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APPLICATION NUMBER: 021068 and 18044/S025

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Weber

OCT 8 1998

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA:	18-044
Compound:	Rocaltrol® (Calcitriol) Solution
Submission Date:	11/18/97
Sponsor:	Hoffmann-La Roche Inc. Nutley, New Jersey
Type of Submission:	Supplemental New Drug Application
Code:	1P
Reviewer:	Xiaoxiong Wei, Ph.D.

SYNOPSIS:

On November 18, 1997, Hoffmann-La Roche submitted supplemental NDA18-044 for Rocaltrol® solution, a synthetic analog of human Vitamin D to FDA for an indication of the treatment of secondary hyperparathyroidism in predialysis patients with chronic renal insufficiency. The proposed dosage range of Rocaltrol® is 0.25 to 0.5 µg/day for adults and patients over 3 years old, and 10-15 ng/kg/day for pediatric patients under 3 years old. The sponsor also is seeking for an approval for a new dosage formulation, Rocaltrol® solution, 1µg/ml. Rocaltrol® capsule was initially approved by the FDA in 1978 for the treatment of hypocalcemia and the resultant metabolic bone disease in patients undergoing chronic renal dialysis. The initial approved dosage range of Rocaltrol® is 0.25 to 1.0 µg/day for patients under hemodialysis. Rocaltrol® is currently supplied with soft gelatin capsules with two dose strengths, 0.25 µg and 0.5 µg. This supplement was submitted in response to the Agency requesting assistance in identification of approved drugs currently being used off label and for which literature is available to support the established off label use. Therefore, most studies except a bioequivalence study in this submission are from published research articles.

1 mcg/mL

Bioequivalence. Clinical trials of Rocaltrol® for supporting an indication for secondary hyperparathyroidism in predialysis patients have used both U.S. and European formulations. The sponsor demonstrated the bioequivalence between the proposed oral solution (1µg/ml), currently marketed European 0.25 µg capsules and the currently marketed U.S. 0.25 µg capsules.

Pharmacokinetics. Calcitriol is 99.9% bound to plasma proteins in human. The absolute bioavailability of Rocaltrol® is unknown in healthy volunteers. But it was reported to be 50% in patients under peritoneal dialysis and 100% in patients under hemodialysis. Single oral doses of calcitriol ranging from 0.25 to 0.5 µg produced peak plasma concentrations within _____ hours after administration in healthy subjects. Peak serum concentrations of calcitriol range from approximately _____ µg/mL above baseline levels (_____ µg/ml) for doses of 0.25 to 2 µg. However, dose proportional increases in serum calcitriol concentrations are observed for a dose range of 0.25-1.0 µg. The terminal elimination half-life for single doses of calcitriol is about _____ hours in healthy subjects. Endogenous synthesis and catabolism of calcitriol play a critical role in the pharmacokinetics of calcitriol. After multiple oral dosing, trough calcitriol serum concentrations fell below predose baseline values while its elimination half-life decreased by as much as 70%, suggesting that the synthesis of calcitriol is inhibited and its clearance induced following prolonged administration.

Population pharmacokinetics. Renal disease has been observed to increase the elimination half-life of calcitriol for 2 to 6 fold. The effect of liver disease on calcitriol has not been examined. No controlled studies examining the influence of gender and age on calcitriol pharmacokinetics have been conducted. No differences in baseline calcitriol serum concentrations are observed between men and women. Concentrations of calcitriol are observed in cord blood during pregnancy, and in milk from

lactating women. Following the administration of calcitriol to pediatric patients, serum concentrations of calcitriol are correlated with dose, corrected for body surface area.

Relationship of pharmacokinetics and pharmacodynamics. Although several studies have examined calcitriol's efficacy in various disease states, no clear relationship between calcitriol serum concentrations and drug efficacy has been observed. Urinary calcium excretion is commonly used as a pharmacodynamic response marker for calcitriol. Urinary calcium excretion correlates with serum concentration of calcitriol following 1-2 weeks' treatment but not after longer treatment.

Metabolism. Calcitriol is excreted primarily in the bile with smaller amounts in the urine. The synthesis and metabolism of calcitriol depend primarily on cytochrome P450 enzymes in the liver and kidney. Exogenous calcitriol inhibits endogenous synthesis and may expedite its own metabolism by inducing enzymes.

Drug-Drug Interactions. Cholestyramine may inhibit the absorption of Rocaltrol®. Thiazides are known to induce hypercalcemia through reduction in calcium excretion in urine and may trigger hypercalcemia when co-administered with Rocaltrol®. Prolonged usage of phenytoin is known to produce osteomalacia. Studies showed that the coadministration of phenytoin or phenobarbital with calcitriol will affect serum levels of 25(OH)D₃, not calcitriol, by inhibiting 25(OH) hydroxylase in the liver. Caution should be observed when giving Rocaltrol® to patients on digitalis since hypercalcemia in these patients may precipitate cardiac arrhythmias. Concomitant administration of Rocaltrol® and magnesium containing antacids to chronic dialysis patients may contribute to the development of hypermagnesemia. Although ketoconazole inhibits the main enzymes responsible for endogenous synthesis and metabolism of calcitriol, no in vivo studies between ketoconazole and exogenous calcitriol have been conducted.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 18-044 for Rocaltrol submitted on 11-18-97. The overall Human Pharmacokinetic Section is acceptable to OCPB provided the drug interaction section in proposed package insert is worked out between the Agency and the sponsor. The recommendation and labeling comments (p. 12) should be sent to the sponsor as appropriate.

/S/

Xiaoxiong Wei, Ph.D.
Division of Pharmaceutical Evaluation II
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RD initialed by Hae-Young Ahn, Ph.D., Team Leader 10/5/98

CPB Briefing on 10/08/98: Hunt, Selen, Uhl, Madani, Ahn, Wei.

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CC: NDA 18-044 (orig., 1 copy), HFD-510 (Weber, Colman), HFD-870 (Wei, Ahn, Hunt, M. Chen), HFD-850 (Lesko, Huang), CDR (Barbara Murphy).

CD: AP

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(Appendices and/or Attachments available from DPE-II upon request)

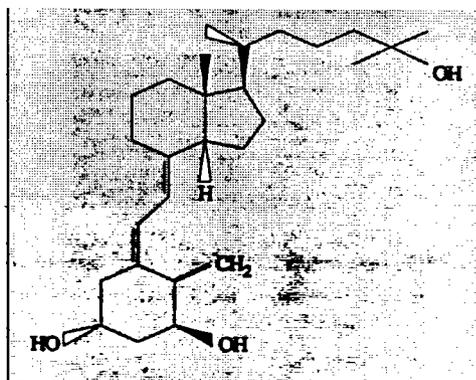
BACKGROUND:

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A. Physical and Chemical Properties:

Rocaltrol® is a synthetic Vitamin D analog, and its chemical name is 9,10-seco (5Z, 7E)-5,7,10(19)-cholestatriene-1 α , 3 β , 25-triol. It has a molecular weight of 416.65. Other designations for calcitriol include: 1 α , 25(OH)₂D₃; 1,25-DHCC; 1,25D-diOHC; 1,25-dihydroxycholecalciferol; and 5-dihydroxyvitamin D₃. Calcitriol is a colorless, crystalline compound that is sensitive to light and air, relatively insoluble in water, and soluble in organic solvents. Figure 1 illustrates the structure of calcitriol.

