PRODUCT MONOGRAPH

[Pr]ONE-ALPHA®

Alfacalcidol

Capsules, 1 and 0.25 mcg

Oral Drops, 2 mcg/mL

Injection, 2 mcg/mL

Vitamin D Analogue

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NAME OF DRUG

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Injection, 2 mcg/mL

THERAPEUTIC CLASSIFICATION

Vitamin D Analogue

ACTION AND CLINICAL PHARMACOLOGY

1∝-hydroxyvitamin D_3(1∝-OHD_3) stimulates intestinal calcium and phosphorus absorption, the reabsorption of calcium from bone and possibly the renal reabsorption of calcium.

To be effective in disorders resulting from vitamin D deficiency, vitamin D must undergo two metabolic conversions, first in the liver to 25-hydroxyvitamin D and then in the kidney to the physiologically active metabolite, 1,25-dihydroxy vitamin D_3 (1,25-$(OH)_2D_3$). In patients with chronic renal failure, progressive nephron destruction blocks the production of 1,25-$(OH)_2$ D_3 by the kidneys resulting in diminished serum levels of this metabolite.

When ONE-ALPHA (alfacalcidol) is administered in this clinical situation, it is rapidly converted to 1,25-$(OH)_2D_3$ in the liver, effectively bypassing the critical renal metabolic conversion. This hepatic conversion of ONE-ALPHA is accomplished very rapidly, before any stimulation of the intestine or bone occurs.

The biological half-life of ONE-ALPHA has been shown to be approximately 3 hours in the presence of renal insufficiency. However, serum levels of 1,25$(OH)_2D_3$ peak approximately 12 hours after a single dose of oral ONE-ALPHA and approximately 4 hours after a single dose of intravenous ONE-ALPHA. Levels of 1,25$(OH)_2D_3$ remain measurable for at least 48 hours. The effect of 1 mcg of oral

ONE-ALPHA on intestinal calcium absorption has been observed within 6 hours of ingestion and was maximal at 24 hours. There is evidence that vitamin D, its 1∝-hydroxylated metabolites and analogues are extensively bound to a serum binding protein of the ∝-globulin fraction. 1,25-$(OH)_2D_3$ appears to function in the intestine and bone by a receptor-nuclear activation mechanism.

One of the first abnormalities to be observed in patients with chronic renal failure is the disturbance of calcium metabolism due to increased phosphate retention and impaired production of 1,25-$(OH)_2D_3$. Because calcium metabolism and production of 1,25-$(OH)_2D_3$ is at least partially mediated by the parathyroid glands, hypocalcemia leads to increased parathyroid hormone (PTH) secretion and high plasma PTH levels. Therefore, the patients with renal bone disease most likely to benefit from ONE-ALPHA therapy are those characterized by abnormally low plasma calcium levels, elevated alkaline phosphatase and PTH levels, and histological evidence of osteitis fibrosa and osteomalacia.

In the majority of patients treated with ONE-ALPHA, clinical symptoms of bone pain and muscle weakness begin to remit promptly, within 2 weeks to 3 months of the start of therapy. Malabsorption of calcium is rapidly corrected. In patients on daily oral therapy, plasma alkaline phosphatase and PTH levels generally begin to fall within 3 months, but plasma calcium levels may not normalize for several months. This delay should not necessarily be construed as a poor response but may indicate that calcium is being utilized for bone mineralization. The decrease in PTH levels may be more rapid in patients on intermittent intravenous therapy, with significant reductions being achieved within 3 months of therapy.

By contrast, hypercalcemia may occur at any stage of treatment, the risk being higher just after treatment is started and later when the plasma alkaline phosphatase level falls towards normal (See PRECAUTIONS).

Because of a modest action on intestinal phosphorus absorption, ONE-ALPHA may elevate plasma phosphorus levels even further in patients with renal osteodystrophy and this may require increasing the dose of phosphate binding agents.

Normalization of plasma PTH levels frequently correlates well with healing of osteitis fibrosa, but radiographic improvement can occur without significant changes in plasma PTH concentrations.

After 3 to 6 months of treatment, radiological evidence of healing is generally apparent. Histological responses, such as a decrease in the surface of bone undergoing resorption and a decrease in the volume of osteoid, are often much slower.

