ALFACAL

Gelatin Capsules

Composition
Each soft gelatin capsules contains 1 microgram or 0,25 micrograms of Alphacalcidol.

Action
Alfacalcidol (1alpha-OHD_3) is rapidly converted in the liver to 1, 25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$), the metabolite of vitamin D which acts as a regulator of calcium and phosphate homeostasis.

Impaired endogenous production of 1, 25-dihydroxyvitamin D_3 by the kidneys appears to contribute to the disturbances in mineral metabolism found in several disorders, including renal bone disease, hypoparathyroidism, and vitamin D-dependent rickets. These disorders, which require high doses of vitamin D for their correction, will respond to small doses of Alfacal.

As compared to vitamin D, the main advantage of Alfacal is more rapid onset and offset of action. This allows a more accurate titration of dosage and decreases the risk of prolonged hypercalcemia.

Pharmacokinetics
Serum levels of 1,25-$(OH)_2$ D_3 peak approximately 12 hours after a single dose of Alfacalcidol and remain at measurable levels for at least 48 hours. The effect of 1 mcg of Alfacalcidol on calcium absorption has been observed within 6 hours and was maximal at 24 hours. The biological half-life is approximately 35 hours.

Indications
- **Renal Bone Disease**
  most patients with osteitis fibrosa and osteomalacia show a symptomatic and gradual biochemical, radiographic and histological improvement.
- **Hypoparathyroidism**
  Low plasma calcium levels restored to normal relatively quickly with 1alpha-OHD3. Severe hypocalcaemia (e.g. after extensive neck surgery) may decline with higher doses of 1alpha-OHD3, (e.g. 3 -5 micrograms) and calcium supplements. Maintain Normocalcemia with smaller doses within a relatively narrow dose range.
- **Secondary Hyperparathyroidism**
  Following parathyroidectomy, patients with primary or tertiary hyperparathyroidism and bone disease often require large doses of vitamin D and intravenous calcium to avoid severe hypocalcemia. Preliminary studies suggest that pre-operative treatment with 1alpha-OHD3 for two to three weeks alleviates bone pain and myopathy when present without aggravating pre-operative hypercalcemia. Continued post-operative treatment decreases post-operative hypocalcaemia and be continued until the plasma alkaline phosphatase level falls to normal or hypercalcemia occurs.
- **Hypophosphataemic Vitamin D resistant rickets and osteomalacia**
  this is characterized by hypophosphataemia due to defective renal tubular re-absorption and intestinal absorption of phosphorus. Neither large doses of vitamin D nor phosphate supplements are entirely satisfactory, the latter tending to produce hypocalcaemia and hypoparathyroidism. 1alpha-OHD3 relieves myopathy when present, increases calcium and phosphorus retention and promotes bone healing. Phosphate supplements may also be required in some patients.
- **Pseudo-deficiency (D-dependent) rickets**
  This requires large doses of vitamin D probably because of an inherited defect in the production of 1,25-(OH)2D3. 1alpha-OHD3 reverses this condition.
- **Nutritional and malabsorptive rickets and osteomalacia**
  Nutritional rickets and osteomalacia can be cured with physiological doses of 1alpha-OHD3. Patients with malabsorptive osteomalacia responding to large doses of vitamin D will respond to

small doses of 1alpha-OHD3.

Contraindications

Alfacal should not be given to patients with hypercalcemia or evidence of vitamin D intoxication. Alfacal should only be used during pregnancy and lactation when the expected therapeutic benefits clearly outweigh the possible adverse effects.

Warnings

Alfacal is not used in the first trimester of pregnancy.

Adverse Reactions

In general, the adverse effects of Alphacalcidol are similar to those encountered with excessive vitamin D intake.

a- Early symptoms: Pruritus, weakness, headache, "red-eyes", somnolence, nausea, cardiac arrhythmia, vomiting, excessive thirst, dry mouth, constipation, muscle pain, bone pain and metalic taste

b- Late symptoms: Polyuria, polydipsia, anorexia, weight loss, nocturia, conjunctivitis, corneal calcification, photophobia, rhinorrhea, pancreatitis, pruritus, hyperthermia, decreased libido, elevated BUN, albuminuria, hypercholesterolemia, elevated AST and ALT, ectopic calcification, hypertension, cardiac arrhythmias and, rarely, overt psychosis.

Hypercalcemia and possibly an exacerbation of hypophosphataemia are the most frequent adverse reactions that have been reported with Alphacalcidol in patients with renal osteodystrophy. Elevated levels of calcium and phosphorus increase the risk of metastatic calcification and may accelerate the decline in renal function in some patients with chronic renal failure.

