Original Article

Pamidronate as first-line treatment of hypercalcemia in neonatal subcutaneous fat necrosis: A case series

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ABSTRACT

Background: Subcutaneous fat necrosis (SCFN) can be complicated by severe hypercalcemia, which is frequently asymptomatic. Nephrocalcinosis is associated with hypercalcemia and, in other clinical settings, has been linked to furosemide and glucocorticoid use. First-line bisphosphonate therapy treating hypercalcemia in neonatal SCFN is not well described.

Objectives: To describe the biochemical changes and risk of nephrocalcinosis in infants with hypercalcemia, secondary to neonatal SCFN, treated with initial pamidronate.

Methods: A retrospective chart review of five infants treated with initial pamidronate and without furosemide or glucocorticoids. Data were collected on the following: timing of presentation, therapeutic response, and presence of nephrocalcinosis.

Results: Hypercalcemia resolved after 2.8 ± 1.7 days; this is compared to 7.6 ± 2.8 days from previously reported cases utilising alternative therapies ($P=0.012$). There were no episodes of rebound hypercalcemia or hypocalcemia. Nephrocalcinosis was present in four of five cases. When including published cases, age at diagnosis was associated with presenting serum calcium ($P=0.003$) and nephrocalcinosis was associated with higher serum calcium ($P=0.014$) and time from SCFN to hypercalcemia diagnosis ($P=0.002$).

Conclusions: This retrospective case series demonstrates that first-line pamidronate treatment was effective and safe in the resolution of hypercalcemia. Nephrocalcinosis was observed, despite the avoidance of furosemide and glucocorticoid therapy, and associated with greater disease severity and duration of hypercalcemia.

Keywords: Hypercalcemia; Nephrocalcinosis; Pamidronate

Subcutaneous fat necrosis (SCFN) is a rare granulomatous panniculitis; it causes erythematous or purple nodules, which can develop into indurated plaques over the face, trunk, and proximal extremities (1–3). SCFN is preceded by a history of fetal or perinatal distress leading to an ischaemic, hypoxic, or hypothermic insult to adipose tissue (4,5); also, it is a recognized complication of therapeutic hypothermia in 1% of infants (6,7).

The associated complications of SCFN include thrombocytopenia, hyperglycemia, hypertriglyceridemia, and hypercalcemia

(3–5). Severe hypercalcemia requiring intervention typically presents within six weeks of life and can be asymptomatic (4,8).

Treatment regimens for hypercalcemia secondary to SCFN have used hyperhydration with intravenous fluid, a low calcium and vitamin D diet, calcitonin, furosemide, and glucocorticoids (4,8). However, calcitonin use is limited by tachyphylaxis—it has diminished efficacy after repeated doses. The treatment effect of glucocorticoids to normalize serum calcium is gradual (2,9) and both furosemide and glucocorticoids are potential

risk factors for nephrocalcinosis (10–12). Nephrocalcinosis is frequently associated with hypercalcemia secondary to SCFN (2–4,8,9,13,14); it can be transient (8,9) or persistent, with normal renal function reported (4,13,14). Furosemide has been attributed to increasing the risk of nephrocalcinosis (8,15).

Bisphosphonates were first described as treatment for hypercalcemia in SCFN over 16 years ago (14). Initial reports used an oral bisphosphonate, etidronate, and subsequent reports used intravenous agents such as pamidronate. Bisphosphonates reduce serum calcium by decreasing the function and number of osteoclasts, which inhibits bone resorption (16).

Pamidronate has been mostly used following other therapies failing to normalize serum calcium; the response to pamidronate occurs after 0.5 to 4 days with resolution of hypercalcemia in 1 to 9 days (2,8,9,13–15). Pamidronate used as first-line therapy was mainly in response to rebound hypercalcemia (2,8,9).

The short and medium-term outcomes after first-line pamidronate therapy are unclear, particularly given the paucity of cases with hypercalcemia secondary to SCFN. By a retrospective case series, we aim to (1) describe the biochemical response to first-line pamidronate—without concurrent use of furosemide or glucocorticoids—in treating hypercalcemia secondary to neonatal SCFN; (2) to compare our experience with published cases that used pamidronate as second-line therapy; and (3) to describe the observed rate and associations with nephrocalcinosis.

METHODS

A retrospective study was approved by The Hospital for Sick Children Research and Ethics Board. Five infants were identified by the endocrine division and included in this case series as they: presented with severe hypercalcemia secondary to neonatal SCFN, were treated first-line with pamidronate, and did not receive glucocorticoids or furosemide.