The beneficial effects of alfacalcidol on the development of renal bone disease in patients with renal failure not yet undergoing dialysis has been demonstrated in a large, randomized, placebo controlled study. Long-term administration of oral ONE-ALPHA (maximum dose of 1 mcg/day for up to 2 years) improved bone histology and halted the progression of changes in serum alkaline phosphatase activity and parathyroid hormone levels compared to placebo. Long-term administration of alfacalcidol proved to be well tolerated and had no adverse effect on renal function in patients for whom the dose was titrated to prevent persistent hypercalcemia. Although elevation of serum calcium was observed, marked hypercalcemia (> 3.00 mmol/L) was uncommon (4.5% of patients) and readily responded to decreases in drug dosage.

INDICATIONS AND CLINICAL USE

Management of hypocalcemia, secondary hyperparathyroidism, and osteodystrophy in patients with chronic renal failure.

CONTRAINDICATIONS

Known hypersensitivity to 1α-hydroxyvitamin D_3, vitamin D or any of its analogues and derivatives.

ONE-ALPHA (alfacalcidol) is contraindicated when there is biochemical evidence of hypercalcemia, hyperphosphatemia, or evidence of vitamin D overdose.

WARNINGS

ONE-ALPHA (alfacalcidol) is a potent cholecalciferol derivative with a profound positive effect on intestinal absorption of dietary calcium. The effect of ONE-ALPHA on inorganic phosphorus absorption is less marked, although it is important to recognize that the drug may increase plasma phosphorus concentrations, which may increase the requirements for phosphate binding agents.

ONE-ALPHA should not be used concomitantly with other vitamin D products or derivatives.
As with all vitamin D preparations and metabolites, hypercalcemia must be anticipated when using ONE-ALPHA. Regular monitoring of plasma calcium is essential. Indeed, ONE-ALPHA should only be used when adequate facilities are available for monitoring of blood and urine chemistries on a regular basis.

During treatment with ONE-ALPHA, progressive hypercalcemia either due to hyper-responsiveness or overdose may become so severe as to require emergency treatment. Chronic hypercalcemia can lead to generalized vascular calcification, nephrocalcinosis or calcifications of the cornea or other soft tissues. During treatment with ONE-ALPHA, the TOTAL SERUM CALCIUM (mg/dL) TIMES SERUM INORGANIC PHOSPHATE (mg/dL) PRODUCT (Ca x P) SHOULD BE MAINTAINED AT ACCEPTED LEVELS. A dialysate calcium level of 1.75 mmoles/L or above, in addition to excess dietary calcium supplements may lead to frequent episodes of hypercalcemia.

To control serum inorganic phosphate levels and dietary phosphate absorption, appropriate oral phosphate binding agents in association with a low phosphate diet may be necessary to prevent hyperphosphatemia and extra-skeletal calcifications. Serum phosphate levels were maintained below 2.0 mmol/L in the study that demonstrated the benefits of daily oral ONE-ALPHA on the development of bone disease in pre-dialysis patients.

Antacids containing magnesium should be avoided as they may contribute towards hypermagnesemia.

In patients on digitalis hypercalcemia may precipitate cardiac arrhythmias. In such patients ONE-ALPHA should be used with extreme caution.

The safety of ONE-ALPHA in women who are or may become pregnant has not been established; use of ONE-ALPHA in these cases may be considered only when the potential benefits have been weighed against possible hazards to mother and fetus.

ONE-ALPHA may be excreted in human milk, therefore, breast feeding during treatment should be avoided.

PRECAUTIONS

Patient Selection and Follow-up

The therapeutic margin with ONE-ALPHA (alfacalcidol) is narrow, therefore, the optimal daily dose must be carefully titrated for each individual patient (See DOSAGE AND ADMINISTRATION).

The occurrence of hypercalcemia depends on such factors as the degree of bone mineralization, the state of renal function and the dose of ONE-ALPHA. Excessive doses of the drug induce hypercalcemia and hypercalciuria.

Pre-Dialysis Administration of ONE-ALPHA

Serum calcium and phosphate levels should be monitored at monthly intervals or as is considered necessary if hypercalcemia develops.

If hypercalcemia develops at any time during treatment then the dose of alfacalcidol should be reduced by 50% and all calcium supplements stopped until calcium levels return to normal.

Administration of ONE-ALPHA to Patients Undergoing Dialysis

Plasma calcium should be measured at weekly intervals depending on the progress of the patient. In early treatment during dosage adjustment, serum calcium should be determined at least twice weekly. In the later stages of treatment when there is evidence of bone healing (e.g., when the plasma alkaline phosphatase level falls toward normal), weekly estimations are recommended.

