

Bon Secours Richmond
Pharmacy & Therapeutics Committees
Synthetic Vitamin D Analogs Used in Secondary Hyperparathyroidism
8/2004

Recommendations: MEC Approved RCH/MRMC/SMH

- Doxercalciferol (Hectorol) and paricalcitol (Zemplar) injection are therapeutically equivalent products. Hectorol injection cost 50% less than an equivalent dose of Zemplar injection. Pharmacy will stock and autosubstitute the most cost effective injectable product.
- At this time Hectorol injection is the most cost effective injectable product, therefore pharmacy will stock and autosubstitute Hectorol injection for Zemplar and Calcijex injection. Annual cost savings of \$14,915.04 will be realized by this conversion.
- Doxercalciferol (Hectorol) injection and oral are therapeutic equivalent products. Hectorol oral cost 40% of an equivalent dose of Hectorol injection. Pharmacy will autosubstitute oral Hectorol for injectable Hectorol, injectable Zemplar, and oral Zemplar at an equivalent dose in patients who can take oral medications.
- Calcitriol has an increased incidence of hypercalcemia and hyperphosphatemia when compared to doxercalciferol and paricalcitol. Calcitriol will remain on formulary as it is used to increase calcium in post parathyroidectomy patients.
- Cinacalcet is recommended for formulary inclusion for treatment of secondary hyperparathyroidism in patients with chronic kidney disease.
 - Cinacalcet (Sensipar) tablets are expensive, costing \$55-\$330.54 per week of therapy (30-180 mg once per day) versus \$28.35-\$113.43 for Hectorol injection (2-8 mcg three times a week) and \$11.07-\$44.16 for Hectorol oral (5-20 mcg orally three times a week).

Dosage Equivalence (mcg)				
Calcijex (calcitriol) Injection	Zemplar (paricalcitol) Injection	Zemplar (paricalcitol) Oral	Hectorol (doxercalciferol) Injection	Hectorol Oral (doxercalciferol)
0.75	2.5	4	1	2.5
1.5	5	8	2	5
2.25	7.5	10	3	7.5
3	10	14	4	10
3.75	12.5	18	5	12.5
4.5	15	20	6	15
5.25	17.5	24	7	17.5
6	20	28	8	20

Reference: K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease
1 mcg of doxercalciferol inj. is approximately equivalent to 2.5 mcg of paricalcitol inj. or 0.75 mcg calcitriol inj.

Findings:

Vitamin D Analogs

- Vitamin D analogs increase oral absorption of calcium and phosphate, increase tubular reabsorption of calcium by the kidneys, and in conjunction with PTH mobilize calcium from the skeleton.
- The kidneys filter about 10,000 mg of non-protein bound calcium per day, 98% is reabsorbed by the renal tubules.
- Kidney disease decreases 25-hydroxy D-1-alpha hydroxylase activity and causes a decrease in 1 alpha, 25-(OH)₂D₂ production and serum calcium which leads to secondary hyperparathyroidism.
- Hypocalcemia, reduced calcitriol synthesis, and elevated serum phosphorus levels stimulate the production of PTH (Parathyroid Hormone) and the proliferation of parathyroid cells, resulting in secondary hyperparathyroidism.
- PTH acts via a plasma membrane receptor and cyclic AMP, to increase osteoclastic bone resorption, to increase the renal tubular reabsorption of calcium and increase excretion of phosphate, and to increase 1,25-(OH)₂-D synthesis in the kidney. Normally the increase excretion of phosphate by the kidney is greater than increase absorption from the gut and bone resorption.
- PTH and calcium form a negative feedback pair. PTH is released in response to decreases in plasma calcium level. PTH synthesis and secretion are suppressed when calcium levels are high.
- Vitamin D is hydroxylated to 25-OH-D---which can undergo hydroxylation of the 1 position to 1,25(OH)₂D or the 24 position to 24,25(OH)₂D. The 1 position is preferred when calcium, phosphate and Vitamin D levels are low. The 1 position gives way to the biologic activity of Vitamin D. The 24 position is 1/20 as potent as 1,25 (OH)₂D
- Doxercalciferol and paricalcitol are synthetic vitamin D analogs (1,25(OH)₂D). Doxercalciferol undergoes metabolic activation to form a biologic active form of Vitamin D (1alpha,25-(OH)₂D₂).

- Doxercalciferol and paricalcitol act directly on osteoblasts to stimulate skeletal growth, and on the parathyroid gland to suppress PTH synthesis and secretion.
- Doxercalciferol and paricalcitol may increase serum phosphorus, calcium and [calcium x phosphorus] product.
- Hyperphosphatemia causes resistance to PTH suppressing effects of vitamin D analogs and directly stimulates PTH release and increase the risk of high $[Ca^{++} \times PO_4]$ product which can lead to soft tissue and vascular calcification
- Doxercalciferol capsules are not currently reimbursed by medicare.

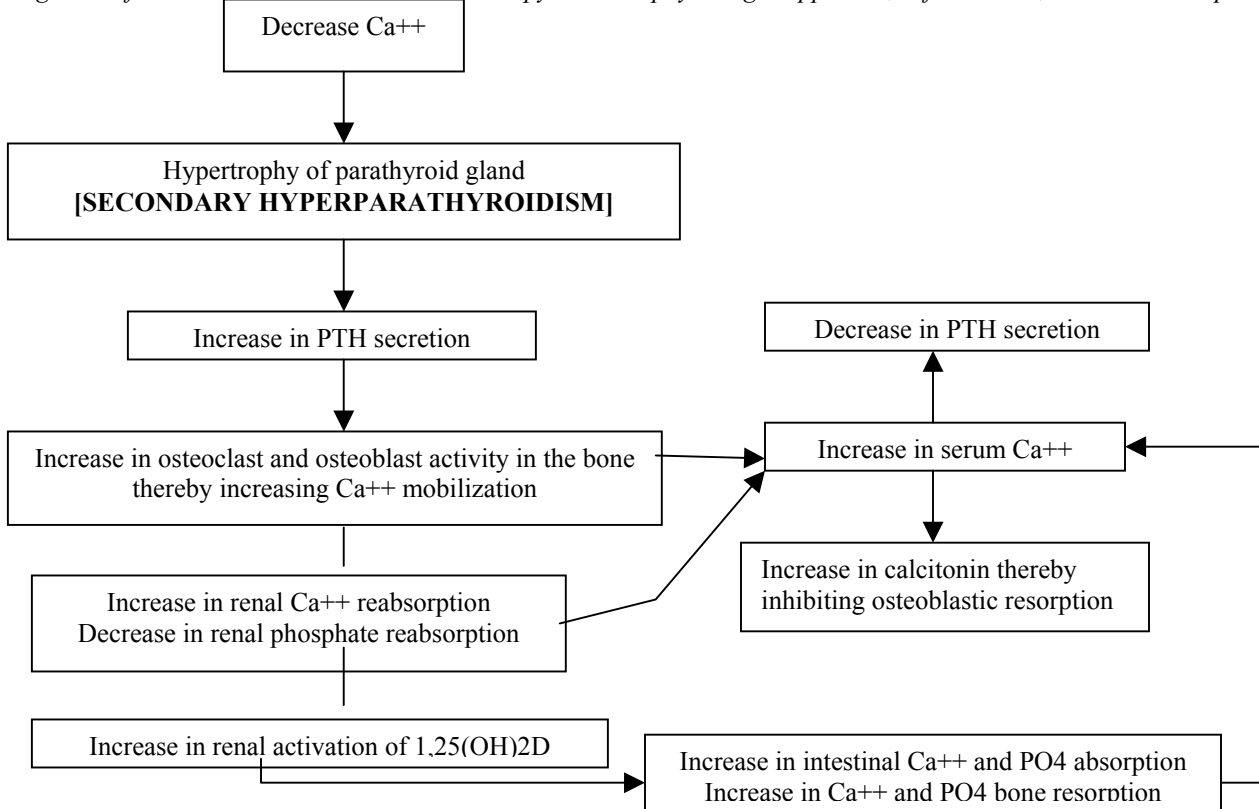
Calcimimetic Agents

- Cinacalcet is a calcimimetic agent that increases the sensitivity of calcium-sensing receptor of the chief cell in the parathyroid gland to activation by extracellular calcium and reduces PTH secretion.
- Cinacalcet is indicated for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease and treatment of hypercalcemia in patients with parathyroid carcinoma.
- Cinacalcet has not been studied as primary treatment for secondary hyperparathyroidism of CKD.
- Nausea and vomiting are the most common side effects.