Figure 1. Structure of Calcitriol



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B. Clinical Uses

Approved Uses in the United States. Rocaltrol® was approved for the management of hypocalcemia and the resultant metabolic bone disease in patients undergoing chronic renal dialysis in 1978. In 1982, Rocaltrol® was approved for the management of hypocalcemia and its clinical manifestations in

patients with postsurgical hypoparathyroidism, idiopathic hypoparathyroidism and pseudohypoparathyroidism. In 1986, it was approved for the treatment of osteitis fibrosa cystica and defective bone mineralization in dialysis patients. In these patients, Rocaltrol administration enhances calcium absorption, reduces serum alkaline phosphatase levels, and may reduce elevated parathyroid hormone levels and the histological manifestations of osteitis fibrosa cystica and defective mineralization.

Other off-label uses: Calcitriol has been used for the treatment of many conditions characterized by abnormal changes in endogenous calcium levels. These disorders include postmenopausal osteoporosis (Dechant, 1994), renal osteodystrophy (Cano, 1995; Dahl, 1996), vitamin D-dependent rickets (Glorieux, 1990), hypophosphatemic vitamin D-resistant rickets (Petersen, 1992; Friedman, 1993) and psoriasis (Perez, 1996). The antiproliferative properties of calcitriol have stimulated clinical investigation of its use as an antineoplastic and immunomodulatory agent (Christakos, 1994; Feldman, 1995; Yu, 1995; Casteels, 1995).

DRUG FORMULATION:

Rocaltrol® was first marketed in the United States in 1978 as soft gelatin capsules containing 0.25 µg and 0.5 µg calcitriol. Rocaltrol® marketing in Europe was also started in 1978 with the introduction of a capsule formulation in Switzerland. A new, oral solution formulation (1 µg/ml) is proposed for approval in this submission. The three Rocaltrol formulations contain various percentages of excess calcitriol due to differences in manufacturing process. Manufacturing sites for U.S. and European capsules have not been changed since the initial marketing of Rocaltrol.

The quantitative composition of these formulations is listed under Table 1.

Table 1. Formulation of Rocaltrol

Component	Function	US Capsule 0.25 µg	[REDACTED]	US Solution (1 µg/ml) 0.25 µg/0.25 ml	US Capsule 0.5 µg
Calcitriol	Active substance	_____	_____	_____	_____
Butylated hydroxyanisole	Antioxidant	_____	_____	_____	_____
Butylated hydroxytoluene	Antioxidant	_____	_____	_____	_____
Fractionated coconut oil	_____	_____	_____	_____	_____
[REDACTED]	_____	_____	_____	_____	_____

* _____ overage

** _____ overage

*** _____ overage

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

I. Bioavailability/Bioequivalence

A. Absolute Bioavailability

Information on absolute bioavailability in healthy subjects is not available. Two studies in literature have evaluated the absolute bioavailability of calcitriol in patient populations. In peritoneal dialysis patients over a 24 hour period, an absolute bioavailability estimate of _____ was observed (Salusky, 1990). However, in a study of hemodialysis patients (Levine, 1996), calcitriol was administered with the 2nd and 8th dialysis period during a 3 week study period (3 dialyses per week). Comparisons of plasma concentrations of calcitriol after intravenous and oral doses of calcitriol showed that, although the AUC for the first hour was significantly higher following intravenous administration, there were no differences in the AUCs over the full 48-hour sampling period. The authors concluded that calcitriol demonstrated 100% bioavailability in hemodialysis patients.

B1. Bioequivalence

Clinical trials conducted to support the proposed indication for Rocaltrol in the treatment of secondary hyperparathyroidism in predialysis patients used both currently marketed U.S. and European capsule formulations. In support of the submission for the new oral solution formulation, and to facilitate the comparison of the European and U.S. marketed capsule formulations, a bioequivalence study of these three formulations was conducted by the sponsor (Oo, 1997). The study was an open-label, three period, multiple-dose crossover study in 30 healthy volunteers where 0.5 µg of calcitriol was administered twice daily for 14 days, with a 14-day washout between periods. In addition to standard pharmacokinetic parameters, pharmacodynamic responses (ie, 24-hour urinary calcium excretion, 24-hour urinary phosphorus excretion and serum parathyroid hormone level) were included in regimen comparisons. Based on the results of Schuirmann's two one-sided test procedure on the pharmacokinetic and pharmacodynamic parameters, the European capsule formulation and the new solution are bioequivalent to the U.S. capsule formulation. The mean pharmacokinetic and pharmacodynamic parameters are listed under Table 2 (Oo, 1997). The 90% confidence intervals of the ratios of the means (Regimen B versus Regimen A and Regimen C versus Regimen A) are summarized in Table 3.

Table 2. Summary of Multiple-Dose (14 day) Pharmacokinetic and Pharmacodynamic Parameters by Regimen (Mean ± SD)

Multiple-Dose Parameter	Regimen A U.S. Capsule	Regimen B European Capsule	Regimen C Solution
C_{max} (pg/mL)	71.3 ± 13.2	70.4 ± 15.9	65.4 ± 15.0
AUC _{0-24h} (pg·h/mL)	690 ± 154	664 ± 149	631 ± 165
24-h Urinary Calcium excretion (mg/24 hour)	388.5 ± 119.9	368.9 ± 104.6	357.1 ± 110.1
24-h Urinary Phosphorus excretion (mg/24 hour)	1015.0 ± 196.0	951.3 ± 143.3	984.7 ± 173.7
Serum Parathyroid Hormone (pmol/L)	2.2 ± 0.9	2.2 ± 1.1	2.3 ± 1.0

Table 3. The 90% Confidence Intervals of the Ratios of the Means:

Multiple-Dose Parameter	Regimen B /Regimen A	Regimen C /Regimen A
C_{max} (pg/mL)	0.92-1.04	0.85-0.97
AUC ₀₋₁₂ (pg·h/ml)	0.90-1.02	0.85-0.97
24-h Urinary Calcium excretion (mg/24 hour)	0.90-1.01	0.87-0.98
24-h Urinary Phosphorus excretion (mg/24 hour)	0.91-0.99	0.93-1.01
Serum Parathyroid Hormone (pmol/L)	0.91-1.09	0.95-1.14

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B2. Bioanalytical Assay

Rocaltrol® concentrations were determined by a specific receptor binding assay.