If hypercalcemia occurs, ONE-ALPHA should be discontinued immediately. Upon discontinuation of the drug, serum calcium levels generally normalize within a few days to a week. Calcium levels should be re-checked in another week and if still at normal levels, ONE-ALPHA may be re-instituted at half the previous dose.

Patients with renal bone disease and a relatively high initial plasma calcium and "autonomous" hyperparathyroidism are liable to early hypercalcemia, as are the minority of dialysis patients with low plasma alkaline phosphatase.

Essential Laboratory Tests

Laboratory tests considered essential to adequate patient monitoring include: serum calcium,

inorganic phosphorus, magnesium, alkaline phosphatase, creatinine, BUN and protein (for correction of plasma calcium in instances of hypercalcemia). For pre-dialysis patients treated with ONE-ALPHA, serum calcium and phosphate levels should be monitored at monthly intervals or as is considered necessary if hypercalcemia develops. For patients undergoing dialysis serum calcium should be determined at least twice weekly during dose titration. During maintenance therapy with ONE-ALPHA, 24-hour urinary calcium and phosphorus should be determined periodically.

Periodic ophthalmological examinations and radiological evaluation of suspected anatomical regions for early detection of ectopic calcifications are advisable.

Drug Interactions

ONE-ALPHA 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 ONE-ALPHA.

Patients concurrently treated with barbiturates and other anticonvulsant drugs may require higher doses of ONE-ALPHA, as these drugs may interfere with the action of vitamin D.

Information for the Patient

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 non-prescription drugs or medications.

Patients should be made aware of symptoms of hypercalcemia and should be instructed to seek medical attention if such symptoms appear. (See ADVERSE REACTIONS).

Pediatric Use

The safety and efficacy of ONE-ALPHA in children has not been established.

ADVERSE REACTIONS

In general, the adverse effects of ONE-ALPHA (alfacalcidol) are similar to those encountered with excessive vitamin D intake.

The early and late signs and symptoms associated with vitamin D intoxication and hypercalcemia may include:

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

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

Hypercalcemia and possibly an exacerbation of hyperphosphatemia are the more frequent adverse reactions that have been reported with ONE-ALPHA 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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Dosages of ONE-ALPHA (alfacalcidol) in excess of daily requirements can cause hypercalcemia, hypercalciuria and hyperphosphatemia. Conversely, a high intake of calcium and phosphate concomitantly with therapeutic doses of ONE-ALPHA may cause similar abnormalities.

Treatment of Hypercalcemia Due to Overdose

General treatment of serum calcium levels more than 1 mg/dL or 0.25 mmol/L above the upper limit of the normal range (usually 8.0 - 10.4 mg/dL or 2.2-2.6 mmol/L) consists of immediate discontinuation of ONE-ALPHA, institution of a low calcium diet and withdrawal of calcium supplements. Serum calcium levels should be determined daily until the patient achieves

normocalcemia. Hypercalcemia frequently resolves in 2 to 7 days. ONE-ALPHA therapy can be re-instituted at half the previous dose when serum calcium levels have returned to within normal limits. Serum calcium levels should be carefully monitored (at least twice weekly) during this period of dosage adjustment and subsequent dosage titration. Persistent or markedly elevated serum calcium levels in hemodialysis patients may be corrected by dialysis against a calcium-free dialysate.

Treatment of Accidental Overdosage

The treatment of acute accidental overdosage with ONE-ALPHA should consist of general supportive measures. If drug ingestion is discovered within a relatively short time, induction of emesis or gastric lavage may be of benefit in preventing further absorption. If the drug has passed through the stomach, the administration of mineral oil may promote its fecal elimination. Serial serum electrolyte determinations (especially calcium ion), rate of urinary calcium excretion and assessment of electrocardiographic abnormalities due to hypercalcemia should be obtained. Such monitoring is critical in patients receiving digitalis. Discontinuation of supplemental calcium and low calcium diet are also indicated in accidental overdosage. Due to the relatively short pharmacological action of ONE-ALPHA, further measures are probably unnecessary. However, if persistent and markedly elevated serum calcium levels occur, there are a variety of therapeutic alternatives which may be considered depending on the underlying condition of the patient. These include the use of drugs such as phosphates and corticosteroids as well as measures to induce an appropriate forced diuresis. The use of dialysis against a calcium-free dialysate has also been reported.

DOSAGE AND ADMINISTRATION

The daily dose of ONE-ALPHA (alfacalcidol) must be carefully individualized and titrated according to such factors as the state of renal function, degree of bone mineralization and initial plasma calcium and alkaline phosphatase concentrations. Other factors which may be taken into account are urinary calcium excretion, plasma PTH and phosphorus.

