12-1-2017

Successful Reversal of Furosemide-Induced Secondary Hyperparathyroidism With Cinacalcet.

Tarak Srivastava
Children's Mercy Hospital

Shahryar Jafri

William E. Truog
Children's Mercy Hospital

Judith Sebestyen VanSickle
Children's Mercy Hospital

Winston M. Manimtim
Children's Mercy Hospital

See next page for additional authors

Recommended Citation

Srivastava T, Jafri S, Truog WE, Sebestyen VanSickle J, Manimtim WM, Alon US. Successful Reversal of Furosemide-Induced Secondary Hyperparathyroidism With Cinacalcet. Pediatrics. 2017;140(6):e20163789. doi:10.1542/peds.2016-3789

Successful Reversal of Furosemide-Induced Secondary Hyperparathyroidism With Cinacalcet

Tarak Srivastava, MD,[a] Shahryar Jafri,[a] William E. Truog, MD,[b] Judith Sebestyen VanSickle, MD,[a] Winston M. Manimtim, MD,[b] Uri S. Alon, MD[a]

abstract

Secondary hyperparathyroidism (SHPT) is a rare complication of furosemide therapy that can occur in patients treated with the loop diuretic for a long period of time. We report a 6-month-old 28-weeks premature infant treated chronically with furosemide for his bronchopulmonary dysplasia, who developed hypocalcemia and severe SHPT, adversely affecting his bones. Discontinuation of the loop diuretic and the addition of supplemental calcium and calcitriol only partially reversed the SHPT, bringing serum parathyroid hormone level down from 553 to 238 pg/mL. After introduction of the calcimimetic Cinacalcet, we observed a sustained normalization of parathyroid hormone concentration at 27 to 63 pg/mL and, with that correction, of all biochemical abnormalities and healing of the bone disease. No adverse effects were noted. We conclude that in cases of SHPT due to furosemide in which traditional treatment fails, there may be room to consider the addition of a calcimimetic agent.

Furosemide therapy in the neonatal/infantile period is well known to be associated with medullary nephrocalcinosis from hypercalciuria caused by the loop diuretic.[1,2] A less known complication of chronic treatment with furosemide is the development of secondary hyperparathyroidism (SHPT).[3–6] The latter is attributed to the hypercalciuria, leading to the development of hypocalcemia, which stimulates parathyroid hormone (PTH) secretion,[6,7] but recent literature also suggests an additional, direct stimulating effect of furosemide on the parathyroid glands.[8] It is expected that discontinuation of the loop diuretic, at times combined with supplementation with calcium and active vitamin D metabolites, will reverse the SHPT. However, if the parathyroid glands achieve a significant level of hyperplasia, the task of controlling SHPT will be difficult, and the endocrinopathy may persist for a prolonged period.

In recent years, a calcimimetic agent, Cinacalcet, which acts on the calcium-sensing receptor has become available to suppress PTH.[9] The calcimimetic agent changes the configuration of the calcium-sensing receptor in the parathyroid glands, making them more sensitive to circulating serum calcium, resulting in decreased secretion of PTH. Although originally created for use in adults with SHPT, there have been now several reports of successful use of this agent in children with SHPT from various genetic and acquired etiologies.[10–13] We report our novel experience in a premature infant with severe bronchopulmonary dysplasia (BPD) necessitating long-term treatment with furosemide who developed SHPT. After observing only partial response to traditional therapy with calcium and calcitriol, the SHPT

[a]Sections of Nephrology, Bone and Mineral Disorder Clinic, and [b]Neonatology, The Children's Mercy Hospitals and Clinics, University of Missouri at Kansas City, Kansas City, Missouri

Drs Srivastava and Alon conceptualized and designed the study and drafted the initial manuscript; Drs Truog, Manimtim, Sebestyen VanSickle, and Mr Jafri carried out the initial analyses and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

DOI: https://doi.org/10.1542/peds.2016-3789

Accepted for publication Mar 10, 2017

Address correspondence to Uri S. Alon, MD, Section of Nephrology, The Children's Mercy Hospital, 2401 Gillham Rd, Kansas City, MO 64108. E-mail: ualon@cmh.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by the Sam and Helen Kaplan Research Fund in Pediatric Nephrology and Eric McClure Research Fund in Pediatric Bone and Mineral Disorders.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Srivastava T, Jafri S, Truog WE, et al. Successful Reversal of Furosemide-Induced Secondary Hyperparathyroidism With Cinacalcet. *Pediatrics.* 2017;140(6):e20163789

was successfully reversed with Cinacalcet.

