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ROCALTROL

Roche

Composition

Active Ingredient: synthetic calcitriol (1,25-dihydroxycholecalciferol)

Capsules 0.25 µg and 0.5 µg.

Excipients: Capsules: butylated hydroxyanisole, butylated hydroxytoluene, fractionated coconut oil, gelatin, glycerol, hydrogenated products of partially hydrolysed starch, titanium dioxide E171, canthaxanthin E161 g.

Properties

Calcitriol is one of the most important active metabolites of vitamin D_3. It is normally formed in the kidney from its precursor, 25-hydroxycholecalciferol (25-HCC). Physiological daily production is normally 0.5-1.0 µg, and is somewhat higher during periods of increased bone synthesis (e.g. growth and pregnancy). Calcitriol promotes intestinal absorption of calcium and regulates bone mineralization.

The key role of calcitriol in the regulation of calcium homeostasis, which includes stimulating effects on osteoblastic activity in the skeleton, provides a sound pharmacological basis for its therapeutic effects in postmenopausal osteoporosis.

In patients with marked renal impairment, synthesis of endogenous calcitriol is correspondingly limited or may even cease altogether. This deficiency plays a key role in the development of renal osteodystrophy.

In patients with renal osteodystrophy, oral administration of Rocaltrol normalizes reduced intestinal absorption of calcium, hypocalcemia, increased serum alkaline phosphatase and serum parathyroid hormone concentration. It alleviates bone and muscle pain and corrects the histological alterations that occur in osteitis fibrosa and other mineralization defects.

In patients with postsurgical hypo-parathyroidism, idiopathic hypo-parathyroidism and pseudo-hypoparathyroidism, hypocalcemia and its clinical manifestations are alleviated by Rocaltrol therapy.

In patients with vitamin D-dependent rickets the serum levels of calcitriol are low or absent. As the endogenous production of calcitriol in the kidney is insufficient, Rocaltrol is considered as a replacement therapy.

Patients with vitamin D-resistant rickets and hypophosphatemia in whom plasma calcitriol levels are reduced, treatment with Rocaltrol reduces tubular elimination of phosphates and, in conjunction with concurrent phosphate treatment, normalizes bone development.

Patients with various other forms of rickets, for example in association with neonatal hepatitis, biliary atresia, cystinosis and dietary calcium and vitamin D deficiency, have also benefited from Rocaltrol therapy.

Pharmacokinetics

Absorption

Calcitriol is rapidly absorbed from the intestine. Peak serum concentrations following a single dose of 0.25-1.0 µg Rocaltrol were found within 3-6 hours. Following multiple administration, serum calcitriol levels reached a steady state within 7 days.

Distribution

After a single oral dose of 0.5 µg Rocaltrol, the average serum concentrations of calcitriol rose from a baseline value of 40.0±4.4 µg/ml to 60.0±4.4 µg/ml after two hours, and then fell to 53.0± -6.9 after four hours, to 50.0±7.0 after eight hours, to 44±4.6 after twelve hours and to 41.5±5.1 µg/ml after 24 hours.

During transport in the blood, calcitriol and other vitamin D metabolites are bound to specific plasma proteins.

It can be assumed that exogenous calcitriol passes from the maternal blood into fetal bloodstream and the breast milk.

Elimination

The elimination half-life of calcitriol is 3-6 hours. However, the pharmacological effect of a single dose of calcitriol lasts about 3-5 days. Calcitriol is

excreted in the bile and is subject to enterohepatic circulation. After intravenous administration of radioactively labelled calcitriol in healthy subjects, about 27% of the radioactivity is found in the feces and about 7% in the urine within 24 hours. After oral administration of 1 µg radioactive calcitriol in healthy subjects, about 10% of the entire radioactivity was found in the urine within 24 hours. On the sixth day after intravenous administration of radioactively labelled calcitriol, urine and feces accounted for an average of 16% and 49% respectively of the cumulative excretion of radioactivity.

Indications

Postmenopausal osteoporosis; renal osteodystrophy in patients with chronic renal failure, particularly those undergoing hemodialysis; postsurgical hypo-parathyroidism; idiopathic hypo-parathyroidism; pseudohypo-para-thyroidism; vitamin D-dependent rickets; hypophosphatemic vitamin D-resistant rickets.

Contraindications

Rocaltrol (or drugs of the same class) is contraindicated in all diseases associated with hypercalcemia. Use of Rocaltrol in patients with known hypersensitivity to its constituents is also contraindicated,

Side Effects

Rocaltrol does not produce Side Effects as long as the dosage does not exceed the individual patient's needs. Since calcitriol exerts vitamin D activity, adverse effects may occur which are similar to those found when an excessive dose of vitamin D is taken, i.e. hypercalcemia syndrome or calcium intoxication (depending on the severity and duration of hypercalcemia).