The success of ONE-ALPHA is also based on the assumption that the patient is receiving an adequate daily intake of calcium during treatment. The recommended daily allowance of calcium in adults is about 800-1000 mg (from all sources such as dialysate, diet and calcium supplements).

The physician should ensure that each patient receives an adequate daily intake of calcium by prescribing a calcium supplement or instructing the patients in appropriate dietary measures.

Pre-Dialysis Patients on Daily Oral Therapy

Dose Titration: A dose of ONE-ALPHA that maintains serum calcium (adjusted for albumin concentration) within the normal range should be selected. An initial dose of 0.25 mcg/day is recommended, followed by dose adjustment until an appropriate dose is achieved. ONE-ALPHA has been shown to be safe and effective in the prevention of renal bone disease when doses were maintained at or below 1 mcg/day. ONE-ALPHA is usually administered as a single dose each day taken with food.

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

Serum calcium and phosphate levels should be monitored at monthly intervals or as is considered necessary if hypercalcemia develops. Calcium supplements should not exceed 500 mg of elemental calcium per day.

Dialysis Patients on Daily Oral Therapy

Dose Titration: The recommended initial dose of ONE-ALPHA is 1 mcg daily. If a satisfactory response in the biochemical parameters and clinical manifestations is not observed within 4 weeks, the daily dose may be increased by 0.5 mcg every 2 to 4 weeks. Most patients respond eventually to a dose of between 1 and 2 mcg per day. Only exceptionally, a dose of 3 mcg is required.

During this titration period, serum calcium levels should be obtained at least twice weekly and, if hypercalcemia is noted, the drug should be discontinued immediately until serum calcium levels normalize.

Maintenance Doses: Once serum calcium levels are normalized or only slightly reduced, the dose requirement of ONE-ALPHA generally decreases. Maintenance doses usually range from 0.25 - 1.0 mcg per day. If this small maintenance dose still proves too high, adequate control can usually be achieved by giving the dose on alternative days or even less frequently.

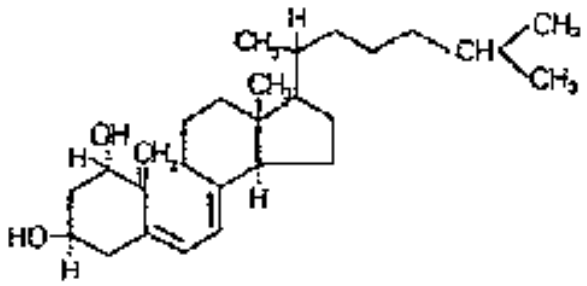
Dialysis Patients on Intermittent Intravenous Therapy

Dose Titration: A dose of ONE-ALPHA that maintains total serum calcium in the upper half of the normal range should be selected. Calcium levels should be measured weekly during the dose titration period. The recommended initial dose of ONE-ALPHA is 1 mcg per dialysis (2-3 times weekly). If a satisfactory response in biochemical parameters is not observed within 1 week, the dose may be increased in weekly increments of 1 mcg per dialysis to a maximum of 12 mcg per week. The total dose titration period should not exceed 6 weeks. If hypercalcemia is noted, the drug should be discontinued immediately until serum calcium levels normalize. Once calcium levels return to the normal range, ONE-ALPHA should be re-introduced at lower doses.

Maintenance Doses: Doses required to maintain serum calcium levels in the upper half of the normal range are usually around 6 mcg per week but can range from 1.5 to 12 mcg per week. Serum calcium and phosphate levels should be monitored every other week or as is considered necessary if hypercalcemia is noted. If hypercalcemia develops, adequate control can usually be achieved by temporarily stopping treatment. Once calcium levels normalize, ONE-ALPHA should be re-introduced at lower doses.

PHARMACEUTICAL INFORMATION

Drug Substance Alfacalcidol (1α-hydroxycholecalciferol)



Molecular Formula: $C_{27}H_{44}O_2$

Molecular Weight: 400.65

Chemical Name: (5Z, 7E)-9,10-secocholesta-5,7,10(19)-triene-1∝, 3β-diol

Description: Alfacalcidol is a colorless crystalline compound with a melting range of 136°-144°C. It is sensitive to light and very soluble in methanol, ethanol and chloroform, soluble in ether, sparingly soluble in methylformate and acetronitrile.

Composition

1 mcg soft gel Capsules: Non-medicinal ingredients: sesame oil and ∝-tocopherol; shell composition: gelatin, glycerol, potassium sorbate, red iron oxide E172 and black iron oxide E172.

