Intraperitoneal Calcitriol for Treatment of Severe Hyperparathyroidism in Children with Chronic Kidney Disease: A Therapy Forgotten

Active Vitamin D sterols such as calcitriol and alfacalcidol are quite effective in the treatment of mineral bone disease secondary to chronic kidney disease. However, some children on peritoneal dialysis (PD) are resistant to oral formulations of active Vitamin D, and use of an intravenous formulation in such patients is inconvenient. In these children, intraperitoneal (IP) calcitriol has been shown to be effective in the treatment of secondary hyperparathyroidism. However, its use has declined. We report 2 children, aged 1 and 9.5 years, on chronic cycler PD with severe secondary hyperparathyroidism refractory to oral active Vitamin D who were successfully treated with IP calcitriol for a period of 12 and 4 months, respectively. We also discuss the published literature on the efficacy of IP calcitriol for treatment of secondary hyperparathyroidism and specific considerations for its use in PD patients.

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Mineral bone disease (MBD) is a major cause of growth failure in children with chronic kidney disease (CKD). Its management involves maintaining appropriate levels of calcium, phosphorus, parathyroid hormone (PTH), and 25-hydroxy vitamin D3 and appropriate use of active vitamin D preparations.

Oral alfacalcidol and calcitriol are active forms of vitamin D with well-documented efficacy in reducing PTH levels (1). However, some children are refractory to oral therapy, and in these cases, intraperitoneal (IP) calcitriol is useful to treat secondary hyperparathyroidism (2,3). Intraperitoneal calcitriol can be easily self-administered at home, but does constitute an increased burden of care and carries a risk of peritonitis. Moreover, due to the widespread availability of oral-activated vitamin D preparations, the use of IP calcitriol has declined. We resorted to IP calcitriol in 2 children with severe secondary hyperparathyroidism refractory to oral alfacalcidol. Liquid oral calcitriol preparations were not commercially available and the patients could not swallow capsules.

This case report discusses the successful use of IP calcitriol, reviews the supporting literature, and discusses the specific considerations for IP calcitriol administration.

CASE 1

A 1-year-old boy with anuric renal failure due to cystic renal dysplasia was initiated on intermittent manual peritoneal dialysis (PD) using Physioneal (Baxter Healthcare, Deerfield, IL, USA) solution (containing calcium 1.25 mmol/L or 2.5 mEq/L and magnesium 0.25 mmol/L or 0.5 mEq/L) on the 3rd day of

life. He was discharged at 3 months on continuous cycling peritoneal dialysis (CCPD) using the Baxter Home Choice (Baxter, Deerfield, IL, USA) cycler. Two weeks post-discharge, he had a rising PTH (467 ng/L) and his alfacalcidol dose was increased to 0.1 mcg/day (0.03 mcg/kg/d). The PTH level continued to rise (874 ng/L at 4 months) despite normal 25-hydroxy vitamin D (144 nmol/L [57.6 ng/mL]), calcium (2.53 mmol/L [10.12 mg/dL]), and phosphate (1.82 mmol/L [5.63 mg/dL]) levels. The dose of alfacalcidol was further increased to 0.2 mcg/day (0.06 mcg/kg/d). His aluminum level was minimally elevated at 393 nmol/L (normal < 371 nmol/L).

Table 1 shows the variations in lab parameters from 6 months before until 12 months after starting IP calcitriol. Despite normal levels of 25-hydroxy vitamin D (127 nmol/L [50.8 ng/mL]), and 1,25-dihydroxy vitamin D (146 pmol/L [56.1 pg/mL]), PTH continued to increase even on increasing doses of alfacalcidol.

Intraperitoneal calcitriol was initiated at 1 mcg twice per week and oral alfacalcidol was continued. Intraperitoneal calcitriol was administered at the end of the dialysis treatment into a day dwell of 30 mL. Using aseptic technique, calcitriol was drawn up via an 18-gauge needle with a 5-micron filter into a 3-mL syringe. The needle was removed and the syringe with calcitriol was attached directly to the patient's transfer set. The medication was instilled into the transfer set and flushed with 10 mL of normal saline. The transfer set was closed and a minicap attached.

Within 1 week, the PTH fell from 1,386 ng/L to 631 ng/L, indicating appropriate absorption of calcitriol through the IP route. The lowest PTH achieved was 392 ng/L. Two months later, the patient developed hypercalcemia (calcium 2.85 mmol/L; 11.4 mg/dL), and IP calcitriol was first reduced to 0.75 mcg/week and calcium supplements were withheld. Later, IP calcitriol was discontinued for 2 weeks. Parathyroid hormone again rose to 1,137 ng/L. After restarting IP calcitriol, the PTH level fell to 184 ng/L and stabilized. The total duration of therapy was 12 months and was well tolerated. He had 1 episode of peritonitis secondary to *E. coli* during the IP calcitriol therapy. He subsequently received a living donor renal transplant.