The percentage of cross-reactivity of the receptor supplied by the manufacturer is listed in Table 4 and the coefficient of variation for standards and quality control samples are listed in Table 5, and Table 6, respectively.

Table 4. Cross-Reactivity of Bioanalytical Assay

Steroid	% Cross-Reactivity
1,25-dihydroxyvitamin D2	100
1,25-dihydroxyvitamin D3	100
25-hydroxyvitamin D3	0.1
24,25-dihydroxyvitamin D3	<0.1
25,26-dihydroxyvitamin D3	<0.1

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Table 5. Inter-Day CV (%) for Standard Concentrations for Rocaltrol® Assay*

Standard (pg/ml)	7.5	10.0	25.0	37.5	50.0	75.0
CV	3.2-8.4	3.7-8.5	8.6-9.2	6.3-9.9	5.8-11.6	5.6-14.2

*Assay sensitivity limit: 7.5 pg/ml. Calibration range:

Table 6. Inter-Day CV (%) of Quality Control Samples for Rocaltrol® Assay

Standard (pg/ml)	57.3	37.2	16.8
CV	5.0-15.1	7.0-12.5	12.4-15.3

* Dilution factor used. All clinical samples were diluted three-fold prior to sample extraction.

II. Pharmacokinetics

a. Single Dose Administration

A summary of representative pharmacokinetic data for single-dose oral studies is provided in Table 7. Single oral doses of calcitriol ranging from _____ µg produced peak plasma concentrations within _____ after administration with an elimination half-life of _____ hours in healthy subjects. Peak serum concentrations of calcitriol range from approximately _____ pg/mL above baseline levels following doses of 0.25 to 2.0 µg (Blumenthal, 1980; Papapoulos, 1982; Nagant De Deuxchaisnes, 1991). Typically, serum levels of calcitriol return to baseline by approximately 24 hours. Significant increase in $T_{1/2}$ patient's population with chronic renal insufficiency was observed.

Table 7. Pharmacokinetics of Calcitriol after Single Oral Doses

Author (Reference)	Dose (µg)	Study Population*	Calcitriol baseline (pg/mL)	C _{max} (pg/mL)	t _{max} (hr)	t _{1/2} (hr)	Time to return to baseline (hr)
Bell et al. (1979a)	1.0, 5.0	32 healthy subjects	34 ± 1	-	3	5-6	24
Blumenthal et al. (1980)	1) 0.25 2) 0.5	6 healthy subjects (4 female, 2 male)			1) 6	-	24
Papapoulos et al. (1982)	2.0	1) 4 healthy males 2) 6 chronic renal failure patients	1) ~ 40 2) ≤ 8				-
Takahashi et al. (1993)	6.0	7 hemodialysis patients	-	155.2	6.2	23.4	-

+ Gender of subjects/patients provided if known.

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b. Multiple Dose Oral Administration

A summary of representative multiple dose studies from literature is shown in Table 8. In a study examining calcitriol pharmacokinetics in psoriasis patients, values for half-life and AUC were obtained after the first dose and after 6 months of calcitriol administration (Perez, 1993). Although values for baseline and C_{max} were not different, the half-life showed a dramatic decrease from _____ (p < 0.05) after 6 months dosing. Mean AUC values were also different (day 1: 5844 h.pg/mL, 6 months: 4072 h.pg/mL; Perez, 1993). Decreases in half-life were also observed in other studies for administration of calcitriol longer than 2 weeks (Odegaard, 1983, Levine, 1996). Rosen et al. (1977) studied pediatric patients with idiopathic hypoparathyroidism administered 0.4 to 0.5 µg calcitriol once daily. Following several months dosing, calcitriol serum concentrations fell far below predose baseline values. These changes in pharmacokinetics between single and chronic, oral dosing demonstrate the increase in calcitriol clearance which occurs with prolonged administration of calcitriol. A significant increase (2-6 fold) in half-life in patients with chronic renal insufficiency was observed (Levin, 1996).

Table 8. Pharmacokinetics of Calcitriol after Multiple Oral Doses

Author (Reference)	Dose (μg)	Study Population / # dosing days	Calcitriol baseline (pg/mL)	Cmax (pg/mL)	T _{1/2} Hours
Byrce (1980b)	1.) 0.25 BID 2.) 0.50 BID 3.) 1.0 BID	14 healthy subjects - 7 male, 7 female / 14 days dosing	1.) 45 2.) 39 3.) 46	1.) 59 2.) 77 3.) 85	3.5
Levine (1996)	1.) 2.0 / 1 st dose 2.) 2.0* / 2 nd dose	16 male chronic dialysis patients 2 study periods / 10 days apart	-	-	1.) 38 \pm 14 * 2.) 30 \pm 4
Perez (1993)	1.) 2.0 / 1 st dose 2.) 2.0 OD	6 psoriasis patients / 6 months daily dosing	1.) 36.5 2.) 24.3	1.) 123 2.) 137	1.) 8.6 2.) 2.8

* Gender of subjects/patients provided if known.

* Calcitriol administered twice 20 days apart, 1) 1st dose, 2) 2nd dose.

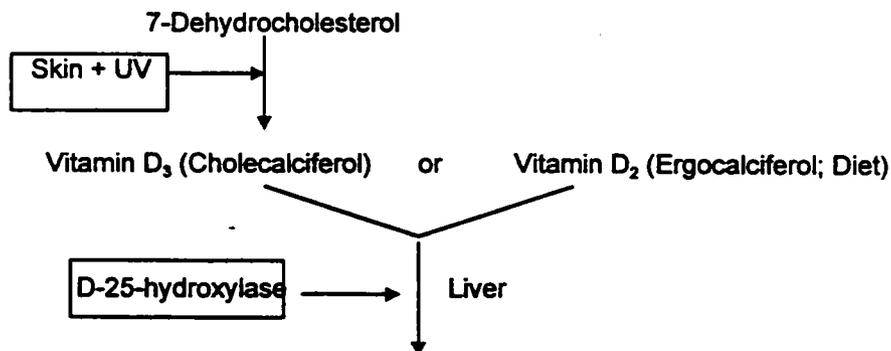
c. **Food Effects:** No food effects were studied.

III. Metabolism

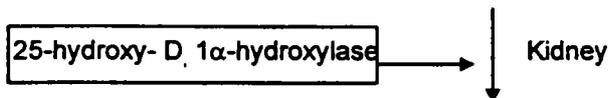
The endogenous synthesis and catabolism of calcitriol, as well as the physiological control mechanisms affecting these processes, play a critical role in the pharmacokinetics of calcitriol.