SCFN was diagnosed by the presence of characteristic subcutaneous nodules on clinical examination and supported by associated risk factors for SCFN in the clinical history. Hypercalcemia was attributed to SCFN based on the supporting clinical history and biochemistry that did not suggest an alternative diagnosis (raised total and ionized calcium, normal phosphate, suppressed parathyroid hormone, raised urine calcium/creatinine ratio). Standard of care for treating hypercalcemia alongside pamidronate included the following: intravenous fluid hyperhydration; low calcium enteral formula; and considering calcitonin 2 to 4 mg/kg every 12 hours. Pamidronate was given as recommended by the consulting endocrine team. Nursing observations (temperature, pulse, blood pressure, respiratory rate) were taken at baseline and then hourly during the 4-hour pamidronate infusion.

A chart review collected data on perinatal history; age and symptoms at diagnosis of SCFN and hypercalcemia; biochemistry; pamidronate treatment timing and dose; and

ultrasound findings. A literature search identified published cases of hypercalcemia secondary to neonatal SCFN treated with pamidronate.

Descriptive statistics characterized the case series and the comparisons made with data reported in published cases. Correlations between continuous variables were analyzed by Spearman regression. Comparison of means was analyzed by the Mann–Whitney test. Categorical variables were analyzed by the Fisher exact test.

RESULTS

Case series

Five infants were treated at The Hospital for Sick Children, Toronto, between 2013 and 2018, born at term and had a median birth weight of 3.41 kg, range 2.76 to 4.10 kg (Table 1). Perinatal distress, predisposing to SCFN, was present in all cases: case 1 was born by emergency cesarean section after fetal decelerations; case 2 was born by emergency cesarean section following maternal pre-eclampsia, underwent therapeutic hypothermia, and had a seizure; case 3 was born by emergency cesarean section for a concerning fetal heart rate, required non-invasive positive pressure respiratory support and had a seizure; case 4 had a delivery complicated by meconium and shoulder dystocia; and case 5 was born by emergency cesarean section, underwent therapeutic hypothermia and had a seizure.

SCFN was diagnosed at a median 17 days, range 3 to 28 days; in all cases, this preceded hypercalcemia presenting, which was diagnosed at a median 28 days, range 19 to 56 days (Table 1). Hypercalcemia presented incidentally in four infants following routine biochemistry and as symptomatic hypercalcemia in one infant (case 1) with irritability, poor feeding, and weight gain. The presenting total calcium level was greater than 3.0 mmol/L (12.0 mg/dL) in all cases; median 3.47 mmol/L (13.88 mg/dL), range 3.06 to 4.48 mmol/L (12.24 to 17.92 mg/dL). At their presentation with hypercalcemia, all cases had a normal phosphate, suppressed parathyroid hormone, and increased urine calcium/creatinine ratio.

Pamidronate was used as first-line therapy in all cases—0.25 to 0.5 mg/kg/day for 1 to 2 days; one infant received one additional dose (Table 1). Additional therapies were used alongside pamidronate (Table 1): hyperhydration; low calcium formula; and calcitonin, which was used as a temporizing therapy in two infants but not suitable for ongoing therapy due to the risk of tachyphylaxis. Furosemide and glucocorticoids were not used in this case series.

Pamidronate was safely used in all infants without hypocalcemia or documented observation of an acute phase reaction. The mean time to calcium normalization from hypercalcemia diagnosis was 2.8 ± 1.7 days and from first pamidronate therapy was 2.1 ± 1.8 days. Figure 1 presents the timing of pamidronate doses and trend in the normalization of calcium.

Table 1. Case series of five infants with hypercalcemia secondary to SCFN who were treated first-line with intravenous pamidronate

	Gestation and birth weight	SCFN: age at diagnosis	Hypercalcemia: age at diagnosis	Other treatments	Pamidronate treatment	Time to resolution*	Nephrocalcinosis
Case 1	39 weeks 2.78 kg	24 days	56 days	Low Ca milk Calcitonin 2 units/kg	0.25 mg/kg/day for 2 days. Additional 0.5 mg/kg once.	138 h	0.2 years: bilateral 1.8 years: stable 3.8 years: stable
Case 2	37 weeks 2.76 kg	9 days	24 days	Calcitonin 4 units/kg twice	0.25 mg/kg once	37 h	0.3 years: normal 2.6 years: bilateral 3.6 years: stable
Case 3	41 weeks 4.07 kg	17 days	19 days	Hyperhydration	0.25 mg/kg once	18 h	None
Case 4	41 weeks 4.10 kg	28 days	28 days	Hyperhydration	0.5 mg/kg once	44 h	4 months: bilateral
Case 5	39 weeks 3.41 kg	3 days	46 days	Hyperhydration low Ca milk	0.5 mg/kg once	26 h	6 weeks: bilateral

Ca Calcium; SCFN Subcutaneous fat necrosis.