0.25 mcg soft gel Capsules: Non-medicinal ingredients: sesame oil and ∝-tocopherol; shell composition: gelatin, glycerol, potassium sorbate and titanium dioxide.

2 mcg/mL Oral Drops: Non-medicinal ingredients: citric acid monohydrate, ethanol, methyl parahydroxybenzoate, polyoxyl 40 hydrogenated castor oil, purified water, sodium citrate, sorbitol and α-tocopherol.

2 mcg/mL Injection: Non-medicinal ingredients: citric acid monohydrate 0.16 mg/ml,

ethanol 80 mg/ml, sodium citrate 6.8 mg/ml, propylene glycol 415 mg/ml and water up to 1 ml.

Stability and Storage Recommendations

1 mcg soft gel Capsules: Protect from direct sunlight. Store at 15-25 °C.

0.25 mcg soft gel Capsules: Protect from direct sunlight. Store at 15-25°C.

2 mcg/mL Oral Drops: Protect from direct sunlight. Keep refrigerated (2-8°C).

2 mcg/mL Injection: Keep ampoules in outer carton to protect from light. Keep refrigerated (2-8°C). Shake well before use. Single use ampoules - discard unused portion.

AVAILABILITY OF DOSAGE FORMS

1 mcg soft gel Capsules: Each brown, egg-shaped soft gelatin capsule contains 1 mcg alfacalcidol. Available in tropical blisters of 100 (10x10 blisters).

0.25 mcg soft gel Capsules: Each cream-coloured, egg-shaped soft gelatin capsule contains 0.25 mcg alfacalcidol. Available in tropical blisters of 100 (10x10 blisters).

2 mcg/mL Oral Drops: A clear or slightly opalescent colourless solution containing 2 mcg alfacalcidol per mL. Available in amber glass bottles of 10 mL fitted with a polyethylene dropping device.
Drop size: 1 drop equals 0.1 mcg alfacalcidol.

2 mcg/mL Injection: A sterile aqueous solution intended for intravenous injection containing 2 mcg alfacalcidol per mL. Available in cartons of 10 ampoules. Each amber glass ampoule contains a unit dose of 1 mcg/0.5 mL or 2 mcg/1 mL. Shake well before use.

INFORMATION FOR THE CONSUMER

One-Alpha® (alfacalcidol)
Capsules (0.25mcg and 1 mcg) and Oral Drops (2 mcg/mL)

This leaflet is intended to give you some important information about using One-Alpha. If you have any questions please talk to your doctor or pharmacist.

What is One-Alpha?

One-Alpha is a medication used to help your body absorb calcium from your diet. Calcium is needed for good bone development and muscular activity. One-Alpha is available as an oral preparation (capsules and liquid drops) and as an intravenous injection.

Before using One-Alpha

Tell your doctor or pharmacist:

- about all other medicines or vitamins you may be taking. Do not use any prescription or non-prescription medications (including antacids and calcium supplements) without first checking with your doctor or pharmacist.
- if you are pregnant or breast feeding or if you become pregnant during your treatment.

How should I take One-Alpha?

The amount of One-Alpha will be tailored exactly for your body's needs. FOLLOW YOUR DOCTOR'S INSTRUCTIONS PRECISELY ABOUT WHEN AND HOW TO USE THIS MEDICINE. READ THE LABEL CAREFULLY. Your doctor will send you for blood tests to determine if a dosage adjustment of One-Alpha is needed.

Do not stop taking One-Alpha without first checking with your doctor. If a dose is forgotten, take it as soon as possible. If it is almost time for the next dose, do not double the dose. One-Alpha Capsules and Oral Drops may be taken with water or milk.

Your doctor may also prescribe other medications and a special diet in order to help improve your medical condition. It is very important to follow your doctors' instructions carefully.

When using the One-Alpha Oral Drops, remove the protective cap but not the plastic dropper which is inserted into the bottle. To use the dropper, hold the bottle upside down. The liquid should flow immediately, but if it does not, tap the bottle gently. Do not shake the bottle.

One-Alpha Injection is to be given only by a doctor or nurse during haemodialysis in patients with chronic renal failure.

Side-effects

One-Alpha is generally safe, but side-effects can occur. Your doctor should be notified if any of the following symptoms occur:

More common: Itching, headache

Less common: Nausea, vomiting, constipation, loss of appetite, dry mouth, muscle or bone pain, drowsiness, irregular heart beat, red eyes, increased urination

Rare: Weight loss

Side-effects can be reduced by following your doctors' instructions carefully.