Calcitriol Synthesis. Calcitriol ($1\alpha, 25(\text{OH})_2\text{D}_3$) synthesis in vivo from either vitamin D_3 or vitamin D_2 requires 2 steps (Figure 2). The enzyme responsible for the first hydroxylation (D-25-hydroxylase) is a microsomal cytochrome P450 (CYP27) present in the liver. A second hydroxylation by 25-hydroxy-D, 1α -hydroxylase at the 1α position results in the production of calcitriol. Except during pregnancy, 1α -hydroxylation is restricted to mitochondria in the proximal convoluted tubules of the kidney. This second step in calcitriol synthesis (25-hydroxy-D, 1α -hydroxylation) is sensitive to feedback control from several sources. Elevated parathyroid hormone and low serum calcium and phosphate concentrations increase 1α -hydroxylation activity, while increased serum concentrations of calcitriol decreases 25-hydroxy-D, 1α -hydroxylase activity.

Figure 2. Synthesis of Calcitriol from Vitamin D:



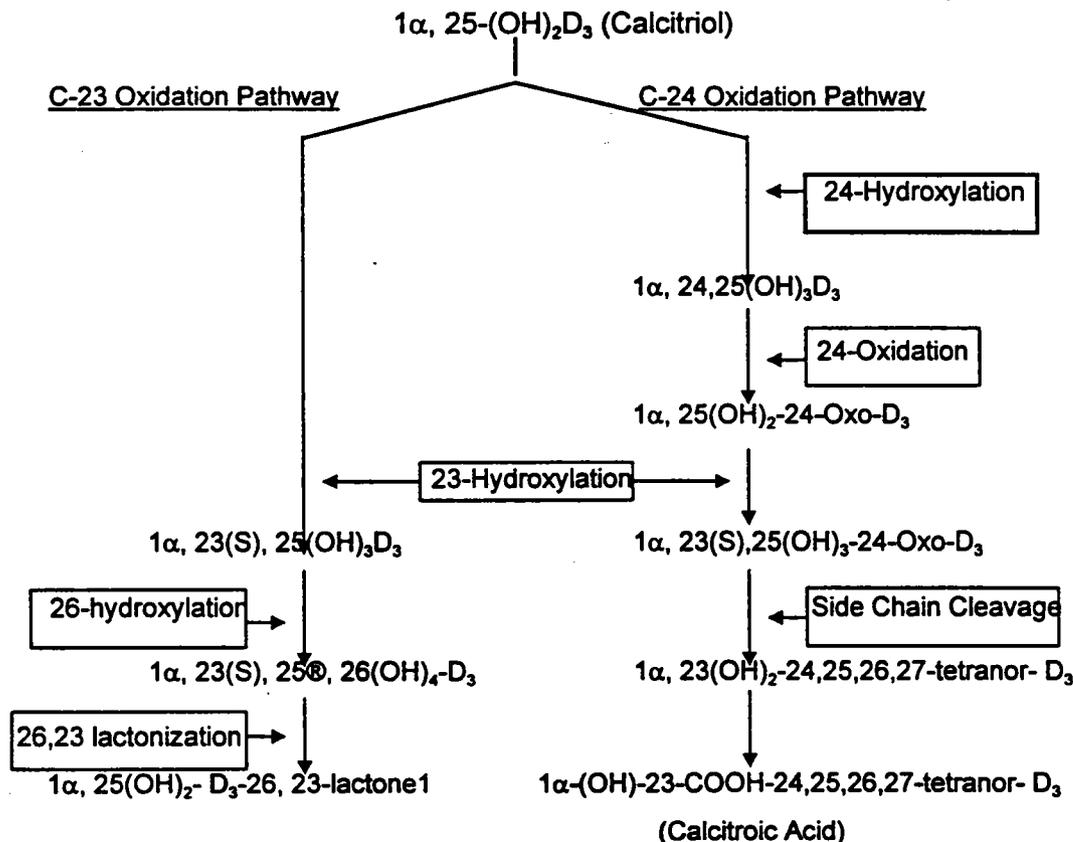
25 (OH) D₃ (Major vitamin D metabolite in circulation)



1α, 25-(OH)₂D₃ (Calcitriol)

Calcitriol Metabolism. Figure 3 shows the specific metabolic pathway of calcitriol from vitamin D₃ sources. A similar metabolic pathway is believed to exist for vitamin D₂.

Figure 3. Metabolism of Calcitriol:



A renal cytochrome P450, 1α, 25-dihydroxy-D, 24-hydroxylase identified as CYP24 has been linked to hydroxylation at the 24 position (Ohyama, 1991). The enzyme responsible for C-23 hydroxylation and the resulting lactone formation has not been fully resolved. However, recent work with a recombinant form of human 24-hydroxylase (CYP24) has demonstrated that this enzyme is capable of producing intermediates for both C-23 and C-24 pathways. Based on these findings, it is suggested that a single enzyme (CYP24) may be responsible for both C-23 and C-24 metabolic pathways. Unlike the 1α-hydroxylase enzyme responsible for calcitriol synthesis, which is normally restricted to the kidney, the 24-hydroxylase enzyme has been observed under basal metabolic conditions in human osteoblasts, kidney, keratinocytes and intestinal.

IV. Dose Proportionality

After single or multiple oral doses for a short duration (≤ 8 days), ranging from _____ μg per day, calcitriol concentrations were observed to increase with increasing doses of calcitriol (Blumenthal, 1980; Bryce, 1980a; Gray, 1980). In a 14-day multiple dose study of 0.25, 0.5 and 1.0 μg BID regimens, expected dose related increases were observed for the 0.25 and 0.5 μg BID dosages only. Calcitriol concentrations following the 1 μg BID dosage showed no clear increasing trend compared with concentrations following the 0.5 μg BID dose (Bryce, 1980b). As the elimination half-life of calcitriol decreases with multiple dosing, it is likely that self-induction of metabolism is contributed to the absence of dose-proportional increases in calcitriol concentrations.

V. Special Populations

Renal

The pharmacokinetics of calcitriol in disease states has been primarily studied in patients with renal failure. Comparing C_{max} concentrations following the oral administration of calcitriol, concentrations were highest in healthy subjects, followed by patients with nephrotic syndrome. The lowest C_{max} values were observed for hemodialysis patients (Ohno, 1982). In a study using tracer doses of ^3H -calcitriol administered intravenously, the production rate and clearance of calcitriol were compared in healthy subjects and chronic renal failure patients (Hsu, 1991). Both production rate and clearance rate were decreased in renal failure patients (Hsu, 1991). The elimination half-life of calcitriol has also been observed to increase in chronic renal failure and hemodialysis patients by at least 2 fold compared with healthy subjects receiving single oral doses of calcitriol (Ohno, 1982; Papapoulos, 1982). No evidence of deteriorating renal function has been observed in stabilized chronic renal failure patients administered calcitriol for periods of 4 or 12 months (Bertoli, 1990; Baker, 1980).

Hepatic:

No study has examined the pharmacokinetics of calcitriol in hepatic disease.

Age:

No studies have examined the pharmacokinetics of calcitriol in the elderly.

Gender:

Although pharmacokinetic studies have analyzed both healthy subjects and patients, no comparisons of calcitriol pharmacokinetics based on gender have been reported.