Cost Analysis

Item Description	Units/ Package	Cost / Package	Cost/Unit	Ordered Quantity (Package) 01/01/04 to 05/31/04			Total Units	Total Cost
				Memorial Regional Medical Center	Richmond Community Hospital	St. Mary's Hospital		
Zemplar 5mcg/mL	25	\$506.54	\$20.26	9	4	10	575	\$11,650.42
Hectorol 4mcg/2ml amp	50	\$945.36	\$18.91	0	0	2	100	\$1,890.72
Hectorol 2mcg/ml amp	50	\$472.68	\$9.45	0	0	0	0	
						Total Units	675	
Potential Annual Cost Saving By Converting to Hectorol 2 mcm/ml 1 ml amps								\$14,915.04

Diagram Reference: *DiPiro, J.T. Pharmacotherapy: A Pathophysiologic Approach, Fifth Edition, 2002 McGraw p.965*



Data from Package Insert

	<u>Sensipar (Cinacalcet)</u>	<u>Zemplar (paricalcitol) injection</u>	<u>Hectorol (doxercalciferol) injection</u>
<u>Chemical Name</u>	Cinacalcet	19-nor-1,25dihydroxy vitamin D2	1alpha-hydroxy vitamin D2
<u>Indication</u>	Treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis Hypercalcemia in patients with parathyroid carcinoma.	Prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure in hemodialysis patients	Treatment of secondary hyperparathyroidism in patients with chronic kidney disease.
<u>How Supplied</u>		1mL vial (5mcg/mL) 5mcg \$20.26 2mL vial (5mcg/mL) 10mcg \$40.52	1 mL (2.0 mcg/ampule) \$9.45 2ml (4.0 mcg/ampule) \$18.90
	30 mg \$7.87 per tablet 60 mg \$15.74 per tablet 90 mg \$23.61 per tablet	1, 2, 4 mcg Capsule	2.5 mcg Capsule \$1.84
<u>Ingredients per mL of Injection</u>	NA	Paricalcitol 5mcg	Doxercalciferol - 2mcg
		Propylene glycol 30% (v/v)	Tween Polysorbate 20 – 4mg
		Alcohol 20% (v/v)	Sodium Chloride - 1.5mg
			Sodium ascorbate – 10mg
			Sodium phosphate dibasic – 7.6mg
			Sodium phosphate monophasic – 1.8 mg
			Sodium edetate – 1.1mg
<u>Molecular Weight</u>	394	416	412
<u>Bioavailability of Capsule</u>		72%	42%
<u>Administration</u>		IV bolus during dialysis	IV bolus at the end of dialysis
<u>Dose</u>		See package insert table	
<u>Pharmacokinetics</u>			
<u>Protein Binding</u>	95%	99.90%	No data
<u>Half Life</u>	30-40 hours, linear kinetics	14-15 hours (hemodialysis pt) 5-7 hours (healthy pt)	32 to 37 hours (all patients)
<u>Excretion</u>	15% feces as metabolites, 80% urine as metabolites	74% feces (59% metabolites), 16% urine (51% metabolites)	No data
<u>Volume of Distribution</u>	1000 liters	6L (hemodialysis patients) 17 to 25 L (healthy pt)	No Data

	<u>Sensipar (Cinacalcet)</u>	<u>Zemplar (paricalcitol) injection</u>	<u>Hectorol (doxercalciferol) injection</u>
<u>Mechanism of Action</u>	Cinacalcet is a calcimimetic agent that increases the sensitivity of calcium-sensing receptor of the chief cell in the parathyroid gland to activation by extracellular calcium and reduces PTH secretion.	<p>*Active Vitamin D metabolites control the intestinal absorption of dietary calcium, the tubular reabsorption of calcium by the kidney and, in conjunction with PTH, the mobilization of calcium from the skeleton.</p> <p>*Vitamin D metabolites act directly on osteoblasts to stimulate skeletal growth and on the parathyroid gland to suppress PTH synthesis and secretion.</p>	
<u>Laboratory Tests</u>	Serum iPTH, calcium, and phosphorus 1-4 weeks after initiation of dose adjustment. Monthly serum calcium and phosphorus, and iPTH every 1-3 months.	serum levels for iPTH, calcium and phosphorus should be determined prior to initiation of treatment and should be monitored weekly during the first 12 weeks of treatment	
<u>Contraindications</u>		patients with tendency towards hypercalcemia	

	<u>Sensipar (Cinacalcet)</u>	<u>Zemplar (paricalcitol) injection</u>	<u>Hectorol (doxercalciferol) injection</u>
<u>Warnings</u>	<p><i>Moderate to severe hepatic impairment increase the AUC by 2.4 and 4.2 times higher, respectively.</i></p> <p><i>Unaffected by renal insufficiency</i></p>	<p>*Excess doses can cause hypercalcemia, hypercalciuria, hyperphosphatemia, and over suppression of PTH secretion leading to adynamic bone disease</p> <p>*High intake of calcium and phosphate concomitant with Hectorol/Zemplar may lead to similar abnormalities.</p> <p>*Chronic hypercalcemia can lead to generalized vascular calcification and other soft tissue calcification.</p>	<p>*Serum calcium times serum phosphorus (Ca X P) product should not be allowed to exceed 70.</p> <p>*Pharmacologic doses of Vitamin D and its derivatives should be withheld during treatment to avoid possible additive effects.</p> <p><i>*Studies examining the influence of hepatic insufficiency on the metabolism of Hectorol were inconclusive. Patients with hepatic insufficiency may not metabolize doxercalciferol appropriately, the drug should be used with caution in patients with impaired hepatic function.</i></p>
<u>Drug Interactions</u> (specific interactions studies have not been conducted)	<p>Cinacalcet is a strong inhibitor of CYP2D6 (flecainide, vinblastine, thioridazine, tricyclic antidepressants)</p> <p>Ketoconazole increases cinacalcet AUC 2.3 fold, other CYP3A4 inhibitors are erythromycin, itraconazole</p>	<p>Digitalis toxicity is potentiated by hypercalcemia of any cause, caution should be applied when digitalis compounds are prescribed concomitantly with Zemplar.</p>	<p>*Magnesium-containing antacids and Hectorol should not be used concomitantly in patients on chronic renal dialysis because such use may lead to the development of hypermagnesemia.</p> <p>*Enzyme inducers may affect 25-hydroxylation of Hectorol and may require dosage adjustments (No data in package insert)</p>

Reference: K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease: Clinical Practice Guidelines :
Guideline 8 Table 28 ; http://www.kidney.org/professionals/kdoqi/guidelines_bone/Images/Table28L.jpg

Recommended Initial Dosing for Vitamin D Sterols by Serum Levels of Intact PTH, Calcium, Phosphorus, and Ca-P Product

				Calcitriol		Paricalcitol		Doxercalciferol	
Plasma PTH pg/mL or (pmol/L)	Serum Ca mg/mL (mmol/L)*	Serum P mg/ML (mmol/L)	Ca-P Product	Dose per HD	Cost (1 mcg/ml 1ml amp)	Dose per HD	Cost (5 mcg/ml 1ml amp)	Dose per HD	Cost (2 mcg/ml 1ml amp)
300-600 (33-66)	<9.5 (2.37)	<5.5 (1.78)	<55	IV: 0.5-1.5 mcg	\$21.81	2.5-5.0 mcg	\$20.26	IV: 2 mcg	\$9.45
				Oral: 0.5-1.5 mcg				Oral: 5 mcg	\$3.68
600-1000 (66-100)	<9.5 (2.37)	<5.5 (1.78)	<55	IV: 1.0-3.0 mcg	\$32.71	6.0-10 mcg	\$40.53	IV: 2-4 mcg	\$18.91
				Oral: 1-4 mcg				Oral: 5-10 mcg	\$7.36
>1000 (110)	<10.0 (2.50)	<5.5 (1.78)	<55	IV: 3.0-5.0 mcg	\$54.52	10-15 mcg	\$60.80	IV: 4-8 mcg	\$37.81
				Oral: 3-7mcg				Oral: 10-20 mcg	\$14.72

* Corrected serum Calcium = total calcium(mg/dl) + 0.8 x (4-serum albumin(g/dl))

Package Insert Dosing

Hectorol (doxercalciferol)	
Initial Dose	
> 400 pg/ml	4.0 mcg every other day at the end of dialysis
Dose Titration based on PTH Level	
>300 pg/mL AND has decreased by <50%	Increase by 1-2 mcg at 8 week intervals
150-300 pg/mL	Maintain
<100 pg/mL	Suspend for 1 week, resume at a dose at least 1.0 mcg lower
Max Dose	18 mcg weekly
Cinacalcet (Sensipar)	
Initial Dose	30 mg every day
Dose Titration based on PTH level	Measure in 1 to 4 weeks
150-300 pg/ml	Maintain
	Increase every 2-4 weeks through sequential doses of 60, 90,120,180 mg