Precautions

1alpha-OHD3 should be given with care to patients with impaired renal function. If hypercalcemia induced by 1alpha-OHD3, it can be rapidly corrected by stopping treatment. Throughout treatment, regular plasma calcium determinations are essential. Facilities for monitoring plasma calcium and other appropriate biochemical parameters should be available when 1alpha-OHD3 is used. If hypercalcemia occurs, 1alpha-OHD3 should be stopped until the plasma calcium returns to normal (about one week) and then restarted at half the dose

The risk of hypercalcemia depends on such factors as the degree of any mineralization defect, renal function and the dose of 1alpha-OHD3 that is used. Thus, hypercalcemia is less likely in osteomalacia and more likely in renal failure. Hypercalcemia will occur when there is biochemical evidence of bone healing (e.g. a return towards normal in the level of plasma alkaline phosphatase) and the dose of 1alpha-OHD3 is not reduced appropriately. Prolonged hypercalcemia should be avoided, particularly in chronic renal failure. Plasma calcium levels should be measured at weekly to monthly intervals depending on the progress of the patient. Frequent estimations are necessary in the early stages of treatment and later when there is evidence of bone healing. Plasma calcium levels should also be estimated regularly during the initial treatment of disorders without significant bone involvement, e.g. hypoparathyroidism.

Drug interactions

Alphacalcidol should be used with extreme caution in patients on digitalis, as hypercalcemia may trigger cardiac arrhythmias. Resins such as cholestyramine and mineral oil used as a laxative may interfere with the intestinal absorption of Alphacalcidol.

Patients concurrently treated with barbiturates and other anticonvulsant drugs may require higher doses of Alphacalcidol, as these drugs may interfere with the action of vitamin D. Patients and their immediate relatives should be informed about the need for compliance with the dosage instructions, strict adherence to prescribed calcium intake, dietary and supplementary, and avoidance of unapproved nonprescription drugs or medications.

Dosage and Administration

An initial dose of 0.25 µg/day is administered for 2 months, unless hypercalcemia develops. If hypercalcemia occurs then the dose should be reduced to 0.25 µg on alternate days. If serum calcium is below the desired range, the dose may be adjusted in increments of 0.25 µg/day every 2 months. Most patients are maintained on a dose of 0.5 µg/day. However, doses up to 1 µg/day may be necessary to maintain serum calcium within the desired range. If hypercalcemia develops at any time during treatment then the dose of Alphacalcidol should be reduced by 50% and all calcium supplements stopped until calcium levels return to normal.

Serum calcium and phosphate levels needs monitoring at monthly intervals or necessary if hypercalcemia develops. Calcium supplements should not exceed 500 mg of elemental calcium per day.

Dose Titration for Hemodialysis Patients: The recommended initial dose is one µg daily. If a satisfactory response in the biochemical parameters and clinical manifestations has not observed within 4 weeks, the daily dose might be increased by 0.5 µg every 2 to 4 weeks. Most patients respond eventually to a dose of between one and two µg/day. Exceptionally, a dose of three µg is required.

Maintenance Therapy: Once serum calcium levels are normalized or only slightly reduced, the dose requirement of Alphacalcidol generally decreases. Maintenance doses usually range from 0.25 to 1.0 µg/day. If this small maintenance dose still proves too high, adequate control can usually be achieved by giving the dose on alternate days or even less frequently.

Over Dosage

Manifestation

The initial signs and symptoms of vitamin D intoxication associated with hypercalcemia include weakness, fatigue, somnolence, headache, anorexia, nausea, vomiting, diarrhea, and pruritus. If hypercalcemia is allowed to persist, the following may also develop conjunctivitis, a shortened Q-T interval and cardiac arrhythmias, as well as manifestations of impaired renal function consisting of Polyuria, polydipsia, nocturia, hyposthenuria, dehydration, and mild proteinuria.
Agitation, apprehension, pain in the extremities, paralytic ileus, abdominal pain and, rarely, overt psychosis have also been reported with hypercalcemia. Some mild elevations in SGOT and SGPT have been reported in a small percentage of patients treated with Alfacal.

Treatment of hypercalcemia and over dosage in patients on Hemodialysis

General Treatment of hypercalcemia (greater than 0.25 mmol/L above the upper limit of the normal range) consists of immediate discontinuation of therapy, institution of a low calcium diet and withdrawal of calcium supplements. Serum calcium levels should be determined daily until Normocalcemia ensues. Hypercalcemia frequently resolves in two to seven days. When serum calcium levels have returned to within normal limits, therapy may be reinstituted at a dose of 0.25 µg /day less than prior therapy. Serum calcium levels should be obtained at least twice weekly after all dosage changes and subsequent dosage titration. Persistent or markedly elevated serum calcium levels a corrected by dialysis against a calcium-free dialysate.

Presentation

Alfacal 0.25 µg capsule

Box of 30 soft gelatin capsules

Alfacal 1.0 µg capsule

Box of 30 soft gelatin capsules