Storing your One-Alpha

Oral Drops should be stored in its carton in your refrigerator (2-8°C) preferably on a lower shelf. Protect from direct sunlight.

Oral Capsules should be stored at room temperature (15-25°C) and protected from direct sunlight.

Keep away from children. One-Alpha contains enough medication to seriously harm a child.

Do not use One-Alpha after the expiry date indicated on the label.

PHARMACOLOGY

In normal and anephric rats given 6.25 - 62500 pmol 1α-OHD_3 and in the chick treated with 0.3-0.6 nmol 1α-OHD_3 , the stimulation of intestinal calcium transport and bone mobilization was between one-half and equal to that of 1,25-$(OH)_2D_3$. In both species, the conversion of 1α-OHD_3 to 1,25-$(OH)_2D_3$ has been demonstrated by the isolation of radioactive 1,25-$(OH)_2D_3$ after administration of labelled 1α-OHD_3 . Further studies on the transformation have demonstrated 25-hydroxylation in the liver homogenates from both the rat and the chick and also in intestinal mucosa from the chick. Whereas the hepatic 25-hydroxylation of vitamin D_3 is feedback regulated, the corresponding conversion of 1α-OHD_3 to 1,25-$(OH)_2D_3$ seems to be quantitative.

The 25-hydroxylation of 1 α -OHD_3 in the liver occurs very rapidly. Vitamin D-deficient rats were dosed with the radio-labelled compound (a single dose of 0.125 mcg 1 α -OH(6-^{3}H)D_3 orally or i.v.). The intestinal calcium transport in orally dosed animals was noted after 4 hours and reached a maximum at 12 hours; in animals receiving the i.v. dose, there was insignificant intestinal calcium transport at 4 hours, but a maximal response was attained at 6 hours. Following both routes, a high level of transport was maintained for up to 96 hours. Intestinal tissue concentrations of 1,25-$(OH)_2$

(6-^{3}H)D_3 appeared rapidly, within 2 hours of either the i.v. or oral dose of 1 α -OH(6-^{3}H)D_3. These concentrations maximized by 4 hours at 310 and 250 pg/g following the oral and i.v. dose, respectively. Although intestinal levels of 1 α -25$(OH)_2D_3$ are similar following a single oral or i.v. dose of 1∝-OHD_3 , blood and bone concentrations are much lower in the orally dosed animals than in animals dosed parenterally.

Blood levels and intestinal absorption of both 1 α -OHD_3 and 1,25-$(OH)_2D_3$ have also been determined in chicks following the oral or i.v. administration of 0.125 mcg 1 α -OH(6-^{3}H)D_3 . As early as 1 hour after the i.v. injection, intestinal concentrations of 1,25-$(OH)_2$ (6-^{3}H)D_3 were noted, which maximized at 6 hours. In orally dosed animals, no 1,25-$(OH)_2$ (6-^{3}H)D_3 was measured at 1 hour, but at 4 hours the maximum concentration of 1.5 ng/g was reached which was 1.5 times higher than that reached after the i.v. dose. However, the i.v. dose yielded higher bone and blood concentrations than the oral dose.

These studies demonstrate that the transformation of 1 α -OHD_3 to 1,25-$(OH)_2D_3$ occurs rapidly enough to account for the biological response to 1 α -OHD_3 . Although it cannot be excluded that 1 α -OHD_3 may have a direct effect on the intestine when present at a relatively high concentration immediately after oral administration, it seems reasonable to conclude that it functions mainly after conversion to 1,25-$(OH)_2D_3$.

Apart from these effects, 1 α -OHD appears devoid of pharmacological action.

CLINICAL PHARMACOLOGY

Metabolism of Vitamin D and Its Therapeutic Implications

It is now generally agreed that vitamin D is itself biologically inactive and only expresses its physiological effects after undergoing two metabolic conversions. Before any physiological action can take place, vitamin D must first be hydroxylated at the 25 position in the liver to the metabolic intermediary 25-OHD_3 . Secondly, 25-OHD_3 undergoes a 1 α -hydroxylation in the kidney to the physiologically active metabolite, 1,25-dihydroxy-vitamin D_3 [1,25-$(OH)_2D_3$].

This final critical conversion in the kidney becomes impaired or blocked in patients with renal failure or disorders of calcium and phosphorus metabolism. Therefore, these patients respond poorly to

even high doses of vitamin D.