Pregnancy and Lactation:

Vitamin D binding protein increases in pregnant women (Haddad, 1976a; Bouillon, 1981). Calcitriol concentration measured in cord serum in a patient with hereditary insensitivity to calcitriol, who received exogenous calcitriol during pregnancy, was 470 pg/mL . The infant manifested mild hypercalcemia during the first 2 days of life, but the high concentrations of calcitriol in maternal serum throughout gestation was apparently not toxic to the fetus (Marx, 1980). Vitamin D metabolites have been measured in human breast milk. Concentrations of calcitriol in milk were low, about 10% of normal serum levels (Weisman, 1982).

Pediatric:

One study has reported T_{max} , C_{max} and the time for calcitriol concentrations to return to baseline after administration of 2 μg of calcitriol to pediatric patients (3 to 16 years) with chronic renal failure (Klaus, 1994). Peak serum concentrations of calcitriol were directly correlated to calcitriol dose when dose was corrected for body surface area (Klaus, 1994).

Table 9. Summary of Pharmacokinetic Studies in Renal Disease - Pediatric Patients

Reference	Drug	Dose/Route/ Duration	Design	Population	Objective	Results/Conclusion
Jones et al. (1994)	Calcitriol	0.01-0.02 µg OD/kg/PO/3 mo 0.01-0.02 µg OD/kg/PO/3 mo dose adjusted during study	1 mo run-in, MD, CO, no WO	9 pts (5M,2F)	To compare the PK of PO & IP calcitriol in children w/CRF.	T _{max} = 1.5 h for PO and IP dosing, T _{1/2} = 27.4 & 19.2 h respectively, Cl = 15.3 & 18.4 mL/h/kg, respectively.
Klaus et al. (1994)	Calcitriol	2µg OD/PO/1dose	SD	10 pts (6M, 4F)	To describe PO profile for calcitriol and assess the suppressive effect of calcitriol on 1,84iPTH conc and correlation with calcitriol peak serum conc in children w CRF (age: 3-16 yrs).	Calcitriol T _{max} = 3-12 h; C _{max} = 125 pg/mL, calcitriol returned to baseline by 48 h post dose. 1,84iPTH conc signif. suppressed by 6-72 h. Prolonged suppression not explained by PK of calcitriol

VI. Drug Interactions

Studies examining the potential for other drugs to affect calcitriol pharmacokinetics are restricted to observations of changes in endogenous calcitriol concentrations following drug administration, or after dietary restrictions of mineral intake.

No studies have directly examined the effect of cholestyramine on calcitriol. This drug is known to inhibit the absorption of vitamin D and other fat soluble vitamins, and it is possible that it may inhibit calcitriol absorption and therefore plasma concentrations could be decreased by concomitant use of cholestyramine (Matsui, 1982).

Hypercalcemia has been observed following administration of chlorothiazide, bendrofluazide, methylchlorothiazide and hydrochlorothiazide (Parfitt, 1969; Parfitt, 1972; Lemann, 1985). There is no evidence that thiazides alter calcitriol serum concentrations. Based on the findings of Sakhaee et al. (1993), thiazides induced hypercalcemia (Parfitt, 1969; Parfitt, 1972; Lemann, 1985) appears to be related to a reduction in urinary excretion of calcium.

Prolonged usage of phenytoin is known to produce osteomalacia (Cantu, 1987). Although serum concentrations of calcitriol remain unchanged or increased with phenytoin therapy, concentrations of its precursor 25-(OH)-D₃ are frequently decreased from normal values (Bell, 1979b; Cantu, 1987). Some studies showed that phenytoin inhibits 25-hydroxylase in liver (Tomita, 1991).

Reductions in serum levels of endogenous calcitriol have been observed following administration of ketoconazole doses of 300-1200 mg/day for 1 week to healthy men (Glass, 1986). At the highest dose (1200 mg/day), calcitriol concentrations were declined to 33% of baseline levels. In vitro studies have shown ketoconazole to be a competitive inhibitor of the 1α-hydroxylase responsible for calcitriol synthesis (Henry, 1985). Other studies suggest that the 24-hydroxylase important in calcitriol clearance is also inhibited by ketoconazole (Loose, 1983; Kan, 1985). However, in vivo drug interaction studies between exogenous calcitriol and ketoconazole have not been conducted.

No information is available showing that the pharmacokinetics of digitalis is altered by calcitriol administration. However, hypercalcemia resulting from calcitriol administration may reduce the tolerance of a patient to digitalis or provoke latent digitalis intoxication (Braunwald, 1987).

Magnesium-containing antacids and calcitriol should not be used concomitantly in patients on chronic renal dialysis, because such use may lead to the development of hypermagnesemia.

VII. Pharmacokinetic/Pharmacodynamic Relationships

In multiple dose calcitriol studies of 1 to 2 weeks duration, urinary excretion of calcium increased in relation to dose (Bryce, 1980a; Bryce, 1980b). However, different results with respect to serum calcitriol concentration and urinary excretion of calcium were observed with multiple dosing of calcitriol for prolonged usage. In a one year study which examined the effects of calcitriol in patients with moderate renal failure, serum calcitriol and urinary excretion of calcium and phosphorus were not significantly different between patients receiving placebo and patients treated with calcitriol for 1 year (Baker, 1989). However, serum phosphate and alkaline phosphatase concentrations were reduced. In addition, based on histologic evidence from transiliac crest bone biopsies, a significant amelioration of hyperparathyroid changes occurred (Baker, 1989). Another study compared calcitriol and 25(OH)D₃ concentrations in serum and bone from post-menopausal women with subcapetal fractures of the femurs (mean ± SD age of 78 ± 2 years), to concentrations in serum and bone from young cadavers. Serum concentrations of calcitriol were similar between groups, while bone concentrations of calcitriol were significantly reduced in post-menopausal women (Lidor, 1993). It is suggested that oral administration of calcitriol, which resulted in higher calcitriol concentrations locally in the intestine, could be responsible for the observed increases in calcium absorption (Francis, 1987). It is possible, therefore, that calcitriol concentrations at the site of action (ie, intestine, bone, etc.) are not correlated with total calcitriol concentrations in serum. Although free concentrations of calcitriol might correlate better with calcitriol concentrations at sites of action, the presence of endogenous control mechanisms which limit the magnitude and duration of changes in serum calcitriol appear to limit the ability to use serum calcitriol concentrations (total or free) as a meaningful guide to efficacy.

yes, /S/

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LABELING

Appendix 1. Draft labeling

Appendix 2. Study summaries

ROCALTRON REPORT
 Protocol NR15059 GCR N-136309, Module I/C. Oo. et al.

SYNOPSIS OF REPORT (PROTOCOL NR15059)

SPONSOR: Hoffmann-La Roche Inc.

INDICATION: Not applicable.