Package Insert Dosing	Zemlar (paricalcitol) Injection	Zemlar (paricalcitol) Capsule
Initial Dose	2.8-7 mcg (0.04-0.1mcg/kg)	IPTH ≤ 500 pg/ml: 1 mcg daily or 2 mcg three times a week
	Every other day at anytime during dialysis	IPTH > 500 pg/ml: 2 mg daily or 4 mcg three times as week
Dose Titration based on PTH Level	(Adjust by 2-4 mcg per dose at 2 to 4 week intervals)	(Adjust dose at 2 to 4 week intervals)
Same or >	Increase dose	Increase by 1mcg/day or 2 mcg three times a week
Decreased by <30%	Increase dose	Increase by 1mcg/day or 2 mcg three times a week
Decreased by >30% but <60%	Maintain	Maintain
1.5 to 3 x Upper Limit of Normal	Maintain	
Decreased by >60%	Decrease dose	Decrease by 1 mcg/day or 2 mcg three times a week
IPTH < 60 pg/ml		Decrease by 1 mcg/day or 2 mcg three times a week
Max Dose	0.24 mcg/kg per dose	

Table 1. Effects of Sensipar™ on iPTH, Ca x P, Serum Calcium, and Serum Phosphorus in 6-month Phase 3 Studies (Patients on Dialysis)

	Study 1		Study 2		Study 3	
	Placebo (N = 205)	Sensipar™ (N = 205)	Placebo (N = 165)	Sensipar™ (N = 166)	Placebo (N = 101)	Sensipar™ (N = 294)
iPTH						
Baseline (pg/mL): Median	535	537	556	547	670	703
Mean (SD)	651 (398)	636 (341)	630 (317)	652 (372)	832 (486)	848 (685)
Evaluation Phase (pg/mL)	563	275	592	238	737	339
Median Percent Change	+3.8	-48.3	+8.4	-54.1	+2.3	-48.2
Patients Achieving Primary Endpoint (iPTH ≤ 250 pg/mL) (%) ^a	4%	41%**	7%	46%**	6%	35%**
Patients Achieving ≥ 30% Reduction in iPTH (%) ^a	11%	61%	12%	68%	10%	59%
Patients Achieving iPTH ≤ 250 pg/mL and Ca x P < 55 mg ² /dL ² (%)	1%	32%	5%	35%	5%	28%
Ca x P						
Baseline (mg ² /dL ²)	62	61	61	61	61	59
Evaluation Phase						48
Median Percent Change						-15.7

** p < 0.001 compared to placebo

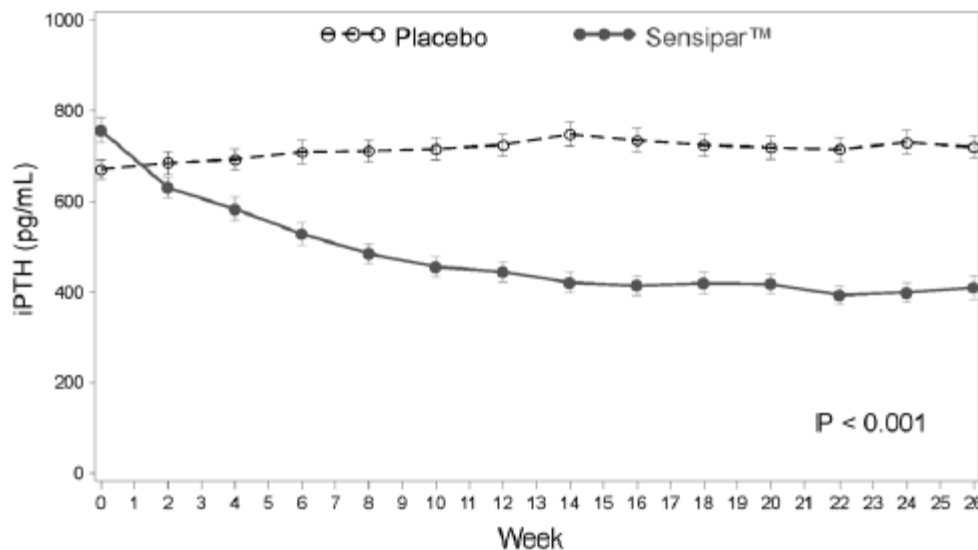
Table 1 (cont'd)

Calcium	
Baseline (mg/dL)	9.8
Evaluation Phase	9.1
Median Percent Change	-6.0
Phosphorus	
Baseline (mg/dL)	6.0
Evaluation Phase	5.3
Median Percent Change	-8.6

** p < 0.001 compared to placebo

^a iPTH value based on baseline values shown are n

Figure 1. Mean (SE) iPTH Values (Pooled Phase 3 Studies)

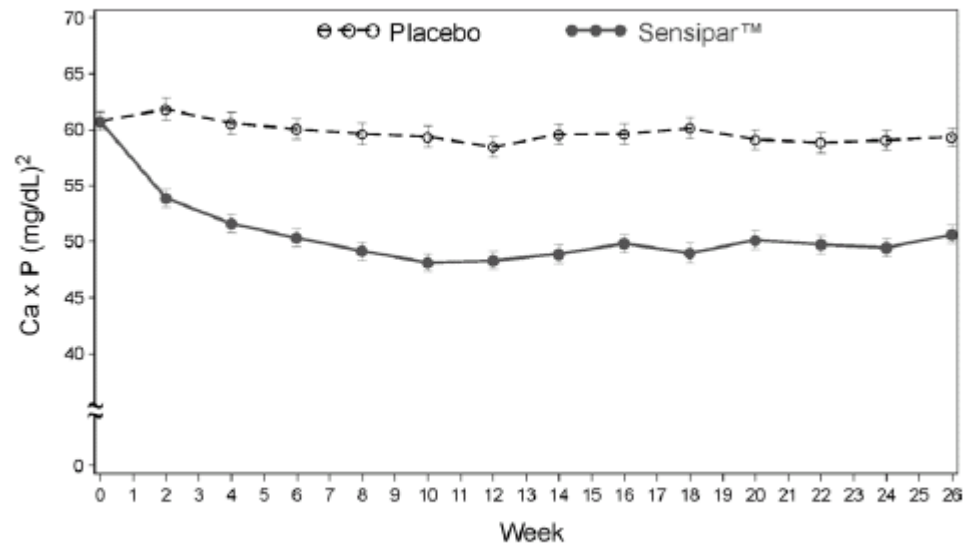


Data are presented for patients who completed the studies; Placebo (N = 342), Sensipar™ (N = 439).

Table 1 (cont'd)

Study 3	
Sensipar™ (N = 294)	
	9.8
	9.1
	-6.0
	6.0
	5.3
	-8.6

Figure 2. Mean (SE) Ca x P Values (Pooled Phase 3 Studies)



Data are presented for patients who completed the studies; Placebo (N = 342), Sensipar™ (N = 439).

Intermittent doxercalciferol (1alpha-hydroxyvitamin D(2)) therapy for secondary hyperparathyroidism.
Frazao JM, Elangovan L, Maung HM, Chesney RW, Acchiardo SR, Bower JD, Kelley BJ, Rodriguez HJ, Norris KC, Robertson JA, Levine BS, Goodman WG, Gentile D, Mazess RB, Kylo DM, Douglass LL, Bishop CW, Coburn JW.
 Medical and Research Services, Veterans Affairs West Los Angeles Healthcare Center, Los Angeles, CA, USA
 Am J Kidney Dis. 2000 Sep;36(3):550-61.

Hypercalcemia and hyperphosphatemia frequently necessitate vitamin D withdrawal in hemodialysis patients with secondary hyperparathyroidism. In short-term trials, doxercalciferol (1alpha-hydroxyvitamin D(2) [1alphaD(2)]) suppressed intact parathyroid hormone (iPTH) effectively with minimal increases in serum calcium and phosphorus (P) levels. This modified, double-blinded, controlled trial examined the efficacy and safety of 1alphaD(2) use in 138 hemodialysis patients with moderate to severe secondary hyperparathyroidism by using novel dose titration; 99 patients completed the study. Hemodialysis patients with secondary hyperparathyroidism were enrolled onto this study, consisting of washout (8 weeks), open-label 1alphaD(2) treatment (16 weeks), and randomized, double-blinded treatment with 1alphaD(2) or placebo (8 weeks). Oral 1alphaD(2) was administered at each hemodialysis session, with doses titrated to achieve target iPTH levels of 150 to 300 pg/mL. Baseline iPTH levels (897 +/- 52 [SE] pg/mL) decreased by 20% +/- 3.4% by week 1 ($P < 0.001$) and by 55% +/- 2.9% at week 16; iPTH levels returned to baseline during placebo treatment but remained suppressed with 1alphaD(2) treatment. In 80% of the patients, iPTH level decreased by 70%, reaching the target level in 83% of the patients. Grouping patients by entry iPTH level (<600, 600 to 1,200, and >1,200 pg/mL) showed rapid iPTH suppression in the group with the lowest level; greater doses and longer treatment were required in the group with the highest level. During open-label treatment, serum calcium and P levels were 9.2 +/- 0.84 (SD) to 9.7 +/- 1.05 mg/dL and 5.4 +/- 1.10 to 5.9 +/- 1.55 mg/dL, respectively. During double-blinded treatment, serum calcium levels were slightly greater with 1alphaD(2) than placebo, but P levels did not differ. During double-blinded treatment, 3.26% and 0.46% of serum calcium measurements exceeded 11.2 mg/dL with 1alphaD(2) and placebo, respectively ($P < 0.01$); median level was 11.6 mg/dL during hypercalcemia. Intermittent oral 1alphaD(2) therapy effectively suppresses iPTH in hemodialysis patients with secondary hyperparathyroidism, with acceptable mild hypercalcemia and hyperphosphatemia.