CASE REPORT

The child was born at 28 weeks' gestation with a birth weight of 830 g. He was transferred from his birth hospital at 2 months of age for ongoing needs of prematurity, severe BPD, and possible need for tracheostomy. On admission to our institution, furosemide was added to his ongoing thiazide therapy to treat his respiratory condition. At age 5.5 months, he underwent tracheostomy and placement of ventriculoperitoneal shunt for hydrocephalus. MRI of the brain performed for evaluation of the ventriculoperitoneal shunt showed severe demineralization of the bones (Fig 1). The skeletal survey conducted the next day showed abnormal bony demineralization concerning for a metabolic bone disorder. That day serum ionized calcium (iCa) was 0.99 mmol/L (normal 1.13–1.37), and he was started on calcium supplementation. Further detailed evaluation in the coming days (Table 1, week −7.0), when his chronological age was 6 months and weight 6.3 kg, detected decreased serum calcium (8.9 mg/dL); iCa 1.09 mmol/L; elevated PTH (553 pg/mL), alkaline phosphatase (ALP; 420 U/L), and $1,25(OH)_2$-vitamin D (689 pg/mL); and normal phosphorus (5.4 mg/dL), 25(OH)-vitamin D (65 ng/mL), and urine calcium/creatinine ratio (0.22 mg/mg). At that time, his treatment of BPD included furosemide (3 mg/kg/day), chlorothiazide (22.5 mg/kg/day), and prednisone (0.5 mg/kg every 48 hours). Renal ultrasound showed no medullary nephrocalcinosis. His nutritional formula provided elemental calcium, phosphorus, and vitamin D of 603 mg/day, 437 mg/day, and 260 U/day, respectively. Genetic mutation analysis for conditions associated with inherited forms of rickets and/or osteopetrosis (namely *VDR*, *CASR*, *PHEX*, *CYP27B1*, *CYP2R1*, *DMP1*, *CLCN7*, *SOST*, *LRP4*, *SNX10*, *TMFSF11*, *TNFRSF11A*, and *OSTM1*) were negative. A microarray did not identify any deletion or duplication. Calcitriol was added to address his hypocalcemia. Over the next 3 weeks, his serum PTH decreased but remained elevated at 257 pg/mL (Table 1, week −3.4). At this point, our team was consulted, and the diagnosis of furosemide-induced SHPT was made. Furosemide was discontinued and the chlorothiazide dose doubled. In coming weeks, a further decrease in PTH levels was noted, but the dose of calcitriol and calcium supplementation had to be decreased to avoid hypercalcemia. Nevertheless, despite sustained normalization of serum calcium over this 6-week period, his serum PTH remained elevated (Table 1, week 0). After discussion with the family, a decision was made to initiate oral Cinacalcet 3 mg/day (0.4 mg/kg/day) in 2 divided doses. Over the next 2 weeks (Table 1: Cinacalcet Course A), PTH normalized at 15 to 25 pg/mL. Due to hypocalcemia, calcium supplementation was increased. With serum PTH and calcium levels within their normal range, Cinacalcet was subsequently discontinued (Table 1, week 2.0). Within the next 2 weeks, the serum PTH rebounded to 151 to 234 pg/mL. This suggested significant hyperplasia of the parathyroid glands requiring sustained pharmacological suppression of PTH. An attempt to image the parathyroid glands by using neck ultrasound failed because of neck size and presence of tracheostomy. At this point, Cinacalcet was reinitiated (Table 1: Cinacalcet Course B) with concomitant calcitriol and calcium supplementation. Serum PTH eventually normalized and stayed within the normal range for the next 12 weeks. Calcitriol was discontinued first, calcium supplementation was tapered and discontinued next, and finally Cinacalcet was stopped (Table 1, weeks 11.5–16.5). The child was then able to maintain serum calcium and PTH levels in their normal ranges until discharge 8 weeks later. At follow-up a month later, serum calcium and PTH were normal at 10.2 mg/dL and 78 pg/mL, respectively. The child tolerated therapy with Cinacalcet without any adverse effects. Throughout this course, his serum creatinine and urine calcium/creatinine ratio remained normal. The renal ultrasound on last follow-up showed no nephrocalcinosis. Serum ALP, which was originally elevated, gradually normalized. Follow-up radiographs done at 1 year of age showed normal mineralization with resolution of metaphyseal cupping and fraying (Fig 1).