DRUG/TITLE OF THE STUDY A comparison of the bioavailability of the U.S. 0.25 µg capsule, the European 0.25 µg capsule, and a 1.0 µg/mL solution formulation of Rocaltrol® (calcitriol).

INVESTIGATOR: _____

PERIOD OF TRIAL: October 3 to December 18, 1995.

OBJECTIVE: To determine the bioequivalence between the European 0.25 µg Rocaltrol capsule and the 1.0 µg/mL new proposed solution formulation with the U.S. 0.25 µg Rocaltrol capsule.

STUDY DESIGN: Open-label, multiple-dose, randomized, three-period crossover study with a minimum 14-day washout period between regimens.

NUMBER OF VOLUNTEERS:

	<u>No. Evaluable</u>		<u>No. Withdrawn for Adverse Events</u>	<u>Deaths</u>
	<u>Safety</u>	<u>PK / PD</u>		
	30	29	1	0

DEMOGRAPHIC DATA:
 (All Volunteers Enrolled)

	<u>All Regimens (Safety)</u> N = 30	<u>All Regimens (Pharmacokinetics & Pharmacodynamics)</u> N = 29
Sex (M/F)	16/14	15/14
Age (yr) (Mean ± SD)	38.2 ± 15.22	38.8 ± 15.12
Range	_____	_____

ROCALTROL REPORT

Protocol NR15059 GCR N-136309, Module I/C, Oo, et al.

SYNOPSIS OF REPORT

Continued

TRIAL DRUG:	Rocaltrol 0.25 µg capsules
	Rocaltrol 0.25 µg capsules
	Rocaltrol 1.0 µg/mL solution

DOSE/ROUTE/REGIMEN:

Regimen A	Two 0.25 µg U.S. Rocaltrol capsules every 12 hours daily for 14 days.
Regimen B	Two 0.25 µg European Rocaltrol capsules every 12 hours daily for 14 days.
Regimen C	0.5 mL (0.5 µg) of 1 µg/mL new proposed Rocaltrol solution every 12 hours daily for 14 days.

ANALYTICAL METHODS:

Plasma concentrations of calcitriol were determined by a specific receptor binding assay procedure.

MAIN PARAMETERS:

EFFICACY:	None.
SAFETY:	Plasma and urine calcium, phosphate, creatinine, magnesium, and plasma PTH; adverse events; and hematology and plasma chemistry laboratory findings.
PHARMACOKINETICS:	Multiple-dose pharmacokinetic parameters: AUC_{0-12h}^* and C_{max}^* .
PHARMACODYNAMICS:	24-hour urinary calcium excretion, 24-hour urinary phosphorus excretion, and plasma PTH level.

PROCEDURE:

Thirty healthy volunteers participated in an open label, multiple-dose, randomized, three-period crossover study with a minimum 14-day washout period between regimens. Doses were administered on a fixed-time interval basis (every 12 hours for 14 days). Volunteers received the three dosage regimens described above, followed by blood sampling for determination of multiple-dose plasma calcitriol concentrations. Plasma concentrations of calcitriol were determined by a specific receptor binding assay procedure. Samples for pharmacodynamic assessment were collected at the end of each period for analysis. Baseline endogenous values of plasma calcitriol concentration, 24-hour urinary calcium excretion, 24-hour urinary phosphorus excretion and plasma PTH level were obtained from Day -3 to 1. Adverse events and were monitored throughout the study.

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ROCALTROL REPORT

Protocol NR15059 GCR N-136309, Module I/C. Oo, et al.

SYNOPSIS OF REPORT (Continued)

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS:

The calcitriol concentrations before and after Rocaltrol oral administration were highly variable. There was no accumulation of calcitriol after multiple-dose administration of Rocaltrol. Maximum calcitriol concentration (C_{max}^*) was about 50% higher than the baseline endogenous calcitriol concentration ($C_{baseline}$) [which occurred at 3-4 hours after dosing (T_{max})]. The terminal half-life of calcitriol could not be calculated because of a limited number of evaluable points at the terminal phase of the concentration-time profiles. Mean values of the primary pharmacokinetic parameters (C_{max}^* and AUC_{0-12h}^*) are summarized in the following table:

Summary of Pharmacokinetic Parameters by Regimen [Mean \pm SD (%CV)]

Pharmacokinetic Parameter	Regimen A	Regimen B	Regimen C
	(0.25 μ g)	(0.25 μ g) ^{ie}	(1 μ g/mL)
$C_{baseline}$ (pg/mL)	46.8 \pm 14.2 (30%)	44.6 \pm 11.4 (26%)	45.1 \pm 11.7 (26%)
C_{max}^* (pg/mL)	71.3 \pm 13.2 (19%)	70.4 \pm 15.9 (23%)	65.4 \pm 15.0 (23%)
AUC_{0-12h}^* (pg.h/mL)	690 \pm 154 (22%)	664 \pm 149 (22%)	631 \pm 165 (26%)

Similarly, the pharmacodynamic data before and after Rocaltrol oral administration were highly variable. Compared to baseline values, calcitriol increased the 24-h urinary calcium excretion and 24-h urinary phosphorus excretion by about 50% and 5%, respectively, while the plasma PTH level decreased by about 20%. The pharmacodynamic results are summarized in the following table:

Summary of Pharmacodynamic Parameters by Regimen [Mean \pm SD (%CV)]

Pharmacodynamic Parameter	Regimen A	Regimen B	Regimen C
	(0.25 μ g)	(0.25 μ g)	(1 μ g/mL)
Baseline Urinary Calcium (mg/24h)	202.8 \pm 113.4 (56%)	191.2 \pm 93.0 (49%)	189.7 \pm 96.7 (51%)
Urinary Calcium (mg/24h)	388.5 \pm 119.9 (31%)	368.9 \pm 104.6 (28%)	357.1 \pm 110.1 (31%)
Baseline Urinary Phosphorus (mg/24h)	924.7 \pm 202.0 (22%)	897.9 \pm 165.8 (18%)	932.8 \pm 182.8 (20%)
Urinary Phosphorus (mg/24h)	1015.0 \pm 196.0 (19%)	951.3 \pm 143.3 (15%)	984.7 \pm 173.7 (18%)
Baseline Plasma PTH level (pmol/L)	2.9 \pm 1.2 (41%)	2.6 \pm 1.2 (46%)	2.8 \pm 0.9 (32%)
Plasma PTH level (pmol/L)	2.2 \pm 0.9 (41%)	2.2 \pm 1.1 (50%)	2.3 \pm 1.0 (43%)

Analysis of variance for AUC_{0-12h}^* and analysis of covariance using baseline as a covariate for C_{max}^* , 24-hour urinary calcium excretion, 24-hour urinary phosphorus excretion and plasma PTH levels were performed. Carryover effects were not significant for any evaluated parameters (all p-values \geq 0.35). Period effect was statistically significant for the C_{max}^* , AUC_{0-12h}^* , 24-hour urinary phosphate excretion and plasma PTH level (all p-values \leq 0.04), but not for 24-hour urinary calcium excretion (p=0.63). The period effect was probably due to the effect of calcitriol homeostasis subsequent to Rocaltrol treatment, which persisted throughout the washout period. The two one-sided test procedure results showed that for the two primary pharmacokinetic parameters (ie, C_{max}^* and AUC_{0-12h}^*) and the three pharmacodynamic parameters (ie, 24-hour urinary calcium excretion, 24-hour urinary phosphorus excretion and plasma PTH level), Regimens B and C were bioequivalent to reference Regimen A (The 90% confidence intervals of the ratio of the means are 0.92-1.04; 0.90-1.02; 0.90-1.04; 0.91-0.99; 0.91-1.09 for Regimen B versus Regimen A, respectively; and 0.85-0.97; 0.85-0.97; 0.87-0.98; 0.93-1.01; 0.95-1.14 for Regimen C versus Regimen A, respectively.)