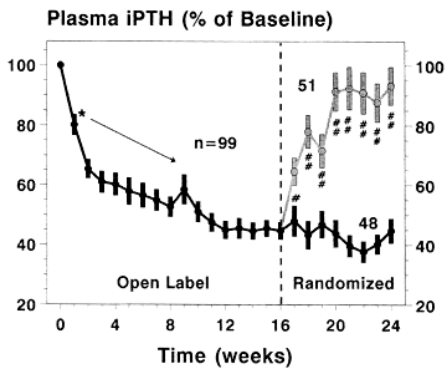


Figure 1. Changes in plasma iPTH values shown as percentage of baseline value (see text). All patients were administered 1alphaD₂ during open-label treatment; after week 16, they were randomized to either continued 1alphaD₂ treatment (dark line) or placebo (shaded line). Includes 99 patients completing 24 weeks per protocol. Data expressed as mean ± SE. Significantly different from baseline, * $P < 0.001$. Significant difference between placebo and 1alphaD₂ treatment, # $P < 0.01$, ## $P < 0.001$.

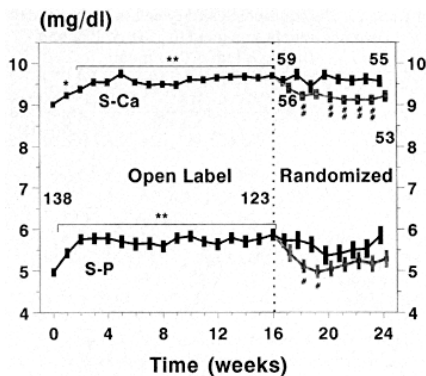


Figure 2. Values of serum calcium (S-Ca) and phosphorus (S-P) during open-label treatment with 1alphaD₂ and after patients were randomized to continued 1alphaD₂ treatment (dark line) or placebo (lighter shaded line). Includes all 138 patients (intent to treat) who entered open-label treatment; numbers indicate the number of patients at the various times of observation. Data expressed as mean ± SE. Significantly different from baseline (week 0), * $P < 0.01$, ** $P < 0.001$. Significant difference between placebo and 1alphaD₂ treatment, # $P < 0.05$; ## $P < 0.01$.

Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism.

Sprague SM, Llach F, Amdahl M, Taccetta C, Batlle D.

Division of Nephrology/Hypertension and Department of Medicine, Northwestern University Feinberg School of Medicine, Evanston, Illinois 60201, USA. ssprague@northwestern.edu

Kidney Int. 2003 Apr;63(4):1483-90.

BACKGROUND: Management of secondary hyperparathyroidism has included the use of active vitamin D or vitamin D analogs for the suppression of parathyroid hormone (PTH) secretion. Although, these agents are effective, therapy is frequently limited by hypercalcemia, hyperphosphatemia, and/or elevations in the calcium-phosphorus (Ca x P) product. In clinical studies, paricalcitol was shown to be effective at reducing PTH concentrations without causing significant hypercalcemia or hyperphosphatemia as compared to placebo. A comparative study was undertaken in order to determine whether paricalcitol provides a therapeutic advantage to calcitriol. **METHODS:** A double-blind, randomized, multicenter study comparing the safety and effectiveness of intravenous paricalcitol and calcitriol in suppressing PTH concentrations in hemodialysis patients was performed. A total of 263 randomized patients were enrolled at domestic and international sites. Following the baseline period, patients with serum Ca x P < 75, and a PTH level > or =300 pg/mL were randomly assigned to receive either paricalcitol or calcitriol in a dose-escalating fashion for up to 32 weeks. Dose adjustments were based on laboratory results for PTH, calcium, and Ca x P. The primary end point was the greater than 50% reduction in baseline PTH. Secondary end points were the occurrence of hypercalcemia and elevated Ca x P product. **RESULTS:** Paricalcitol-treated patients achieved a > or =50% reduction from baseline PTH significantly faster than did the calcitriol-treated patients (P = 0.025) and achieved a mean reduction of PTH into a desired therapeutic range (100 to 300 pg/mL) at approximately week 18, whereas the calcitriol-treated patients, as a group, were unable to achieve this range. Moreover, paricalcitol-treated patients had significantly fewer sustained episodes of hypercalcemia and/or increased Ca x P product than calcitriol patients (P = 0.008). **CONCLUSION:** Paricalcitol treatment reduced PTH concentrations more rapidly with fewer sustained episodes of hypercalcemia and increased Ca x P product than calcitriol therapy.

Efficacy and side effects of intermittent intravenous and oral doxercalciferol (1alpha-hydroxyvitamin D(2)) in dialysis patients with secondary hyperparathyroidism: a sequential comparison.

Maung HM, Elangovan L, Frazao JM, Bower JD, Kelley BJ, Acchiardo SR, Rodriguez HJ, Norris KC, Sigala JF, Rutkowski M, Robertson JA, Goodman WG, Levine BS, Chesney RW, Mazess RB, Kylo DM, Douglass LL, Bishop CW, Coburn JW.

Medical and Research Services, Veterans Affairs West Los Angeles Healthcare Center, USA.

Am J Kidney Dis. 2001 Mar;37(3):532-43

Most reports on the effectiveness and side effects of oral versus parenteral calcitriol or alfacalcidol in hemodialysis patients with secondary hyperparathyroidism show no advantage of parenteral treatment. The efficacy and safety of intravenous doxercalciferol (1alphaD(2)) were studied in hemodialysis patients with secondary hyperparathyroidism (plasma intact parathyroid hormone [iPTH]: range, 266 to 3,644 pg/mL; median, 707 pg/mL). These results were compared with those of a previous trial using intermittent oral 1alphaD(2); the same 70 patients were entered onto both trials, and 64 patients completed both trials per protocol. Twelve weeks of open-label treatment in both trials were preceded by identical 8-week washout periods. Degrees of iPTH suppression from baseline were similar in the two trials, with iPTH level reductions less than 50% in 89% and 78% of patients during oral and intravenous treatment, respectively. Grouping patients according to entry iPTH levels (<750 and >=750 pg/mL) showed similar but more rapid iPTH suppression in the low-iPTH groups, whereas longer treatment and larger doses were required by the high-iPTH groups. Highest serum calcium levels averaged 9.82 +/- 0.14 and 9.67 +/- 0.11 mg/dL during oral and intravenous 1alphaD(2) treatment, respectively (P: = not significant [NS]). Prevalences of serum calcium levels greater than 11.2 mg/dL during oral and intravenous treatment were 3.62% and 0.86% of calcium measurements, respectively (P: < 0.001). Highest serum phosphorus levels during oral and intravenous treatment averaged 5.82 +/- 0.21 and 5.60 +/- 0.21 mg/dL, respectively (P: = NS). The percentage of increments in serum phosphorus levels during oral treatment exceeded that during intravenous treatment during 5 of 12 treatment weeks. Thus, intermittent oral and intravenous therapy with 1alphaD(2) reduced iPTH levels effectively and similarly, hypercalcemia was less frequent, and serum phosphorus levels increased less during intravenous than oral 1alphaD(2) therapy, suggesting that intravenous 1alphaD(2) therapy may be advantageous in patients prone to hypercalcemia or hyperphosphatemia.

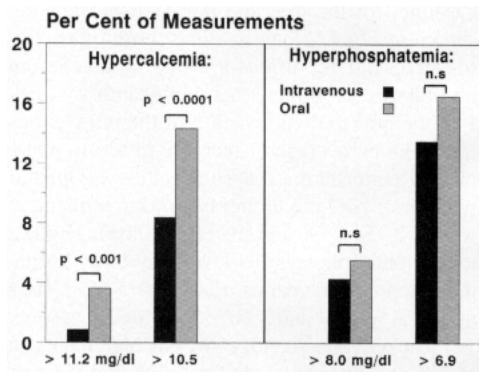


Figure 7. Prevalence of hypercalcemia and hyperphosphatemia, each defined by two separate levels, during oral and intravenous 1alphaD₂ treatment in 70 ITT patients. P values compare the prevalence between oral and intravenous treatment.