DISCUSSION

Furosemide is a potent loop diuretic with action in the loop of Henle that results in decreased sodium and water reabsorption; it is often used in infants with BPD.[14] However, its action also results in decreased calcium reabsorption because calcium and sodium reabsorption are coupled at this site.[15] The increased urinary calcium excretion may result in formation of medullary nephrocalcinosis or stones.[1,2] In older patients, furosemide has also been reported to be associated with decreased bone mineral density, osteoporosis, and high risk for fractures.[16–18] In addition, there have been reports about the association of the loop diuretic with development of SHPT.[3–8] Coe et al[5] in 1973 demonstrated that adults treated with furosemide had elevated PTH similar to adults with persistent hypercalciuria. In 1985, Fujita et al[6] showed that adults treated for a week with oral furosemide had elevated urine calcium (effect on loop of Henle) and cyclic adenosine

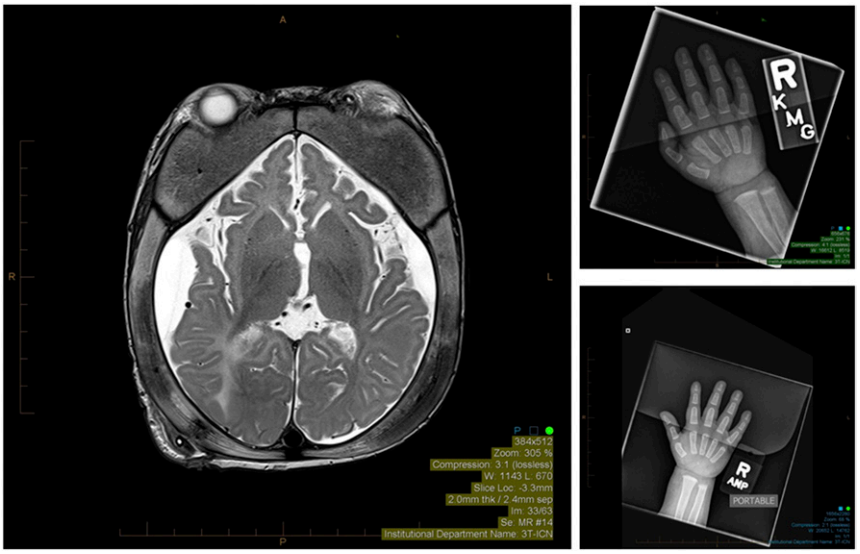

FIGURE 1

MRI (left panel) at 6 months of age showing massive expansion of the calvarial vault suggestive of metabolic bone disease. Radiograph of the right wrist (right upper panel) performed the next day showing diffuse demineralization with widening and flaring of the metaphysis. The follow-up radiograph (right lower panel) done at 1 year of age, 4 months after initiation of Cinacalcet therapy, shows normalization of bone mineralization and metaphyseal anatomy.

monophosphate excretion (effect of elevated PTH). More recently, cross-sectional analyses of large data sets from the United States, Brazil, and Australia have shown the loop diuretic to be associated with SHPT in adults with both normal and reduced renal function.[4,7,19–21] Similarly, Venkataraman et al[3] communicated this complication in 1983 in 4 preterm infants who consequently developed hyperparathyroid bone disease, but no additional pediatric cases have since been reported. Although SHPT from furosemide has been reported in adults, it seems to be a rarity in the pediatric population.