*Time to resolution from diagnosis of hypercalcemia.

Figure 1. Serum calcium response to treatment in five infants with hypercalcemia secondary to subcutaneous fat necrosis treated first-line with pamidronate. P Pamidronate; C Calcitonin

No infants had rebound hypercalcemia within their first admission, however, one (case 1) was re-admitted with hypercalcemia, which was treated with 0.5 mg/kg pamidronate and calcitonin and resolved in 1.8 days.

Nephrocalcinosis was present in four of five (80%) infants (Table 1). There was no biochemical evidence of renal dysfunction.

Comparison with published cases

Ten cases of neonatal SCFN have been published (Table 2) using pamidronate to treat hypercalcemia secondary to SCFN (2,8,9,13–15) but only one as first-line treatment (8). From the nine cases reporting pamidronate use as second-line therapy, the

mean time to calcium normalization from hypercalcemia diagnosis was 7.6 ± 2.8 days and from first pamidronate therapy was 4.2 ± 3.1 days. The mean time to resolution from hypercalcemia diagnosis is shorter in our case series by 4.9 days (95% confidence interval [CI]: 1.3, 7.5; $P=0.012$). The mean time to resolution from pamidronate administration is shorter in our case series by 1.7 days but not statistically significant ($P=0.131$).

From the published cases, three of nine had rebound hypercalcemia within the same admission; this compares to zero of five from this case series. Persistent nephrocalcinosis was present in six of nine of the published cases and a further two of nine had transient nephrocalcinosis. There was no reported renal dysfunction. There was no difference in the occurrence of nephrocalcinosis between this case series and those previously published ($P>0.99$).

When analyzing all available cases—both this case series ($n=5$) and published cases ($n=10$)—the age of hypercalcemia diagnosis positively correlated with the presenting serum calcium level ($r=0.67$; 95% CI: 0.22, 0.88; $P=0.008$). Also, those with nephrocalcinosis were diagnosed with hypercalcemia later (median 29 days) compared with those without nephrocalcinosis (median 19 days); actual difference 10 days (95% CI: 5, 34 days; $P=0.004$). A higher calcium was associated with being symptomatic at presentation (median calcium 4.37 mmol/L versus 3.38 mmol/L, $P=0.003$) and having any nephrocalcinosis (median calcium 4.17 mmol/L versus 3.06 mmol/L, $P=0.018$). Infants with nephrocalcinosis (transient or permanent) were on average diagnosed younger with SCFN by 4 days (95% CI: -12, 24; $P=0.47$) and were diagnosed later with hypercalcemia following their diagnosis of

Table 2. Published cases using pamidronate therapy for hypercalcemia secondary to neonatal SCFN

Reference	SCFN: age at diagnosis	Hypercalcemia: age at diagnosis	First-line treatment	Pamidronate treatment	Time to resolution*	Nephrocalcinosis
(2)	4 days	22 days	HH, furosemide, low Ca milk, GC	0.25 mg/kg/day for 2 days then 0.5 mg/kg once	10 days	Bilateral
(9)	9 days	25 days	HH, furosemide	0.25 mg/kg once then 0.5 mg/kg/day for 3 days	7 days	Present; signs of resolution
(9)	14 days	29 days	HH, furosemide, GC	0.5 mg/kg once	8 days	Bilateral
(8)	41 days	41 days	HH, furosemide, low Ca milk	0.25 mg/kg/day for 3 days	12 days	Bilateral; resolved
(8)	3 days	29 days	HH, furosemide	0.25 mg/kg once and repeated after 3 days	9 days	Mild; resolved
(8)	0 days	12 days	HH, furosemide, low Ca milk	0.25 mg/kg once and repeated after 6 days	7 days	None
(8)**	5 days	19 days	HH, furosemide	0.25 mg/kg once then 0.5 mg/kg/day for 2 days	11 days	None
(14)	4 days	49 days	HH, furosemide, low Ca milk, GC	1 mg/kg/day for 3 days	6 days	Bilateral; persistent
(13)	5 days	33 days	low Ca milk, HH, furosemide, GC	0.25 mg/kg for three doses	2 days	Bilateral; persistent
(15)	21 days	21 days	HH, furosemide, GC, low Ca milk.	0.25 mg/kg then two more doses averaging 0.4 mg/kg/day	7 days	Persistent

Ca Calcium; GC Glucocorticoids; HH Hyperhydration; SCFN Subcutaneous fat necrosis.

*Time to resolution from diagnosis of hypercalcemia.

**Pamidronate given as first-line therapy in this case (in all other cases, pamidronate used subsequent to other therapies).