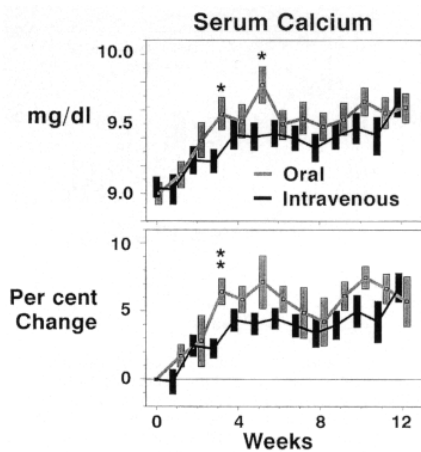


Figure 3. Serum calcium values shown as (top) measured levels and (bottom) percentage of change from baseline in 70 ITT patients. Data expressed as mean ± SE. *P < 0.05. **P < 0.01 for comparison of oral and intravenous trials.

Pharmacokinetics and efficacy of pulse oral versus intravenous calcitriol in hemodialysis patients.

Levine BS, Song M.

Department of Medicine, West Los Angeles VA Medical Center, CA 90073, USA.

J Am Soc Nephrol. 1996 Mar;7(3):488-96

Because intravenous (iv) calcitriol has greater bioavailability than oral calcitriol, it may be more efficacious in suppressing parathyroid hormone (PTH) secretion. In this study, the pharmacokinetics and efficacy of pulse oral and i.v. calcitriol were compared. Patients were randomized to receive 2 micrograms of i.v. or oral calcitriol after each dialysis. Two pharmacokinetic studies (PK1, PK2) were performed 10 days apart, during which the patients received calcitriol after each dialysis. Calcitriol bioavailability was determined from the area under the curve (AUC) time interval (hours) in pg/mL per h. After the PK phase, PTH was lowered to < 200 pg/mL by titrating calcitriol to a maximum of 12 micrograms/wk over 4 wk. Calcitriol was then maintained for another 18 wk unless serum calcium exceeded 11.5 mg/dL or Ca x P product exceeded 70; when these limits were reached, calcitriol was held and then restarted at a lower dose. After i.v. administration, peak serum calcitriol exceeded that achieved orally but by 1 h, calcitriol levels were similar. The AUC_{0-0.5} (105 +/- 12, i.v.; 9 +/- 4, oral) and AUC_{0.5-1} (68 +/- 6, i.v.; 30 +/- 7, oral) were higher with i.v. (P < 0.05), but cumulative AUC₀₋₄₈ did not differ. Individual t_{1/2} values ranged from 10 to 129 h for PK1 and from 10 to 50 h for PK2. The t_{1/2} for oral calcitriol was 38 +/- 14 h for PK1 and 30 +/- 4 h for PK2 (not significant (NS)). The t_{1/2} for i.v. calcitriol was 26 +/- 5 h for PK1 and 19 +/- 3 h for PK2 (NS, PK1 versus PK2 and oral versus i.v.). When the PK1 oral and i.v. data were combined, the mean t_{1/2} was 32 +/- 7 h whereas the t_{1/2} for PK2 (oral and i.v.) was 22 +/- 3 h (P < 0.05). Baseline PTH levels were 510 +/- 90 pg/mL and 499 +/- 79 pg/mL, oral and i.v., respectively. Serum PTH level at 22 wk was not different between oral and i.v. groups, 153 +/- 38 pg/mL and 214 +/- 124 pg/mL in i.v. (NS). The percentage of PTH suppression was 66 +/- 7.4% in the oral group and 69 +/- 12% in the i.v. group (NS). A major degree of serum iPTH suppression occurred during the initial 4 wk of treatment, concomitant with a rise in serum calcium levels. Adverse effects were similar between groups, as were the average dosages of calcitriol and phosphate binders. In conclusion, the efficacy of intravenous and pulse oral calcitriol were similar in hemodialysis patients with secondary hyperparathyroidism. The early rise in serum calcium levels observed with treatment may have contributed significantly to the suppression of serum iPTH levels. The difference in bio-availability between the different routes does not have a clinically apparent effect. The t_{1/2} varied widely among individuals, whereas exposure to calcitriol may decrease the t_{1/2}.

'Pulse oral' versus intravenous calcitriol therapy in chronic hemodialysis patients. A prospective and randomized study.

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Nephron. 1997;77(3):267-72

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The aim of this prospective and randomized study was to compare the efficacy, side effects, and costs of 'pulse oral' versus intravenous calcitriol in the treatment of secondary hyperparathyroidism in hemodialysis (HD) patients. A total of 20 patients were randomized to receive over a 4-month period pulse orally administered calcitriol (pulse oral group; n = 10) or intravenous calcitriol (intravenous group; n = 10). All patients used standard dialysate calcium (1.75 mmol/l) throughout the study period. In accordance with the study design calcium dialysate concentrations were reduced when this was necessary to avoid hypercalcemic crises. The patients were stratified into two subgroups according to their initial serum PTH levels: patients with mild or moderate degree of hyperparathyroidism (17 patients) and patients with severe hyperparathyroidism (3 patients). Intravenous and pulse oral calcitriol did not significantly reduce serum PTH concentrations in patients with severe hyperparathyroidism (1,157 +/- 156 vs. 807 +/- 228 pg/ml [corrected], p = 0.09). Intermittent calcitriol, administered by intravenous or oral route, significantly reduced serum PTH levels (326 +/- 119 vs. 109 +/- 79 pg/ml [corrected], p = 0.0001) in patients with mild or moderate hyperparathyroidism. In patients with mild or moderate hyperparathyroidism, intravenous calcitriol significantly reduced PTH concentrations at the end of the 1st month, before the increase of serum ionized calcium levels, whereas 'pulse oral' calcitriol significantly suppressed parathyroid activity at the end of the 2nd month. Calcium dialysate concentration was reduced in 9 out of 10 (90%) patients of the pulse oral group and in all patients (10/10) of intravenous group. The incidence of hypercalcemic crises was 24% (39/160) in the pulse oral group and 14% (27/160) in the intravenous group. Analysis of costs showed that intravenous calcitriol was more expensive compared to pulse oral calcitriol. These data indicate that intermittent intensive calcitriol therapy, regardless of the route of administration, is effective in suppressing parathyroid activity in HD patients with mild or moderate hyperparathyroidism. In contrast, intermittent calcitriol therapy has a limited ability to achieve sustained serum PTH reductions in HD patients with severe hyperparathyroidism. Intravenous calcitriol was more expensive than pulse oral calcitriol, and we recommend the use of pulse oral calcitriol in HD patients with mild or moderate secondary hyperparathyroidism.

Prospective trial of pulse oral versus intravenous calcitriol treatment of hyperparathyroidism in ESRD.

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Kidney Int. 1994 Jun;45(6):1710-21.

To examine the most effective route (intravenous vs. "pulse" oral), dose (physiologic vs. pharmacologic) and long-term efficacy of calcitriol therapy for secondary hyperparathyroidism in patients with end-stage renal disease (ESRD), we randomized 19 hemodialysis patients with severe hyperparathyroidism to receive over a 36-week study period either pulse orally administered calcitriol and intravenous placebo (pulse oral group; N = 9) or intravenous calcitriol and oral placebo (intravenous group; N = 10). Calcitriol was given intermittently in a double-blinded fashion at an initial dose of 2 micrograms thrice weekly and increased as tolerated up to a maximum dose of 4 micrograms per treatment. All patients received similar daily calcium supplementation (2.5 g of elemental calcium) and low dialysate calcium (1.25 mmol/liter) throughout the study period. At the maximum tolerated calcitriol dose, serum 1,25-dihydroxyvitamin D levels were significantly greater 60 minutes following intravenous (389 pmol/liter) compared to oral administration (128 pmol/liter). In spite of the different pharmacologic profiles, intravenous and oral administered calcitriol resulted in similar reductions of serum PTH over the 36 week period of observation (P = 0.300), achieving an overall maximum average PTH reduction of 43% (P = 0.016). Long-term intensive calcitriol therapy (independent of administration route), however, failed to decrease parathyroid gland size as assessed by high resolution ultrasound and/or magnetic resonance imaging. Calcitriol therapy also failed to alter the calcium sensitivity as assessed by serial PTH measurements in response to calcium loading. Increases in serum calcium, but not calcitriol dose or parathyroid gland size, predicted decrements in serum PTH, whereas hyperphosphatemia and the level of PTH suppression derived from the PTH/ionized calcium response curves predicted refractoriness to calcitriol therapy. Episodes of hypercalcemia and hyperphosphatemia were similar in both treatment groups and limited the dose of calcitriol that could be administered. These data indicate that intermittent intensive calcitriol therapy, regardless of administration route, is poorly tolerated, fails to correct parathyroid gland size and functional abnormalities, and has a limited ability to achieve sustained serum PTH reductions in end-stage renal failure patients with severe hyperparathyroidism.

Pulse oral calcitriol for the treatment of hyperparathyroidism in patients on continuous ambulatory peritoneal dialysis: preliminary observations.

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Am J Kidney Dis. 1992 Jun;19(6):540-5.