The mechanism of furosemide-induced SHPT has been conventionally attributed to increased urinary calcium excretion, but that alone does not completely explain the development of SHPT from calciuria. Riss et al[22] showed that although thiazides decrease urine calcium excretion in primary hyperparathyroidism, they do not affect serum PTH level. Similarly, our case had SHPT despite normal urine calcium excretion, which could be explained by adjunctive thiazide therapy or a calcium-depleted skeleton. Another possible mechanism for the development of SHPT is based on the new observation of a direct stimulatory effect of furosemide on the parathyroid cells acting via the NKCC1 receptor.[8]

In the present case, the infant, with ventilator-dependent BPD, was treated with furosemide for 4 months, when the brain MRI followed by skeletal radiographs showed severe osteopenia (Fig 1). The biochemical evaluation that followed was consistent with furosemide-induced SHPT (Table 1). After calcitriol and calcium supplementation decreased PTH only partially, furosemide was discontinued. Over the next 3 weeks, serum PTH further decreased but remained elevated. It was realized that further suppression of PTH secretion may come at the cost of hypercalcemia. Cinacalcet was therefore added, and subsequently PTH was decreased to its normal range (Table 1: Cinacalcet Course A). After Cinacalcet was stopped, PTH levels immediately rebounded and were brought back to normal with the reintroduction of the calcimimetic. We believe that the hormonal rebound provides a proof of concept that the suppression of PTH was the result of treatment with Cinacalcet and not coincidental.

Coe et al[5] reported that SHPT associated with persistent hypercalciuria was secondary to hyperplasia of the glands and would respond to calcium infusion. Venkataraman et al[3] reported that autopsy in one of the premature infants who developed furosemide-induced SHPT showed enlarged parathyroid glands. Our attempt to image the parathyroid glands was not successful due to presence of tracheostomy. However, on the basis of the course of events, we believe that also in our case, the parathyroid glands achieved a significant level of hyperplasia making the task of controlling SHPT more difficult; specifically, if left to conventional treatment, the state of SHPT would have persisted for a prolonged period. Cinacalcet, a calcimimetic that acts on the calcium-sensing receptor to suppress PTH secretion, was previously shown to be effective and safe in reversing various types of primary and SHPT in both adults and children.[10–13] Furthermore, as recently shown by Muller et al,[8] it negates the direct effect of furosemide on the parathyroid glands. It thus seems to be the ideal drug to use in a circumstance such as in our patient for rapid and safe correction of SHPT. As with our previous experience with vitamin D–resistant rickets and pseudohypoparathyroidism type 1b, and as was the case in our current patient, bringing serum PTH back into the normal range resulted in normalization of serum ALP and healing of the bone disease.[10,11] As previously observed in animals

TABLE 1 Effect of Therapy With Elemental Calcium, Calcitriol, and Cinacalcet Before and On and Off Cinacalcet on Serum Biochemical Variables in a Premature Infant With Furosemide-Induced SHPT

Time, wk	Elemental Calcium, mg/d	Calcitriol, μg/d	Cinacalcet, mg/d	iCa, mmol/L	Serum P, mg/dL	Serum PTH, pg/mL	Serum ALP, U/L
Reference range	—	—	—	1.13–1.37	4.2–7.0	10–89	110–320
Pre-cinacalcet							
−7.0	560		—	1.09	5.4	553	420
−6.1	560	0.15	—	1.21	4.9	531	419
−5.0	560	0.30	—	1.13	5.4	484	553
−3.4[a]	560	0.30	—	1.26	6.6	257	—
−2.6	560	0.30	—	1.43	6.3	161	—
−1.4[b]	280	0.15	—	1.27	5.9	157	336
0.0	280	0.15	—	1.30	5.6	238	335
Cinacalcet course A							
0.6	280	0.15	6.9	1.17	5.4	137	—
1.0	280	0.15	7.8	1.33	5.7	25	—
1.6	280	0.15	6.0	1.01	6.0	15	—
2.0[c]	600	0.15	6.0	1.12	6.0	25	—
Off cinacalcet							
2.6	600	0.15	—	1.27	6.2	234	—
3.6	600	0.15	—	1.31	5.9	151	—
Cinacalcet course B							
4.6	600	0.15	3.5	1.26	5.1	117	216
6.6[d]	780	0.15	7.2	1.21	7.6	119	—
8.0	780	0.15	6.9	1.19	7.1	10	—
9.0	780	0.15	6.6	1.17	7.6	90	—
10.5	780	0.15	3.3	1.31	5.9	63	—
11.5	780	0.15	3.3	1.34	8.7	92	—
12.5	780	—	5.4	1.29	5.7	104	—
13.5	780	—	4.8	1.19	8.2	27	—
14.5	760	—	4.8	1.23	7.2	44	—
15.5	240	—	4.8	1.27	6.9	28	—
16.5	—	—	2.4	1.28	7.6	55	—
Off cinacalcet							
18.0	—	—	—	1.38	7.3	63	190
20.5	—	—	—	1.32	5.8	35	—
24.5	—	—	—	1.37	5.9	45	—