CASE 2

A 9.5-year-old girl with renal dysplasia resumed hemodialysis (HD) following graft loss due to post-transplant lymphoproliferative disease. After 4 months on HD, her PTH rose to 1,348 ng/L despite normal calcium (2.3 mmol/L [9.2 mg/dL]), phosphorus (1.42 mmol/L [4.4 mg/dL]), 1,25 Vitamin D (177 pmol/L [68 pg/mL]), and 25-hydroxy vitamin D (141 nmol/L [56.4 ng/mL]) levels. Intravenous (IV) calcitriol was initiated at 1 mcg twice weekly during HD. A transient improvement was observed with a nadir PTH of 996 ng/L within a month, but it subsequently increased to 2,091 ng/L, and IV calcitriol was increased to 4 times per week. She was transitioned to PD both for parental preference and superior vena cava stenosis.

TABLE 1
Variations in Biochemical Parameters Before and After IP Calcitriol in Both Patients

Time (months)	Cal (mmol/L)	iCal (mmol/L)	PO ₄ (mmol/L)	PTH (ng/L)	Mag (mmol/L)	25-OH Vit D (nmol/L)	Alfacal (mcg/day) [mcg/kg/day]	IP calcitriol
Patient 1								
-6	2.44	1.21	1.95	2081	NA		0.6 [0.12]	-
-5	2.45	1.24	1.60	789	NA	127		-
-4	2.67	1.34	1.68	655	NA		1.2 [0.24]	-
-3	2.66	1.27	1.87	948	0.91			-
-2	2.51	1.27	1.71	875	1.04			-
-1	2.51	1.25	1.92	1199	NA			-
0	2.49	NA	1.98	1386	NA		1.2 [0.16]	1 mcg 2×/wk
1	2.61	1.29	1.77	518	NA			
2	2.56	1.27	2.08	392	1.05	132		0.75 mcg/wk
3	2.70	1.24	2.56	610	NA		withheld 4 days	discontinued
4	2.61	1.19	1.82	1137	NA	185		1 mcg/wk
5	2.63	1.18	2.1	788	0.92	155		1 mcg 2×/wk
6	2.76	1.40	1.72	121	NA		0.5 [0.05]	1 mcg/wk
12	2.87	1.41	1.37	164	NA	149	1 [0.1]	stopped
Patient 2								
-6	2.28	1.20	1.64	2,091	0.78	144	1 (3/week) ^a	
-5	2.45	1.20	2.38	1,562	0.8		1.5 [0.05]	
-4	2.31	1.14	1.7	2,482	0.91	100	2.0 [0.08]	
-3	2.34	1.18	1.71	2,366	NA		2.5 [0.1]	
-2	2.27	1.14	1.69	1,636	NA	111	5 [0.2]	
-1	2.30	1.18	1.68	1,473	0.89			
0	2.32	1.16	1.77	1,691	0.92		5 [0.2]	1 mcg/wk
1	2.24	1.22	1.77	1,464	NA	82		1 mcg, 3/wk
2	2.38	1.23	1.61	909	NA			
3	2.27	1.23	2.01	684	NA		5 [0.2]	Stopped
4	2.48	1.25	1.87	411	NA			Injection calcitriol given orally (1 mcg 3 times a week)
5	2.62	1.27	1.76	169	1.12			1 mcg 2 times a week oral
6	2.68	1.31	2.04	63	1.23		2 [0.07]	

IP = intraperitoneal; Cal = total calcium; iCal = ionized calcium; PO₄ = phosphorus; PTH = parathyroid hormone; Mag = magnesium; 25-OH Vit D = 25-hydroxy Vitamin D level; Alfacal = alfacalcidol dose; NA = not available; CKD = chronic kidney disease.

^a on 1 mcg 3/week IV calcitriol during hemodialysis.

Conversion factor: calcium: mmol/L × 4 = mg/dL; phosphorus: mmol/L × 3.1 = mg/dL; PTH assay normal range = 12–78 ng/L; target range for CKD stage 5 = 150–300; 25-hydroxy vit D normal range = 70–250 nmol/L; magnesium normal range: 0.7–0.95 mmol/L; ionized calcium normal range: 1.22–1.37 mmol/L.