In concurrent hypercalcemia and hyperphosphatemia of >6 mg/100 ml or >1.9 mmol per l, soft-tissue calcification may occur; this can be seen radiographically. Because of the short biological half-life of calcitriol, pharmacokinetic investigations have shown normalization of elevated serum calcium within a few days of treatment withdrawal or of a dosage reduction, i.e. much faster than in treatment with vitamin D_3 preparations.

Precautions

There is a close correlation between treatment with calcitriol and the development of hypercalcemia. In studies of patients with uremic osteodystrophy, hypercalcemia was found to occur in up to 40% of calcitriol-treated patients. An abrupt increase in calcium intake as a result of changes in diet (e.g., increased consumption of dairy products) or uncontrolled intake of calcium preparations may trigger hypercalcemia. Patients and their families should be advised that strict adherence to the prescribed diet is mandatory and they should be instructed on how to recognize the symptoms of hypercalcemia.

Immobilized patients, e.g. those who have undergone surgery, are particularly exposed to the risk of hypercalcemia.

In patients with normal renal function, chronic hypercalcemia may be associated with an increase in serum creatinine.

Caution is required in patients with a history of renal calculi and patients with coronary heart disease.

Calcitriol increases organic phosphate levels in serum. While this is desirable in patients with hypophosphatemia, caution is called for in patients with renal failure because of the danger of ectopic calcification. In such cases, the plasma phosphate level should be maintained at the normal level (2-5 mg/100 ml or 0.65-1.62 mmol/l) by the oral administration of appropriate phosphate-binding agents such as aluminium hydroxide or aluminium carbonate. Patients with vitamin D-resistant rickets (familial hypophosphatemia) which are being treated with Rocaltrol must continue their oral phosphate therapy. However, possible stimulation of intestinal absorption of phosphate by Rocaltrol should be taken into account since this effect may modify the need for phosphate supplementation. The regular laboratory investigations that are required include serum determinations of calcium, phosphorus, magnesium and alkaline phosphatase and of the calcium and phosphate content in 24 hour urine. During the stabilization phase of treatment with Rocaltrol, serum calcium levels should be checked at least

twice weekly (see also Dosage and Administration).

Since calcitriol is the most effective vitamin D metabolite available, no other vitamin D preparation should be prescribed during treatment with Rocaltrol, thereby ensuring that the development of hypervitaminosis D is avoided.

If the patient is switched from ergocalciferol (vitamin D_2) to calcitriol, it may take several months for the ergocalciferol level in the blood to return to the baseline values (see Overdosage).

Patients with normal renal function who are taking Rocaltrol should avoid dehydration. Adequate fluid intake should be maintained.

Pregnancy and Nursing Mothers

Studies of reproductive toxicology in animals have not yielded unequivocal findings, and no controlled studies on the effect of exogenous calcitriol on pregnancy and fetal development have been performed in human subjects.

Consequently, Rocaltrol should be administered only if the benefits outweigh the potential risk to the fetus.

It should be assumed that exogenous calcitriol passes into the breast milk. In view of the possible Side Effects on the infant, mothers should not breastfeed while taking Rocaltrol.

Overdosage

Treatment of asymptomatic hypercalcemia: see Special dosage instructions.

Since calcitriol is a derivative of vitamin D, the symptoms of overdose are the same as for an overdose of vitamin D. Intake of high doses of calcium and phosphate together with Rocaltrol may give rise to similar symptoms. A high calcium level in the dialysate may contribute to the development of hypercalcemia.

Acute symptoms of vitamin D intoxication: anorexia, headache, vomiting, constipation.

Chronic symptoms: dystrophy (weakness, loss of weight), sensory disturbances, possibly fever with thirst, polyuria, apathy, arrested growth and urinary tract infections. Hypercalcemia ensues, with metastatic calcification of the renal cortex, myocardium, lungs and pancreas.

The following measures should be considered in treatment of accidental overdosage: immediate gastric lavage or induction of vomiting to prevent further absorption. Administration of liquid paraffin to promote fecal excretion. Repeated serum calcium determinations are advisable. If elevated calcium levels persist in the serum, phosphates and corticosteroids may be administered and measures instituted to bring about adequate diuresis.

Stability

Store below 30ºC and protect from light.

This medicine should not be used after the expiry date (EXP) shown on the pack.