SCFN by 5 days (95% CI: -12, 31; $P=0.22$); however, these trends are not statistically significant. There was no association between time to resolution of hypercalcemia and the presence of either permanent nephrocalcinosis ($P=0.57$) or any nephrocalcinosis—permanent or transient ($P=0.84$).

DISCUSSION

We present the largest case series demonstrating effective and safe first-line pamidronate therapy for treating severe hypercalcemia secondary to neonatal SCFN. We found that first-line pamidronate therapy, without need for glucocorticoids or furosemide, resulted in earlier resolution of hypercalcemia and reduced frequency of rebound hypercalcemia compared with published cases that used furosemide followed by pamidronate therapy.

In our case series, all had a preceding history of perinatal distress associated with SCFN. Most cases were asymptomatic of severe hypercalcemia, which is consistent with other reports; however, two of five cases presented after six weeks, which is beyond the typical timescale previously reported (4). Case 1 presented symptomatic after eight weeks and case 5 presented

at 6.5 weeks, asymptomatic, after routine monitoring for hypercalcemia following a diagnosis of SCFN at three days of life. Therefore, the risk of severe hypercalcemia continues at least until 8 weeks, which should be reflected in the counselling we offer families and our monitoring protocols.

The etiology of hypercalcemia in SCFN is proposed to be due to increased calcium absorption and bone turnover. Raised 1,25-dihydroxyvitamin D levels (8) support increased calcium absorption through the expression of 1- α -hydroxylase in the inflammatory infiltrate resulting in increased conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (17). A rise in surrogate markers of bone turnover is also found in these patients (14). Pamidronate targets these mechanisms by reducing bone resorption as a long-acting inhibitor of osteoclast action.

This case series was different to those previously published—we used pamidronate as first-line therapy, rather than subsequent to other unsuccessful treatments, and we did not use furosemide or glucocorticoids, of which the former was used in all previous reports (Table 2). Furosemide and glucocorticoids have been implicated in treatment failure and increasing the risk of nephrocalcinosis (8,9,15,18). We found the time to normalization of calcium was shorter in our case series

compared with the published cases and the frequency of rebound hypercalcemia was less. When combining data from our case series with data from published cases, we showed that a later diagnosis of hypercalcemia was associated with the severity of hypercalcemia and an increased likelihood of nephrocalcinosis. However, the time to resolution of hypercalcemia was not associated with nephrocalcinosis and our rate of nephrocalcinosis (four of five cases) was comparable to published cases (six of nine cases). This suggests that delay in diagnosis and treatment of hypercalcemia leads to an increased risk of symptomatic, severe hypercalcemia and nephrocalcinosis that is not offset by optimizing the speed of recovery to normocalcemia. This concurs with the opinion that the duration and severity of hypercalcemia exhibits a greater effect on increasing nephrocalcinosis risk than treatment modality (15).

This case series is limited by the small number of infants and retrospective study design. Additional statistical power could yield significant associations not detected here. The associations described could be confounded, for example, by the variations in treatment protocols between institutions. Our patient follow-up ranged from 6 weeks to 3.8 years; longer follow-up could be informative for nephrocalcinosis outcomes. Nonetheless, the contribution of our data can help optimize therapy and raise awareness of an uncommon paediatric condition. The comparisons with published data and significant associations described prompt the need for future robust studies to better elucidate whether one treatment regimen is superior over another.

We found that that first-line pamidronate, without the need for glucocorticoids and furosemide, can safely hasten the resolution of hypercalcemia and reduce the risk of rebound hypercalcemia when treating severe hypercalcemia secondary to neonatal SCFN; this is in comparison to published cases using pamidronate second-line after routine furosemide therapy. Although expected to reduce the incidence of nephrocalcinosis, similar rates were observed even though furosemide was avoided. Nephrocalcinosis appears to be associated with the duration and severity of hypercalcemia preceding diagnosis.

This experience supports a place for pamidronate as first-line therapy to improve recovery rate and reduce length of hospital stay. Our institution routinely utilizes pamidronate, 0.25 to 0.5 mg/kg, together with hyperhydration and low calcium formula, for the management of severe hypercalcemia secondary to SCFN. In severe or symptomatic cases, calcitonin remains a viable option for short term, acute management. We continue to avoid routine furosemide or glucocorticoids. Our data support an improved biochemical response using first-line pamidronate without these medications; and there is potential for furosemide to exacerbate the identified risks for nephrocalcinosis, which may be under recognized due to the study limitations. Finally, severe hypercalcemia has an insidious, mostly asymptomatic

onset, up to 8 weeks of life after SCFN diagnosis. Therefore, routine and regular monitoring is required in infants with SCFN to ensure prompt management of hypercalcemia is initiated, which may help prevent the development of nephrocalcinosis and symptomatic severe hypercalcemia.

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