A direct effect of calcitriol on the regulation of the secretion of parathyroid hormone (PTH) has been shown in vitro and in vivo. In patients with renal failure on maintenance hemodialysis, it has been shown that intravenous (IV) administration of calcitriol appears to be superior to continuous oral administration. This may be due to the higher levels of calcitriol obtained in blood with consequent improved delivery of calcitriol to peripheral target tissues including the parathyroid glands. However, IV administration of calcitriol, is not practical for patients with end-stage renal disease (ESRD) who are maintained on continuous ambulatory peritoneal dialysis (CAPD). The present studies were designed to investigate whether intermittent administration of large doses of calcitriol orally ("pulse therapy") could mimic the effects of IV calcitriol in hemodialysis patients and achieve suppression of PTH secretion. Studies were performed in five patients who had been maintained on CAPD for more than 6 months. After basal determinations of calcium, phosphorus, and PTH, therapy was begun with calcitriol administered orally in a dose of 5 micrograms given twice per week. Calcium carbonate was continued as a phosphate binder. Dialysate calcium concentration was 1.75 mmol/L (3.5 mEq/L). With this therapy, PTH levels decreased rapidly, and, after 4 to 6 weeks of therapy, reached values 60% lower than pretreatment values. Mean values for serum calcium did not change significantly (2.29 +/- 0.12 mmol/L [9.6 +/- 0.5 mg/dL] before treatment compared with 2.32 +/- 0.08 mmol/L [9.7 +/- 0.25 mg/dL] after therapy). Mean serum phosphorus was also unchanged.(ABSTRACT TRUNCATED AT 250 WORDS)

Comparison of intermittent oral and intravenous calcitriol in hemodialysis patients with secondary hyperparathyroidism.

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Clin Nephrol. 1993 Oct;40(4):216-20.

Both intermittent intravenous and intermittent oral calcitriol have been shown to be effective in the treatment of secondary hyperparathyroidism in hemodialysis patients and it has been claimed that intravenous calcitriol causes less hypercalcemia. However, there has been no published systematic comparison of the two routes of administration of intermittent calcitriol. Therefore in a prospective crossover study 11 (9 male) patients on maintenance hemodialysis were randomized to receive intravenous followed by oral calcitriol for 4 months each, or oral followed by intravenous calcitriol, commencing at 2 micrograms postdialysis three times per week. Initial serum immunoreactive parathyroid hormone (PTH) was 446 +/- 111 (normal < 65) pg/ml. Calcium-containing phosphate binders were not used. Calcitriol was ceased if hypercalcemia developed and restarted at 2 micrograms or 1 microgram when calcium returned to normal. Hypercalcemia was frequent (11 episodes in 8 patients on intravenous calcitriol and 10 episodes in 7 patients on oral calcitriol) and dose reduction to 1 microgram was necessary in 7 patients on intravenous and on 6 patients on oral. Serum PTH fell during both treatments. Parathyroid enlargement was seen in 10 glands from 4 patients, but no size reduction was demonstrated with treatment. There was no reduction in activity on quantitative metabolic bone scan. In summary, intermittent oral calcitriol and intermittent intravenous calcitriol were equally effective in reducing serum parathyroid hormone levels and at a dose of 2 micrograms postdialysis caused hypercalcemia with equal frequency.

Effect of the mode of calcitriol administration on PTH-ionized calcium relationship in uraemic patients with secondary hyperparathyroidism.

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Nephrol Dial Transplant. 1995;10(5):665-70

To assess the effect of the different modes of calcitriol administration on PTH-ionized calcium relationship we conducted a prospective clinical trial in 33 patients on chronic haemodialysis with secondary hyperparathyroidism (four times upper normal limit intact PTH) who were randomly assigned, with stratification to PTH levels, to receive daily oral, intermittent oral, or intermittent intravenous calcitriol at the same dose of 0.045 micrograms/kg/weekly. PTH-iCa curves were generated by inducing hypo- or hypercalcaemia in sequential haemodialysis 1 week apart, before and after 10 weeks on treatment. All patients were dialysed against a dialysate calcium concentration of 2.5 mEq/l throughout the study period. After drop-outs, 26 patients completed the study: 11 on intravenous calcitriol (mean basal PTH +/- SD: 666 +/- 280 pg/ml), eight on intermittent oral calcitriol (mean basal PTH: 831 +/- 361), and seven on daily oral calcitriol (mean basal PTH: 719 +/- 280). Serum ionized calcium and phosphorus significantly increased in intravenous and daily oral groups after calcitriol treatment, but not in the intermittent oral group. Basal PTH did not significantly change in the three groups after 10 weeks on treatment. Maximal PTH significantly decreased in intravenous group (1449 +/- 660 versus 1122 +/- 691 pg/ml, P = 0.0085) and at the limit of statistical significance in the intermittent oral group (1701 +/- 774 versus 1445 +/- 634, P = 0.12), but it did not change in the daily oral group. Minimal PTH did not modify in the three groups. In all three groups, a shift to the right in the PTH-iCa relationships were observed, with significant changes in the set point of calcium.(ABSTRACT TRUNCATED AT 250 WORDS)

Calcitriol pulse therapy is not more effective than daily calcitriol therapy in controlling secondary hyperparathyroidism in children with chronic renal failure. European Study Group on Vitamin D in Children with Renal Failure.

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Pediatr Nephrol. 2000 Jul;14(7):664-8.

Calcitriol oral pulse therapy has been suggested as the treatment of choice for secondary hyperparathyroidism, but its efficacy and safety are still under discussion. The present randomized multicenter study compares the effect of an 8-week course of daily versus intermittent (twice weekly) calcitriol therapy on parathyroid hormone (PTH) suppression in 59 children (mean age 8.4 +/- 4.7 years) with chronic renal insufficiency (mean Ccr 22.4 +/- 11.6 ml/min per 1.73 m²) and secondary hyperparathyroidism. After a 3-week washout period, the patients were randomly assigned to treatment with daily oral calcitriol (10 ng/kg per day) or intermittent oral calcitriol (35 ng/kg given twice a week). The calcitriol dose was not changed throughout the study period of 8 weeks. At start of the study, the median intact PTH (iPTH) level was 485 pg/ml (range 83-2032) in the daily group (n=29) and 315 pg/ml (range 93-1638) in the intermittent group (n=30). After 8 weeks, the respective median iPTH concentrations were 232 pg/ml (range 63-1614) and 218 pg/ml (range 2-1785) (ns). The mean iPTH decrease from baseline was 19.2 +/- 57.8% and 13.7 +/- 46.7% respectively (not significant). Calcitriol reduced the iPTH concentration in 23/29 patients in the daily group and in 21/30 in the intermittent group. One episode of hypercalcemia (>11.5 mg/dl) was observed in both groups and a single episode of hyperphosphatemia (>7.5 mg/dl) was observed in the daily group. It is concluded that oral calcitriol pulse therapy does not control secondary hyperparathyroidism more effectively than

the daily administration of calcitriol in children with chronic renal failure prior to dialysis.

Safety and efficacy of pulse and daily calcitriol in patients on CAPD: a randomized trial.

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Nephrol Dial Transplant. 1998 May;13(5):1234-41.

BACKGROUND: Calcitriol therapy is the mainstay of therapy for the treatment of secondary hyperparathyroidism. Oral administration of calcitriol is necessary in CAPD patients, but no studies have directly compared different routes of administration in this patient population. **METHODS:** To determine if the peak serum calcitriol level (pulse therapy) is more important than the total delivered dose, we randomized CAPD patients with mild to moderate secondary hyperparathyroidism to receive either pulse (3.0 microg twice a week, n = 10) or daily (0.75 microg a day, n = 8) oral calcitriol in comparable weekly doses. The main comparison was the rate of decline of serum intact parathyroid hormone (PTH) levels to reach the desired end-point of 100 pg/ml. The patients were dialysed with low-calcium dialysate and received only calcium-containing phosphate binders. **RESULTS:** Pharmacokinetic analysis after a single dose of 3.0 microg (pulse) vs 0.75 microg (daily) revealed 1,25(OH)₂-vitamin D levels to be higher in the pulse group at 3 and 6 h, but equivalent by 12 h. The area under the curve for 1 week of daily and 1 week of pulse therapy was equal. The patients in the 2 arms had equivalent basal serum levels of PTH (pulse = 562 +/- 291 vs daily = 454 +/- 113 pg/ml), calcium (pulse = 2.32 +/- 0.20 vs daily = 2.32 +/- 0.12 mmol/l) and phosphorus (pulse = 1.32 +/- 0.52 vs daily = 1.35 +/- 0.26 mmol/l). The time required for the PTH to decrease to 100 pg/ml and the rate of decline in PTH were similar (time: pulse = 14.2 +/- 6.8 weeks, daily = 12.2 +/- 7 weeks; rate: pulse = 7.4 +/- 4.2 vs daily = 8.4 +/- 4.2% PTH/week; P = NS). The serum calcium increased similarly in both groups. Hypercalcaemia (> 2.9 mmol/l) was rare (pulse = 3, daily = 2 episodes). **CONCLUSIONS:** This study demonstrates that pulse and daily calcitriol are similarly effective and safe for the treatment of mild to moderate secondary hyperparathyroidism in CAPD patients despite higher peak levels of 1,25(OH)₂-vitamin D with pulse therapy.