In man, ONE-ALPHA (alfacalcidol) is converted directly and rapidly to 1,25-$(OH)_2D_3$ in the liver, thereby totally bypassing the critical renal conversion. Impairment of the hepatic conversion of 1 α -OHD_3 to 1,25-$(OH)_2D_3$ is rare, even in the presence of liver abnormalities.

Pharmacodynamic Effects of 1∝-OHD_3

In patients with renal failure, 1-5 mcg/day of 1 α -OHD_3 increased intestinal calcium and phosphorus absorption in a dose-related manner. This effect was observed within 3 days of starting the drug and conversely, it was reversed within 3 days of its discontinuation.

In patients with nutritional osteomalacia, increases in calcium absorption were noted within 6 hours of giving 1 mcg 1 α -OHD_3 orally and usually peaked at 24 hours. 1 α -OHD_3 also produced increases in plasma inorganic phosphorus due to increased intestinal absorption and renal tubular reabsorption. This latter effect is a result of PTH suppression by 1 α -OHD_3 . The effect of the drug on calcium was about double its effect on phosphorus absorption.

Patients with chronic renal failure have shown increased serum calcium levels within 5 days of receiving oral 1 α -OHD_3 in a dose of 0.5 - 1.0 mcg/day. Serum calcium levels also increase during the first 4 weeks of treatment with intermittent (2-3 times weekly) intravenous 1 α -OHD_3 in a dose of 2.7-8.5 mcg/week. As serum calcium rose, PTH levels and alkaline phosphatase decreased toward normal.

Hypercalcemia has usually been observed with dosages exceeding 4 mcg/day. The appearance of hypercalcemia is predicated on the ease with which calcium is utilized for bone mineralization and on renal excretion. Thus, chronic renal failure is a condition which would dispose patients toward hypercalcemia; conversely, changes induced by 1 α -OHD_3 on the Ca X P product and on PTH secretion may also alter renal function, but in most patients with chronic renal failure, 1 α -OHD_3 has not adversely affected renal function.

A rise in plasma creatinine (or a fall in glomerular filtration rate) has been reported in children with renal failure who are treated with ONE-ALPHA. However, it is still unclear whether this response was due to the action of the drug or to increased creatinine production during growth.

The beneficial effects of ONE-ALPHA on the development of renal bone disease in pre-dialysis patients have been demonstrated in a large, randomized, placebo controlled study. Long-term administration of ONE-ALPHA (maximum dose of 1 mcg/day for up to 2 years) improved bone histology and halted the progression of changes in serum alkaline phosphatase activity and parathyroid hormone levels compared to placebo. Long-term administration of alfacalcidol proved to be well tolerated and had no adverse effect on renal function in patients for whom the dose was titrated to prevent persistent hypercalcemia. Although elevation of serum calcium was observed, marked hypercalcemia (> 3.00 mmol/L) was uncommon (4.5% of patients) and readily responded to decreases in drug dosage.

TOXICOLOGY

Acute Toxicity

Studies performed in mice and rats have revealed that 1 α -OHD_3 has an acute toxicity which is relatively low as compared to therapeutic doses. The following table illustrates the LD_{50} values obtained with both species: the discrepancy in the LD_{50} values reported by two centres are probably attributable to differences in the procedures followed in the two laboratories.

Mice died from 3 to 7 days after dosing by both routes of administration as a result of general calcification.

Rats treated orally with the drug showed progressive general deterioration and were highly emaciated at death. Autopsy revealed general calcification which was most pronounced in the kidneys.

LD Values Obtained with 1 α -Hydroxyvitamin D_3

SPECIES	ROUTE OF ADMINISTRATION	LD_{50} (mcg/kg)
Mice	Oral	490
Mice (Male)	Oral	476
Mice (Female)	Oral	440
Mice	I.V.	290
Mice (Male)	I.V.	71
Mice (Female)	I.V.	56
Rats	Oral	510
Rats (Male	Oral	340
Rats (Female)	Oral	720

Oral Subacute Toxicity

One study in rats showed that repeated dosing with up to 2.5 mcg/kg/day for 30 days did not cause any untoward effects. Higher doses resulted in hypercalcemia and metastatic calcification.

In another study, rats were dosed with 0.4, 2.0 and 10 mcg/kg/day of the drug for 7-8 weeks. From week 3 onwards, the animals showed signs of general deterioration, apathy and weight loss. Post-mortem examinations revealed a lighter colour and calcinosis in the kidneys in the highest dose group. In the other groups, there was a slight but dose-related calcinosis in the kidneys which was

more pronounced in the females than in the males.