At initiation of CCPD with Physioneal (Baxter Healthcare, Deerfield, IL, USA) solution, her PTH was 1,562 ng/L, calcium 2.45 mmol/L (9.8 mg/dL), and phosphorus 2.38 mmol/L (7.4 mg/dL). Intravenous calcitriol was discontinued, and oral alfacalcidol was initiated. Her PTH level remained elevated despite increasing doses of alfacalcidol (see Table 1). Aluminum level was normal at 208 nmol/L.

Intraperitoneal calcitriol was started (1 mcg per week) with the same technique as described above but without the day dwell. After 1 month, the dose was increased to 3 times per week. Three months later, the PTH level dropped to 684 ng/L. Intraperitoneal calcitriol was stopped after 4 months due to supply issues, and she was switched to alfacalcidol 5 mcg

per day. However, the PTH rose again to 767 ng/L and she was started on the IV formulation of calcitriol orally, 1 mcg 3 times a week (personal communication, Dr. Thomas Oliver Carpenter MD, Yale School of Medicine). When the PTH level fell to 169 ng/L, alfacalcidol was stopped, and calcitriol was reduced to 1 mcg 2 times per week orally.

DISCUSSION

Active vitamin D sterols as oral and IV formulations are recommended for use in CKD-MBD after correction of vitamin D deficiency and are pivotal in decreasing PTH production. However, some children on PD are resistant to oral alfacalcidol,

and the use of IV calcitriol is impractical. Calcimimetics such as cinacalcet may also be used in such patients (4), but there are limited data in pediatric dialysis patients, especially infants (5), dosing formulations are not child-friendly, and there are safety concerns with their use (6).

Intraperitoneal calcitriol to treat secondary hyperparathyroidism has long been forgotten despite extensive data demonstrating its effectiveness. Both daily and intermittent IP calcitriol have been shown to improve secondary hyperparathyroidism in pediatric and adult PD patients. Delmez *et al.* first demonstrated effective absorption of IP calcitriol into the systemic circulation and consequent reduction in PTH level in 2 continuous ambulatory PD (CAPD) patients (7). This was followed by a randomized trial comparing oral and IP administration of calcitriol in 46 children on CCPD. Both oral and IP calcitriol were able to reverse the histological abnormalities of secondary hyperparathyroidism. The IP group demonstrated higher calcium levels, a significant reduction in PTH, and lower serum phosphorus levels than the oral group (2). The efficacy of IP calcitriol has also been confirmed in infants on PD (8). None of these studies reported any major side effects related to IP calcitriol administration.

We administered the IV formulation of calcitriol intraperitoneally using a similar technique in 2 CCPD patients for 12 and 4 months, respectively, and demonstrated effective reduction in PTH levels. There were no major side effects except 1 episode of *E. coli* peritonitis, suggesting that touch contamination during IP administration was unlikely to be the cause. The oral administration of the IV formulation of calcitriol also proved effective at suppressing PTH and is another unique aspect of this report.

Several issues should be taken into consideration when prescribing IP calcitriol therapy. Firstly, calcitriol has a tendency to adhere to plastics such as PD bags and tubing (9). Salusky *et al.* showed that 35 – 40% of calcitriol adhered to the plastic component of the PD circuit when it was administered by adding calcitriol into the PD bags (10). This led to modification of the administration technique, with injection of the drug directly into the peritoneal cavity through the universal adaptor of the Tenckhoff catheter (11). Secondly, the medication is light-sensitive and must therefore be drawn up immediately before injection. Finally, absorption is not dependent on the IP concentration of calcitriol as it is with some drugs such as erythropoietin, so a full day dwell can be administered without compromising solute clearance or ultrafiltration.

In summary, IP calcitriol is an effective alternative for PD patients, especially infants, who do not show improvement of secondary hyperparathyroidism with activated oral vitamin D therapy. It is important to note that IV calcitriol (CA\$11 per mcg) is more expensive than equivalent microgram doses of oral alfacalcidol capsules (CA\$1.75 per mcg) but nearly equivalent to alphacalcidol liquid (CA\$10 per mcg). However, given the enormous doses of alphacalcidol required by our 2 patients, IP calcitriol was both cheaper and more effective.

With the availability of effective oral activated vitamin D preparations, further studies to establish the optimal dose, schedule and long-term clinical effects of IP calcitriol are unlikely to happen. An avenue for further investigation is the effectiveness of oral administration of the IV preparation in the absence of commercially available oral calcitriol liquid in some countries.

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