Efficacy and side effects of intermittent intravenous and oral doxercalciferol (1alpha-hydroxyvitamin D(2)) in dialysis patients with secondary hyperparathyroidism: a sequential comparison.

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Am J Kidney Dis. 2001 Mar;37(3):532-43

Most reports on the effectiveness and side effects of oral versus parenteral calcitriol or alfacalcidol in hemodialysis patients with secondary hyperparathyroidism show no advantage of parenteral treatment. The efficacy and safety of intravenous doxercalciferol (1alphaD(2)) were studied in hemodialysis patients with secondary hyperparathyroidism (plasma intact parathyroid hormone [iPTH]: range, 266 to 3,644 pg/mL; median, 707 pg/mL). These results were compared with those of a previous trial using intermittent oral 1alphaD(2); the same 70 patients were entered onto both trials, and 64 patients completed both trials per protocol. Twelve weeks of open-label treatment in both trials were preceded by identical 8-week washout periods. Degrees of iPTH suppression from baseline were similar in the two trials, with iPTH level reductions less than 50% in 89% and 78% of patients during oral and intravenous treatment, respectively. Grouping patients according to entry iPTH levels (<750 and >=750 pg/mL) showed similar but more rapid iPTH suppression in the low-iPTH groups, whereas longer treatment and larger doses were required by the high-iPTH groups. Highest serum calcium levels averaged 9.82 +/- 0.14 and 9.67 +/- 0.11 mg/dL during oral and intravenous 1alphaD(2) treatment, respectively (P = not significant [NS]). Prevalences of serum calcium levels greater than 11.2 mg/dL during oral and intravenous treatment were 3.62% and 0.86% of calcium measurements, respectively (P < 0.001). Highest serum phosphorus levels during oral and intravenous treatment averaged 5.82 +/- 0.21 and 5.60 +/- 0.21 mg/dL, respectively (P = NS). The percentage of increments in serum phosphorus levels during oral treatment exceeded that during intravenous treatment during 5 of 12 treatment weeks. Thus, intermittent oral and intravenous therapy with 1alphaD(2) reduced iPTH levels effectively and similarly, hypercalcemia was less frequent, and serum phosphorus levels increased less during intravenous than oral 1alphaD(2) therapy, suggesting that intravenous 1alphaD(2) therapy may be advantageous in patients prone to hypercalcemia or hyperphosphatemia.

Comparative effect of oral pulse and intravenous calcitriol treatment in hemodialysis patients: the effect on serum IL-1 and IL-6 levels and bone mineral density.

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Nephron. 2002 Feb;90(2):188-94.

INTRODUCTION: Increased serum levels of bone-resorptive cytokines such as interleukin-1 beta (IL-1 beta) and interleukin-6 (IL-6) have been implicated for changes in bone remodeling in hemodialysis patients. In this prospective randomized study, we aimed to compare the effect of oral and intravenous (IV) pulse calcitriol on serum levels of IL-1 beta and IL-6. **PATIENTS AND METHODS:** Twenty-eight hemodialysis patients were included and consecutively randomized to receive either oral (n = 14, M/F = 7/7, mean age 42 +/- 15 years) or IV pulse (n = 14, M/F = 6/8, mean age 38 +/- 14 years) calcitriol treatment. No difference was found between

groups for age, sex distribution, primary renal disease, mean time on hemodialysis and baseline biochemical parameters including serum levels of IL-1 beta and IL-6. RESULTS: The percent fall of intact parathyroid hormone (iPTH) was significantly less with oral compared to IV calcitriol between 0 and the 3rd month (32 +/- 21 vs. 56 +/- 28%, p = 0.03). However, the percent fall in iPTH at the 6th month of the therapy was not different in the oral group compared to the IV group (57 +/- 22 vs. 73 +/- 24%, p = 0.12). The increase in bone mineral densities was higher in the IV group than the oral group. Oral and IV calcitriol caused a significant fall in IL-1 beta (p = 0.02 and p = 0.03, respectively) and IL-6 levels (p = 0.02 and p < 0.001, respectively) at the 6th month of treatment. The percent fall in serum IL-6 levels at the 6th month was significantly greater in the IV compared to the oral group (61 +/- 18 vs. 36 +/- 33%, p = 0.04), while the percent changes in serum IL-1 beta levels were similar. CONCLUSION: IV calcitriol therapy has a greater suppression of PTH at the 3rd month of the therapy. Despite no difference in serum PTH levels at the 6th month, IV therapy has a greater increase in bone mineral densities and a greater decrease in serum IL-6 levels. These findings suggest IV calcitriol treatment has a superior effect on bone remodeling by influencing the levels of bone-resorptive cytokines as compared to the oral therapy group, beyond its suppressive effect on iPTH. Copyright 2002 S. Karger AG, Basel

A crossover comparison of intermittent oral and intravenous administration of calcitriol on the parathyroid hormone concentration in hemodialysis patients.

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Miner Electrolyte Metab. 1997;23(1):13-8

Active vitamin D3 is used commonly in hemodialysis patients with severe secondary hyperparathyroidism. Intermittent pulse therapy with active vitamin D3, either orally or intravenously, has been proven to be effective with less hypercalcemic complication than daily oral vitamin D3. We therefore designed a three-phase crossover study to compare the effect of oral and intravenous calcitriol given by intermittent pulse therapy. Thirteen regular hemodialysis patients were enrolled. In phase 1, 1 microgram calcitriol was given orally at bedtime twice a week for 4 months, and then was stopped for 1 month to washout. In phase 2, 1 microgram calcitriol was given intravenously immediately after hemodialysis twice a week for 2 months, and then was stopped for 1 month to washout. Phase 3 repeated phase 1 but lasted for only 2 months. Calcium carbonate was given as the sole phosphate-binding agent if there was no severe hypercalcemia or hyperphosphatemia. Serum parathyroid hormone (PTH) levels decreased dramatically in all three phase therapies. As a result, mid-molecule PTH decreased from 5.71 +/- 2.65 to 3.97 +/- 2.92 ng/ml in phase 1 (p = 0.010), from 4.34 +/- 3.39 to 1.98 +/- 1.76 ng/ml in phase 2 (p = 0.007), and from 2.72 +/- 0.97 to 1.67 +/- 0.71 ng/ml in phase 3 (p = < 0.001). However, there was no difference in the calculation of the PTH declination among the three phases (32, 50 and 42%, respectively). The incidence of hypercalcemia was higher in using calcitriol than without it (23 vs. 6%, p < 0.05), but there was no difference between intravenous and oral calcitriol (35 vs. 19%). The above results suggested that both oral and intravenous calcitriol, with lower doses and intermittent pulse therapy, were equally effective in controlling secondary hyperparathyroidism. The incidences of hypercalcemia were similar in both oral and intravenous calcitriol using 3.5 mEq/l dialysate calcium concentration and calcium carbonate as the chief phosphate binder.

Comparison of intermittent and continuous oral administration of calcitriol in dialysis patients: a randomized prospective trial.

Herrmann P, Ritz E, Schmidt-Gayk H, Schafer I, Geyer J, Nonnast-Daniel B, Koch KM, Weber U, Horl W, Haas-Worle A, et al.

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Nephron. 1994;67(1):48-53

Intermittent bolus administration of calcitriol--i.e., 1,25-dihydroxycholecalciferol or 1,25-(OH)2D3--is highly efficacious in dialysis patients. In experimental studies, intermittent administration of calcitriol is superior to continuous administration in suppressing preproparathyroid hormone (PTH) mRNA and circulating PTH concentrations. In a randomized, prospective, open multicenter trial 45 dialysis patients with elevated 1,84-iPTH (> or = 20 pmol/l, normal 1-6 pmol/l) levels were randomly allocated to daily administration of 0.75 microgram calcitriol (continuous) or twice weekly administration (intermittent); the two protocols provided an identical total weekly doses of 5.25 micrograms calcitriol. Patients were dialyzed with a dialysate Ca concentration of 1.75 mmol/l and had oral CaCO3 or Ca acetate. 1,84-iPTH (immunoradiometric assay) and serum Ca and Pi levels were measured weekly. At the beginning of the study, the median 1,84-iPTH value was 37 pmol/l (range 20-115) in the intermittent versus 36 pmol/l (range 21-72) in the continuous calcitriol group. After 2 weeks, the median 1,84-iPTH level was 18.5 pmol/l (range 1.4-106) versus 18 pmol/l (range 1.2-48). After 12 weeks, 11 of 21 of the patients in the intermittent and 18 of 24 patients in the continuous group had reached the treatment goal, i.e., 1,84-iPTH < or = 10 pmol/l without hypercalcemia or hyperphosphatemia. There were seven episodes of hypercalcemia (> 2.7 mmol/l) in the intermittent versus two in the continuous group; the mean peak Ca level was 2.8 mmol/l (range 2.76-3.0) versus 2.9 mmol/l (range 2.74-3.06). There were 21 versus 17 episodes, respectively, of hyperphosphatemia (> 2.2 mmol/l).