ROCALTROL REPORT

Protocol NR15059 GCR N-136309, Module I/C, Oo, et al

Rocaltrol was generally well tolerated. Most of the adverse events were mild in intensity; gastrointestinal complaints were the most common events of moderate intensity. Headache was reported in a high percent of volunteers. There were no clinically significant changes in plasma electrolytes, renal, hepatic, thyroid, or hematologic function related to the administration of Rocaltrol. No deaths occurred during this study. Prior to the third period, one subject (Volunteer 1) withdrew from the study due to serious adverse events (symptoms suggestive of nephrolithiasis, including moderate nausea and vomiting, mild abdominal discomfort, and severe abdominal colic); these symptoms resolved over the next two days. Although an abdominal sonogram revealed hydronephrosis, follow-up evaluation of this adverse event did not confirm the presumptive diagnosis of nephrolithiasis. There did not appear to be any differences among the three Rocaltrol formulations in the incidence or severity of adverse events.

Conclusion

The overall results indicate that the European Rocaltrol 0.25 µg capsule and the Rocaltrol solution (1 µg/mL) are bioequivalent to the U.S. Rocaltrol 0.25 µg capsule. The adverse event profiles of the three Rocaltrol formulations are unremarkable, and there did not appear to be any difference among the three formulations in the incidence or severity of adverse events.

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CLINICAL INVESTIGATION

1,25(OH)₂D₃ administration in moderate renal failure: A prospective double-blind trial

LAURENCE R.I. BAKER, S.M. LOUISE ABRAMS, CHRISTOPHER J. ROE, MARIE-CLAUDE FAUGERE, PAOLO FANTI, YAHYA SUBAYTI, and HARTMUT H. MALLUCHE

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1,25(OH)₂D₃ administration in moderate renal failure: A prospective double blind trial. (This study represents the first randomized prospective, double-blind, placebo-controlled trial of the efficacy of 1,25(OH)₂D₃ on bone histology and serum biochemistry in patients with mild to moderate renal failure. Sixteen patients with chronic renal impairment (creatinine clearance 20 to 59 ml per min) received either 1,25(OH)₂D₃ at a dose of 0.25 to 0.5 µg daily (eight patients), or placebo. Transiliac crest bone biopsies were performed before entrance into the study and after 12 months of experimental observation. None of the patients were symptomatic or had radiological evidence of bone disease. Of the thirteen patients who completed the study, initial serum 1,25(OH)₂D levels were low in seven patients and parathyroid hormone levels were elevated in seven patients. Bone histology was abnormal in all patients. 1,25(OH)₂D₃ treatment was associated with a significant fall in serum phosphorus and alkaline phosphatase concentrations as well as with histological evidence of an amelioration of hyperparathyroid changes. In contrast to previous reports, no deterioration of renal function attributable to the treatment occurred, perhaps because a modest dose of 1,25(OH)₂D₃ was employed combined with meticulous monitoring. Further investigation is required to determine whether alternative therapeutic strategies (smaller doses or intermittent therapy) may avoid the potential for suppressing bone turnover to abnormally low levels in the long term.

Bone disease and the need for parathyroid surgery continue to bedevil patients with chronic renal failure. Prevention of bone disease and hyperparathyroidism with vitamin D metabolites appears logical, but long-term placebo-controlled studies in patients with mild to moderate renal impairment are not available. The few published prospective placebo-controlled studies have involved patients with end-stage renal failure [1, 2]. Histological evidence of bone disease is present early in the evolution of chronic renal failure [3] as is evidence of reduced vitamin D effects on the target organs, bone and gut [4, 5]. Blood levels of 1,25(OH)₂D have been reported previously to be normal or high [6-8]. More recent reports indicate serum 1,25(OH)₂D levels to be low in mild to moderate renal impairment [9, 10] and to be inversely correlated with glomerular filtration rate [11]. These values must, however, be interpreted in the light of the biochemical derangements associated with

mild to moderate renal impairment, under which circumstance elevated serum levels of 1,25(OH)₂D would be appropriate [12].

It appears logical, therefore, to substitute 1,25(OH)₂D₃ in patients with mild to moderate renal impairment, but evidence is scant as to whether treatment with this agent at this early stage is of benefit. Treatment involves the risks of hypercalcemia, and it has been claimed [13] that an adverse effect upon renal function may occur even in the absence of hypercalcemia. Consequently, we have carried out a one year, double-blind placebo-controlled trial of 1,25(OH)₂D₃ in patients with mild to moderate renal impairment in an attempt to define whether a beneficial effect upon serum biochemistries and histological abnormalities can be obtained and, in particular, whether this can be achieved without any deleterious effects upon renal function.

Methods

Protocol

Sixteen subjects were recruited from the nephrology out-patient clinic at St. Bartholomew's Hospital. Patients with a creatinine clearance of 20 to 60 ml/min were eligible for the study. Exclusion criteria included: pregnancy, hypercalcemia, renal stones, poorly controlled hypertension, gastrointestinal or liver disease, urinary protein output greater than 3 g daily, psychosis, known tetracycline allergy, treatment with medication known to affect bone (anticonvulsants, heparin, corticosteroids) or vitamin D metabolites in pharmacological doses within the previous six months. Seventy-seven patients were screened, of whom 30 met the inclusion criteria. Sixteen agreed to take part in the study, and written informed consent was obtained. The study was approved by the St. Bartholomew's Hospital and Medical College Ethics Committee.

Three patients were withdrawn from the study: One, on active treatment, had a hypersensitivity reaction to tetracycline and was withdrawn within one week of starting the study; a second (on placebo), suffered a myocardial infarction at 40 weeks; in the third patient (on placebo) no satisfactory bone biopsy was obtained at 12 months. The results of these patients are not included. Individual patient data are shown in Table 1.

