverse reactions have been reported in approximately 2.8% of patients treated with bumetanide.

Other clinical adverse reactions, which may each occurred in approximately 0.1% of patients, are vertigo, chest pain, ear discomfort, fatigue, dehydration, sweating, hyperventilation, dry mouth, upset stomach, renal failure, asthenia, itching, nipple tenderness, diarrhoea, prema- ture ejaculation and difficulty maintaining an erection.

Laboratory abnormalities reported have included hyperuricemia (in 18.4% of patients tested), hypochloremia (14.7%), hyperkalemia (14.7%), astasia (10.6%), hypernatremia (9.2%), increased serum creatinine (7.4%), hyperglycemia (6.3%), and variations in blood phosphorus (4.5%), CO2 content (4.3%), bicarbonate (3.1%) and calcium (2.4%). Although manifestations of the pharmacologic action of bumetanide, these conditions may become more pronounced by intensive therapy.

Also reported were the following abnormalities: thrombocytopenia (0.2%) and deviations in hemoglobin (0.8%), prothrombin time (0.8%), hematocrit (0.6%), WBC (0.3%) and differential counts (0.1%). There have been rare spontaneous reports of thrombocytopenia from postmarketing experience.

Dizziness induced by bumetanide may also rarely be accompanied by changes in LDH (1.0%), total serum bilirubin (0.8%), serum proteins (0.7%), SGOT (0.6%), SGPT (0.5%), alkaline phosphatase (0.4%), cholesterol (0.4%) and triglycerides (0.4%); increased urinary glucose (0.7%) and urinary protein (0.3%) have also been seen.

Overdosage

Overdosage can lead to acute profound water loss, volume and electrolyte depletion, dehydration, reduction of blood volume and circu-