Serum creatinine ranged between 0.22 and 0.29 mg/dL throughout the study period (reference range 0.06–0.45 mg/dL).
[a] Furosemide was discontinued and dose of chlorothiazide doubled.
[b] Calcium and calcitriol supplementation were decreased due to hypercalcemia (iCa 1.43 at week −2.6).
[c] Calcium supplementation was increased due to hypocalcemia (iCa 1.01 at week 1.6).
[d] Calcium supplementation was increased due to hypocalcemia (iCa 1.06 at week 6).

and humans, Cinacalcet's main adverse effect was the development of hypocalcemia, requiring the adjustment of supplemental active vitamin D metabolite to sustain serum iCa concentration within its normal range.[10,11,23]

Several lessons can be learned from the present case. In children chronically treated with a loop diuretic, close attention should be paid to their mineral metabolism, specifically periodic assessment of serum iCa and PTH levels and urine calcium should be performed. Once abnormalities are detected, all efforts should be made to discontinue the loop diuretic, and if diuresis is still required, the use of a thiazide diuretic is preferable. In case this maneuver does not help reverse SHPT, calcium and active vitamin D metabolites need to be added. If satisfactory suppression of PTH is still not noted, we now have in our armamentarium the calcimimetic agent. We recommend, on the basis of others' and our own experience, continuing to monitor serum iCa and urine calcium closely because some patients under calcimimetic treatment develop hypocalcemia responding to calcitriol and/or hypercalciuria responding to thiazides.

ACKNOWLEDGMENTS

The off-label use of Cinacalcet in furosemide-induced SHPT was extensively discussed with the family. The family gave their consent for publication of the case report.

ABBREVIATIONS

ALP: alkaline phosphatase
BPD: bronchopulmonary dysplasia
iCa: ionized calcium
PTH: parathyroid hormone
SHPT: secondary hyperparathyroidism