Drug Interactions

Since calcitriol is one of most important active metabolites of vitamin D_3, vitamin D and its derivatives should be with-held during treatment with calcitriol to avoid possible additive effects and hypercalcemia.

Dietary instructions, especially concerning calcium supplements, should be strictly observed, and uncontrolled intake of additional calcium-containing preparations avoided.

Concomitant treatment with a thiazide diuretic increases the risk of hypercalcemia in patients with hypoparathyroidism. Calcitriol dosage must be determined with care in patients undergoing treatment with digitalis, as hypercalcemia in such patients may precipitate cardiac arrhythmias.

A relationship of functional antagonism exists between vitamin D analogues, which promote calcium absorption, and corticosteroids, which inhibit it.

Magnesium-containing drugs (e.g., antacids) may cause hypermagnesemia and should therefore not be taken during therapy with Rocaltrol by patients on chronic renal dialysis. Since calcitriol also has an effect on phosphate transport in the intestine, kidneys and bones, the dosage of phosphate-binding agents must be adjusted in accordance with the serum phosphate concentration (normal values:

2-5 mg/100 ml, or 0.6-1.6 mmol per l). Patients with vitamin D-resistant rickets (familial hypophosphatemia) should continue their oral phosphate therapy. However, possible stimulation of intestinal phosphate absorption by calcitriol should be taken into account since this effect may modify the requirement for phosphate supplements.

Administration of enzyme inducers such as phenytoin or phenobarbital may lead to increased metabolism and hence reduced serum concentrations of calcitriol.

Cholestyramine can reduce intestinal absorption of fat-soluble vitamins and therefore may impair intestinal absorption of calcitriol.

Dosage and Administration

Standard Dosage

The optimal daily dose of Rocaltrol must be carefully determined for each patient on the basis of the serum calcium level. Rocaltrol therapy should always be started at the recommended dose and should not be increased without careful monitoring of serum calcium.

When the optimal dosage of Rocaltrol has been determined, serum calcium levels should be checked every month (or as specified below for individual indications). Samples for serum calcium estimation should be taken without a tourniquet.

As soon as the serum calcium levels rise to 1 mg/100 ml (250 µmol/l) above normal (9-11 mg/100 ml, or 2250-2750 µmol/l), the dosage of Rocaltrol should be substantially reduced or treatment stopped altogether until normocalcemia ensues.

During the periods of hypercalcemia, serum calcium and phosphate levels must be determined daily. When normal levels have been attained, the treatment with Rocaltrol can be continued, at a daily dose 0.25 µg lower than that previously used.

A prerequisite for optimal efficacy of Rocaltrol is adequate but not excessive calcium intake at the beginning of therapy.

An estimate of daily dietary calcium intake should be made and the intake adjusted when indicated (see Special Dosage Instructions).

In adults, the total daily calcium intake (from dietary and medicinal sources) should be approximately 800 mg and must not exceed 1000 mg.

Because of improved calcium absorption from the gastrointestinal tract, some patients on Rocaltrol may be maintained on a lower calcium intake. Patients who fend to develop hypercalcemia may require only low doses of calcium or no supplementation at all.

Special Dosage Instructions

Postmenopausal Osteoporosis

The recommended dosage is 0.25 µg twice daily. The capsules should be swallowed unchewed. Calcium supplements should be prescribed for patients whose dietary calcium intake is less than 500 mg. Daily calcium must not exceed 1000 mg.

Serum calcium and creatinine levels should be determined at 4 weeks, 3 and 6 months and 6 monthly intervals thereafter.

Renal Osteodystrophy (Dialysis Patients)

The initial daily dose is 0.25 µg. In patients with normal or only slightly reduced serum calcium levels, doses of 0.25 µg every other day are sufficient. If no satisfactory response in the biochemical parameters and clinical manifestations of the disease is observed within two to four weeks, the dosage may be increased by 0.25 µg/day at two to four week intervals. During this period, serum calcium levels should be determined at least twice weekly. Most patients respond to between 0.5 µg and 1.0 µg daily. Higher doses may be necessary in patients receiving concomitant barbiturates or anticonvulsants.

Hypoparathyroidism and Rickets

The recommended initial dose of Rocaltrol is 0.25 µg/day given in the morning. If a satisfactory response in the biochemical parameters and clinical manifestations of the disease is not observed, the dose may be increased at two to four week intervals.

During this period, serum calcium levels should be determined at least twice weekly.

Malabsorption is occasionally noted in patients with hypoparathyroidism hence, larger doses of Rocaltrol may be needed.