Patients continued with their usual antihypertensive medication throughout the study. One patient (Pat. #15) received thyroxine replacement and was clinically and biochemically

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EFFECTS OF PHARMACOLOGIC DOSES OF 1,25-DIHYDROXYVITAMIN D₃ ON SERUM CALCIUM, PARATHYROID HORMONE AND 1,25-DIHYDROXYVITAMIN D₃ IN MAN. K. H. Bell, P. C. Schaefer² and R. Goldsmith. Indiana University Medical School and VA Medical Center, Indianapolis, Indiana, and University of Texas Medical School and VA Medical Center, San Antonio, Texas.

Serum 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) was determined by radioimmunoassay (RIA) in normal subjects over the ensuing 24 hours after oral administration of 1 ug and 5 ug of the metabolite. Serum calcium (Ca) and parathyroid hormone (PTH) were measured by atomic absorption spectroscopy and RIA, respectively. Basal values in 32 normal subjects were 9.7 ± 0.1 mg/dl for serum Ca, 34.1 ± 1.4 pg/ml for serum 1,25(OH)₂D₃ and 216 ± 12 pg/ml for serum PTH (mean \pm SE). After an oral dose the maximal concentration of serum 1,25(OH)₂D₃ was at about 3 hours and the concentration declined exponentially thereafter. After subtraction of basal values half-life was from 5 to 6 hours independent of the dose, and baseline values were observed at 24 hours. Turnover was estimated from the formula $vT = aP$ where vT is the turnover (ug/day), a is the rate constant (0.693/T 1/2 in days) and P is the pool size (ug) based on assumptions that distribution of 1,25(OH)₂D₃ is in plasma and plasma is 5 percent of the body weight. In one normal subject, for example, vT was estimated to be 0.5 ug/day, a value well within the range (0.5 to 3 ug/day) of 1,25(OH)₂D₃ required to treat hypoparathyroidism. Increments of as much as 70 pg/ml and 267 pg/ml in serum 1,25(OH)₂D₃ with 1 and 5 ug doses, respectively, produced increases of about 1.5 mg/dl in serum Ca and measurable decreases in serum PTH. These results with pharmacologic doses of 1,25(OH)₂D₃ indicate a longer half-life than those determined with labeled 1,25(OH)₂D₃ and provide a new means to evaluate the metabolism of the hormone.

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REPORT NO. N- 34279

NUTLEY

AUTHOR(S): H. Peter Slumenthal, M.D.*, Graeme F. Bryce, Ph.D.⁺, John P. Mallon, Ph.D., and Cynthia Rogers-Phillips, R.N.*

DEPARTMENT: Clinical Pharmacology and ⁺Cell Biology and Experimental Biology

DATE: 10/10/80

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TITLE:

Serum concentrations of 1,25 (OH)₂-Vitamin D₃ after 0.25 and 0.5 µg of Rocaltrol® or no drug

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SUMMARY:

Six subjects participated in an incomplete crossover study. Four received both doses of Rocaltrol® while 2 received either 0.25 or 0.5 µg. Three subjects underwent a complete crossover with appropriate drug free intervals. The plasma samples were assayed by the working group of the Biochemical Nutrition Department. The procedure used is a competitive binding assay after chromatographic cleanup. The within- and between assay variance are 11 and 18% respectively.

Results were as follows:

- A. Within each leg of the study the early morning concentrations of 1,25 (OH)₂-D₃ of each subject were stable and in a range of 19 ± 6 to 45 ± 6 pg/ml (mean \pm standard deviation).
- B. Three of 5 subjects receiving 0.25 µg of Rocaltrol® reached a peak at 6 hours after administration increasing from 31, 33 and 36 pg/ml to 40, 45 and 57 pg/ml, respectively. After the 0.5 µg dose all plasma concentration time curves move upward with a peak at four hours in 4 of 5 subjects.
- C. The average curves adjusted for the individual baseline reading show increasing peaks associated with the increase of the dose from 0.25 to 0.5 µg.

CONCLUSIONS:

Administration of Rocaltrol® leads to an increase of serum 1,25 (OH)₂-D₃ concentration in healthy volunteers. The effect of 0.5 µg exceeds that of 0.25 µg.

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NUTLEY

REPORT NO. N- 32179

AUTHOR(S): Graeme F. Bryce, John P. Mallon and O.N. Miller

DEPARTMENT: Cell Biology and Experimental Biology

DATE: June 20, 1980

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ON ORIGINALTITLE: FURTHER STUDIES ON THE PHARMACOKINETICS AND TURNOVER OF
CALCITRIOL IN NORMAL MANAPPEARS THIS WAY
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SUMMARY: The pharmacokinetics and turnover of calcitriol have been studied in normal man. Doses of 0.25 μ g, 0.5 μ g and 1 μ g were given b.i.d. for durations of 2 weeks with 2 week control periods in between. A dose-related biological response was reflected in increases in urinary calcium excretion with the two higher doses. These changes accompanied elevations in the serum level of calcitriol; the steady-state levels attained after dosing with 0.5 or 1 μ g b.i.d. decayed to basal values upon cessation of drug with half-lives of about 3.5 hours. At no time throughout the study were there episodes of hypercalcemia. A crucial observation was that hydroxyproline excretion did not increase with treatment supporting the notion that the urinary calcium was dietary in origin. With a few minor exceptions, all parameters reflecting renal function or mineral homeostasis remained unchanged throughout the study attesting to the safety of extended administration of doses up to 1 μ g b.i.d.

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TWO YEARS 1,25(OH)₂ VIT D₃ TREATMENT IN POST-MENOPAUSAL OSTEOPOROSIS - EFFECT ON 25 OH VIT D AND 1,25(OH)₂ VIT D LEVELS IN SERUM. ¹⁴
O.R. Ødegaard, J.A. Falch, H.M.H. Frey,
J.O. Cordeladze, I. Matheson and U. Hennes

40 women with fracture of the distal forearm (mean age 62, range 57-65) were given 0.25 µg 1,25(OH)₂ Vit D₃ twice daily for two years. In 5, serum calcium concentration slightly exceeded 2.65 mmol/l, and the dose was therefore in these patients reduced to 0.25 µg daily.

The 1,25(OH)₂ Vit D and 25 OH Vit D levels were measured before start of the treatment and after one, six, 12 and 24 months. After one month, a significant increase in mean 1,25(OH)₂ Vit D value compared to the pretreatment mean value was found (37.0 ± 23.3 and 48.2 ± 17.8 pg/ml, respectively, p = 0.05). After six months, mean 1,25(OH)₂ Vit D level decreased, and significant differences compared to pretreatment values were not found during the next 24 months. The mean 25 OH Vit D and the mean calcium concentrations did not change significantly during the study.

The present results indicate that long term administration of 0.5 µg 1,25(OH)₂ Vit D₃ does not increase the mean serum concentration of 1,25(OH)₂ Vit D after six months of treatment in postmenopausal osteoporosis. It remains to be established if this is caused by decreased absorption, increased degradation or suppression of endogenous 1,25(OH)₂ Vit D production.

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