REFERENCES

1. Hufnagle KG, Khan SN, Penn D, Cacciarelli A, Williams P. Renal calcifications: a complication of long-term furosemide therapy in preterm infants. *Pediatrics*. 1982;70(3):360–363
2. Saarela T, Lanning P, Koivisto M, Paavilainen T. Nephrocalcinosis in full-term infants receiving furosemide treatment for congestive heart failure: a study of the incidence and 2-year follow up. *Eur J Pediatr*. 1999;158(8):668–672
3. Venkataraman PS, Han BK, Tsang RC, Daugherty CC. Secondary hyperparathyroidism and bone disease in infants receiving long-term furosemide therapy. *Am J Dis Child*. 1983;137(12):1157–1161
4. Corapi KM, McMahon GM, Wenger JB, Seifter JL, Bhan I. Association of loop diuretic use with higher parathyroid hormone levels in patients with normal renal function. *JAMA Intern Med*. 2015;175(1):137–138
5. Coe FL, Canterbury JM, Firpo JJ, Reiss E. Evidence for secondary hyperparathyroidism in idiopathic hypercalciuria. *J Clin Invest*. 1973;52(1):134–142
6. Fujita T, Delea CS, Bartter FC. The effects of oral furosemide on the response of urinary excretion of cyclic adenosine monophosphate and phosphate to parathyroid extract in normal subjects. *Nephron*. 1985;41(4):333–336
7. Isakova T, Anderson CA, Leonard MB, et al; Chronic Renal Insufficiency Cohort (CRIC) Study Group. Diuretics, calciuria and secondary hyperparathyroidism in the Chronic Renal Insufficiency Cohort. *Nephrol Dial Transplant*. 2011;26(4):1258–1265
8. Muller ME, Forni Ogna V, Maillard M, et al. Furosemide stimulation of parathormone in humans: role of the calcium-sensing receptor and the renin-angiotensin system. *Pflugers Arch*. 2015;467(12):2413–2421
9. Alon US. Diseases and clinical applications of the calcium sensing receptor. *Pediatr Endocrinol Rev*. 2007;5(1):482–488
10. Srivastava T, Krudys J, Mardis NJ, Sebestyen-VanSickle J, Alon US. Cinacalcet as adjunctive therapy in pseudohypoparathyroidism type 1b. *Pediatr Nephrol*. 2016;31(5):795–800
11. Srivastava T, Alon US. Cinacalcet as adjunctive therapy for hereditary 1,25-dihydroxyvitamin D-resistant rickets. *J Bone Miner Res*. 2013;28(5):992–996
12. Silverstein DM, Kher KK, Moudgil A, Khurana M, Wilcox J, Moylan K. Cinacalcet is efficacious in pediatric dialysis patients. *Pediatr Nephrol*. 2008;23(10):1817–1822
13. Alon US, VandeVoorde RG. Beneficial effect of cinacalcet in a child with familial hypocalciuric hypercalcemia. *Pediatr Nephrol*. 2010;25(9):1747–1750
14. Najak ZD, Harris EM, Lazzara A Jr, Pruitt AW. Pulmonary effects of furosemide in preterm infants with lung disease. *J Pediatr*. 1983;102(5):758–763
15. Brater DC. Update in diuretic therapy: clinical pharmacology. *Semin Nephrol*. 2011;31(6):483–494
16. Rejnmark L, Vestergaard P, Heickendorff L, Andreasen F, Mosekilde L. Loop diuretics increase bone turnover and decrease BMD in osteopenic postmenopausal women: results from a randomized controlled study with bumetanide. *J Bone Miner Res*. 2006;21(1):163–170
17. Rejnmark L, Vestergaard P, Mosekilde L. Fracture risk in patients treated with loop diuretics. *J Intern Med*. 2006;259(1):117–124
18. Carbone LD, Johnson KC, Bush AJ, et al. Loop diuretic use and fracture in postmenopausal women: findings from the Women's Health Initiative. *Arch Intern Med*. 2009;169(2):132–140
19. Vasco RF, Moyses RM, Zatz R, Elias RM. Furosemide increases the risk of hyperparathyroidism in chronic kidney disease. *Am J Nephrol*. 2016;43(6):421–430
20. Stein MS, Scherer SC, Walton SL, et al. Risk factors for secondary hyperparathyroidism in a nursing home population. *Clin Endocrinol (Oxf)*. 1996;44(4):375–383
21. Vaidya A, Curhan GC, Paik JM, Kronenberg H, Taylor EN. Hypertension, antihypertensive medications, and risk of incident primary hyperparathyroidism. *J Clin Endocrinol Metab*. 2015;100(6):2396–2404
22. Riss P, Kammer M, Selberherr A, et al. The influence of thiazide intake on calcium and parathyroid hormone levels in patients with primary hyperparathyroidism. *Clin Endocrinol (Oxf)*. 2016;85(2):196–201
23. Pattaragarn A, Fox J, Alon US. Effect of the calcimimetic NPS R-467 on furosemide-induced nephrocalcinosis in the young rat. *Kidney Int*. 2004;65(5):1684–1689

Successful Reversal of Furosemide-Induced Secondary Hyperparathyroidism With Cinacalcet

Tarak Srivastava, Shahryar Jafri, William E. Truog, Judith Sebestyen VanSickle, Winston M. Manimtim and Uri S. Alon

Pediatrics 2017;140;
DOI: 10.1542/peds.2016-3789 originally published online November 30, 2017;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Successful Reversal of Furosemide-Induced Secondary Hyperparathyroidism With Cinacalcet

Tarak Srivastava, Shahryar Jafri, William E. Truog, Judith Sebestyen VanSickle, Winston M. Manimtim and Uri S. Alon

Pediatrics 2017;140;
DOI: 10.1542/peds.2016-3789 originally published online November 30, 2017;