Dogs were treated orally for 3 to 8 weeks with 1 α -OHD_3 in doses of 0.1, 0.4 and 3.2 mcg/kg/day. After 3 and 7 weeks respectively, dogs on the 3.2 mcg dose and dogs on the 0.4 mcg dose showed considerable deterioration with loss of appetite and weight, apathy and subnormal temperature. Post-mortems revealed slight muscular dehydration and reduced fat deposition. Females on 0.4 mcg/kg/day had scattered small foci of calcium deposits and groups of dilated tubules in the cortex and medulla; the male animals, however, showed only traces of calcium deposition. In all 4 dogs on the highest dose, focal groups of dilated tubules with flattened epithelium and interstitial fibrosis in the cortex and medulla of the kidney were observed. Scattered calcium deposits were present in the fundus of the stomach (mucosa and submucosa) and in the bronchi and alveoli and corresponding vessels. In the group of dogs (2 male and 2 female) treated with 0.1 mcg/kg, histopathology showed one case of calcium deposits in the renal medulla. No other untoward effects were noted in the low dose group.

Intravenous Subacute Toxicity

In a 6 week study in rats dosed with 0.1, 0.3 and 0.9 mcg/kg/d of 1 α -OHD_3, the only dose-effect relationship observed was for hemoglobinurea. Animals in the highest dose group exhibited cessation of growth followed by slight weight loss, languid behaviour, moderate reductions in food consumption, hypothermia, and pale mucous membranes. Pigmented corneal granulations were evident and post-mortem examinations showed weight reductions for the pituitary, ovaries and uterus. Renal tubule casts were also present and there was an increase in the intensity of renal microcalculi in females. In the control group receiving vehicle injections, there was slight hyperuremia and small increases in hemoglobinuria.

Sensitivity to vehicle injections was also noted in a 14 day tolerance study in beagle dogs. Dogs receiving high doses of vehicle (0.4 ml/kg) showed a slight degree of hemolysis immediately after injection which disappeared within 4 hours. In a 6 week study in dogs dosed with 0.01, 0.03, 0.09, and 0.18 mcg/kg/day of 1 α -OHD_3, effects were noted only in the highest dose group. Aside from increases in monocyte number, post-mortem examinations showed vascular calcification and dystrophic mineralization in the aorta and stomach. Kidneys had a firmer texture, the kidney cortex zone had a paler colour, tubules were dilated and had chronic inflammatory cell infiltration.

Chronic Toxicity

Rats were dosed orally with 0.2, 0.8 and 3.2 mcg/kg/day with 1 α -OHD_3 for 6 months. Increased serum levels of calcium were recorded in all groups from week 9 onwards; phosphate levels were increased in week 26 and there was a decrease in total protein with the two highest dose levels at the end of the study. Autopsy revealed soft tissue calcification in the kidneys, stomach and aorta with the intermediate and high dose levels. A slight increase in the incidence of calcinosis of the kidney was observed in the low dose group.

In a 6-month study in dogs, the initial oral doses of 1 α -OHD_3 were 0.05, 0.1 and 0.2 mcg/kg/day, but because of adverse effects on bodyweight and food consumption, dosing with 0.2 mcg/kg/day was stopped after 72 days. In some of these animals, dosing continued at 0.025 mcg/kg/day which allowed the animals to recover. Apart from the effects with the 0.2 mcg dose, there were no untoward clinical signs or effects on bodyweight or food consumption. The only macroscopic abnormality noted was enlarged spleens in the treated dogs. Two dogs which were sacrificed after the 0.2 mcg/kg dose and 2 other dogs on 0.1 mcg/kg showed areas of dilated basophilic tubules in the kidneys. One dog on 0.2 mcg/kg had numerous calcified foci in the lamina propria of the fundus and excessive muscle stiffness due to soft tissue calcification. Soft tissue calcification was also noted in a dog treated with 0.1 mcg/kg/day.

Teratogenic Studies

Studies were performed in rats and rabbits using daily doses of 0.1, 0.3 and 0.9 mcg/kg of 1 α -OHD_3. Parent animals dosed with the drug had a lower weight gain than undosed animals. Reduced litter size and lower weights of fetuses were recorded in rabbits at the intermediate and high dose levels, but no significant increase in the incidence of fetal malformations were noted.

The effect of 1 α -OHD_3 on the reproductive function in the rats was investigated using the same doses. At the highest dose level, the pregnancy rate, litter size and birth weights were significantly lower than in control animals, in both the original parent animals and offspring of the first generation. No other parameters were affected and no late effects of the drug were observed in any of the progeny.

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