Intravenous versus oral calcitriol therapy in renal osteodystrophy: results of a prospective, pulsed and dose-comparable study.

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Miner Electrolyte Metab. 1994;20(3):122-9

Intravenous calcitriol is generally considered to be more efficient than oral administration in the treatment of secondary hyperparathyroidism of chronic renal failure, although a comparative and prospective study employing the same doses and modality of drug administration is lacking. We therefore evaluated 12 hemodialysis (HD) patients (51.7 +/- 9.4 years, mean +/- SD, HD for 8.7 +/- 4.7 years) with marked secondary hyperparathyroidism. Based on basal humoral and bone histologic parameters, we divided these patients into 2 comparable groups. Calcitriol (0.015 micrograms/kg) was given at the end of each dialysis intravenously in group A and orally in group B. Humoral parameters were evaluated basally and after 1, 2, 4 and 8 months. Ax bone biopsy was taken at the start and at the end of the study. From the first month of treatment, group A showed an increment in ionized calcium (from 1.28 +/- 0.08 to 1.37 +/- 0.12 mmol/l, $p < 0.01$), with a reduction in intact parathyroid hormone (from 470.1 +/- 349.5 to 255.5 +/- 256.5 pg/ml; $p < 0.0003$) and alkaline phosphatase (from 615.1 +/- 696.3 to 445.3 +/- 577.7 mU/ml, $p < 0.001$). The occurrence of hypercalcemia prompted a reduction in dialysate calcium content in 4 of 6 patients after 4 months, and of the calcitriol dose in 2 of 4 patients after 6 months. Ionized calcium then turned to 1.32 +/- 0.11 ($p = \text{n.s.}$ compared to basal) while the intact parathyroid hormone concentration tended to revert (363.3 +/- 360 pg/ml, $p = \text{n.s.}$ compared to basal) and alkaline phosphatase remained low (420 +/- 638 mU/ml, $p < 0.0005$). (ABSTRACT TRUNCATED AT 250 WORDS)

Oral versus intravenous calcitriol: is the route of administration really important?

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Curr Opin Nephrol Hypertens. 1995 Jul;4(4):307-12

Deficiency of 1,25-dihydroxyvitamin D plays an important role in the pathogenesis of secondary hyperparathyroidism. Adequate replacement of this hormone is required to normalize parathyroid gland function and restore bone homeostasis in patients with advanced renal failure. Controversy exists regarding the best method of administering 1,25-dihydroxyvitamin D. Although initial, uncontrolled clinical trials suggested the superiority of intravenous calcitriol treatment, more recent controlled investigations have shown that different routes (oral versus intravenous), frequency (daily versus intermittent) and dosing (physiologic versus pharmacologic) of calcitriol administration are equivalent. Overall, the response to calcitriol treatment depends more on the severity of secondary hyperparathyroidism and the presence of confounding variables, such as hyperphosphatemia and acquired abnormalities of parathyroid cell function, than on the method of calcitriol administration.

Calcitriol administration in end-stage renal disease: intravenous or oral?

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Pediatr Nephrol. 1996 Jun;10(3):331-6

1,25-Dihydroxyvitamin D deficiency plays an important role in the pathogenesis of secondary hyperparathyroidism, and adequate replacement of this hormone is considered essential to normalize parathyroid gland function and restore bone homeostasis in patients with advanced renal failure. Although initial uncontrolled clinical trials suggested the superiority of intravenous calcitriol treatment, more recent controlled investigations show that different routes (oral versus intravenous), frequency (daily versus intermittent), and dosing (physiological versus pharmacological) of calcitriol administration are clinically equivalent. Overall, the response to calcitriol treatment depends more on the severity of secondary hyperparathyroidism and the presence of confounding variables, such as hyperphosphatemia and acquired abnormalities of parathyroid cell function, than the method of calcitriol administration.

Intravenous versus oral vitamin d therapy in dialysis patients: what is the question?

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The debate regarding the administration of vitamin D (parenteral versus pulse oral) in dialysis patients has centered on the efficacy of parathyroid hormone (PTH) suppression while ignoring other questions related to complications and compliance. Past studies looking at efficacy showed no differences during short-term treatment, although the small number of patients studied reduces the significance of these findings. Long-term studies with larger populations have shown that parenteral calcitriol is more effective than pulse oral calcitriol in suppressing PTH. When considering the questions of complications and compliance the current literature demonstrates that parenteral vitamin D therapy is associated with fewer episodes of hypercalcemia and hyperphosphatemia and that patients receiving pulse oral calcitriol require more phosphate binders. Because of the documented high noncompliance rate with oral medications in the dialysis population, parenterally administered vitamin D is expected to more completely suppress PTH long term and result in fewer parathyroidectomies. Based on these considerations it is suggested that parenteral vitamin D analogs are superior to

pulse oral calcitriol for the long-term control of hyperparathyroidism in dialysis patients.

Intermittent intravenous followed by intermittent oral 1 alpha(OH)D3 treatment of secondary hyperparathyroidism in uraemia.

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OBJECTIVES: To examine whether intermittent oral 1 alpha(OH)D3 treatment of patients on haemodialysis with secondary hyperparathyroidism (HPT) was able to maintain the marked suppression of PTH, which previously had been induced by an intermittent intravenous administration of 1 alpha(OH)D3. Simultaneously, the effect of the different routes of administration of 1 alpha(OH)D3 on the circulating levels of N- and C-terminal PTH fragments was measured. **DESIGN:** An open study of patients on chronic haemodialysis. **SETTING:** Renal division, Rigshospitalet, Copenhagen, Denmark. **SUBJECTS:** A total of 26 patients started and five patients completed the total protocol. **INTERVENTIONS:** The treatment protocol was divided into three parts: (i) 1 alpha(OH)D3 administered intravenously for > 300 days; then (ii) 1 alpha(OH)D3 administered orally for 100 days, followed by (iii) 1 alpha(OH)D3 administered intravenously again for another 100 days. 1 alpha(OH)D3 was given three times a week at the end of each dialysis. **MAIN OUTCOME MEASURES:** Intact PTH, N- and C-terminal PTH. **RESULTS:** Intact PTH levels were significantly ($P < 0.0001$) suppressed by $90.4 \pm 3.3\%$ after 56 days of intermittent intravenous 1 alpha(OH)D3 treatment. This degree of suppression remained stable during the following period of oral treatment and did not change further when intravenous treatment was reinstated. The circulating levels of intact PTH and N- and C-terminal iPTH were not influenced by the administered route of 1 alpha(OH)D3. **CONCLUSIONS:** Intravenous 1 alpha(OH)D3 treatment of the secondary HPT in dialysis patients can safely be changed to oral treatment at the time when optimal suppression of PTH has been achieved.

A review of intravenous versus oral vitamin D hormone therapy in hemodialysis patients.

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BACKGROUND/METHODS: We examined 21 clinical trials (16 articles and 5 abstracts) that compared intravenous (i.v.) and oral vitamin D analogs for the treatment of secondary hyperparathyroidism in hemodialysis patients. Nearly all the studies had severe limitations, especially study size. Only 2 studies utilized more than 25 patients per treatment arm; 11 of the 16 articles and 4 of the 5 abstracts had less than 15 patients per arm. Calcitriol and/or alpha-calcidol were studied in 20 trials of the 21 studies (15 of the 16 articles) while 1 article examined doxercalciferol. **RESULTS:** No difference of efficacy between i.v. and oral dosing was found in 10 of the 15 articles in which efficacy was assessed. The i.v. route provided significantly faster suppression of elevated parathyroid hormone (PTH) and/or a greater degree of suppression in 5 of 15 applicable articles, but in 2 of these 5 studies the i.v. dose was substantially greater than the oral dose. Side effects, chiefly hypercalcemia, were noted in half of the articles. Six of 9 articles with detailed results found no significant difference; only 2 found significantly increased hypercalcemia with oral dosing, and 1 found significantly increased hypercalcemia with i.v. dosing. Only 3 articles reported on hyperphosphatemia and no difference was found for mode of administration. One factor influencing 19 of the 21 comparisons was the use of oral doses that were therapeutically equivalent to about half or less the i.v. dose given the lower bioavailability of oral D hormones. One larger study (70 patients) that compared equipotent dosing of the 2 administration routes found 4 times more hypercalcemia using oral than i.v. dosing ($p < 0.001$). Another factor complicating interpretation is that the treatment periods were short, with half being 16 weeks or less and only 2 lasting 36 weeks. **CONCLUSION:** Conclusions about the comparative efficacy and safety of the 2 administration routes require larger studies of longer duration that utilize therapeutically equivalent doses.