Immobilization Hypercalcemia in Incomplete Paraplegia: Successful Treatment With Pamidronate

Divakara Kedlaya, MBBS, Murray E. Brandstater, MBBS, PhD, Jonathan K. Lee, MD


Immobilization hypercalcemia (IH) occurs in adolescent patients with high-level complete tetraplegia, but it has not been reported in patients with incomplete paraplegia. We describe two adolescent patients with low-level incomplete paraplegia who developed IH during comprehensive rehabilitation. Conventional therapies with hydration, diuresis, and calcitonin were not effective. Finally, a single-dose infusion of pamidronate, an amino-bisphosphonate, completely resolved the hypercalcemia. Although it has a pharmacologic profile similar to etidronate, pamidronate is more potent, being effective in a single dose, has fewer adverse effects, and has a longer action than etidronate. These features make pamidronate more suitable for the treatment of severe IH in rehabilitation settings. It is reasonable to consider immobilization as the cause of hypercalcemia in low-level incomplete paraplegic patients who have other contributing factors.

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PROLONGED IMMOBILIZATION as a cause of osteoporosis and hypercalcemia was first reported in 1941.1 Immobilization hyperparaplegia (IH) in patients with spinal cord injury (SCI) was first reported in 1975 by Claus-Walker and associates.2 It is common in children and adolescents. In one study,3 23.6% of children younger than 16 years of age with SCI developed hypercalcemia (serum calcium >11mg%). In another study,4 11% of 70 tetraplegic patients younger than age 21 developed IH. Higher level of injury and completeness of the neurologic injury are stated as predisposing factors for IH.1,4 which has not been reported in incomplete paraplegic patients. Both patients in this report had incomplete paraplegia and were successfully treated with a single-dose intravenous infusion of pamidronate, after conventional measures and treatment with calcitonin failed. Patients with IH from disorders other than SCI have been successfully treated with intravenous pamidronate.5-9 There is one case report of 16-year-old tetraplegic patient with IH who was treated with intravenous pamidronate.10 We report here that intravenous pamidronate was therapeutically effective and was convenient for use in a rehabilitation unit.

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CASE REPORTS

Case 1
A 16-year-old boy was involved in a motor vehicle accident on September 13, 1995. He suffered a fracture dislocation at L2-L3 level with cauda equina damage and incomplete paraplegia. On September 23, he underwent L2-L3 discectomy, reduction of dislocation, and pedicle fixation with rod and hook from T12-L4. He had an acute abdomen on admission, and laparotomy revealed extensive bowel necrosis from seat belt injury. He required massive small bowel resection with right hemicolectomy, jejunal-transverse colon anastomosis, and distal sigmoid colostomy. Only 30 inches of small bowel remained, causing short bowel syndrome that required long-term total parenteral nutrition. He also had an episode of acute pancreatitis that eventually resolved.

The patient was admitted to the comprehensive SCI rehabilitation unit on October 11 with ASIA C L2 incomplete paraplegia. He weighed 98lb and his height was 66 inches. A colostomy bag was attached to his left lower abdomen, and a subclavian central line was established.

During his rehabilitation stay, he continued to have nausea, vomiting, anorexia, and lethargy. Initially, this was attributed to short bowel syndrome, resolving pancreatitis, gastritis, and gastroparesis. When the symptoms continued, however, with increasing calcium levels, hypercalcemia secondary to immobilization was assumed to be the cause. Beginning with the 6th week, he was given calcium-free total parenteral nutrition with extra fluids. Furosemide was started, and passive range of motion and other therapeutic exercises were continued. Despite all these measures, his calcium levels remained high and his symptoms persisted. Laboratory data are listed in table 1. Salmon calcitonin at the dose of 80U subcutaneously every 12 hours was instituted in the 14th week on December 14. Initially, his calcium levels decreased, and on December 20 the calcitonin dose was decreased to 80U every day. The symptoms recurred, however, along with increasing calcium levels. On January 19, during the 18th week after injury, calcitonin was discontinued.

Five days later, pamidronate at the dose of 40mg in 500cc of normal saline was infused over a period of 4 hours as per recommendation of an endocrinology consultant. The patient’s calcium levels returned to normal, and his symptoms resolved. He had no untoward effects. There was no febrile reaction and no significant change in the leucocyte count. His calcium levels remained in the normal range during the rest of his hospital stay and subsequent follow-up, and no additional dose of pamidronate was necessary (fig 1). Other complications during the patient’s course were episodes of urinary tract infection and chronic left hip pain, with computed tomography showing chronic avascular necrosis of the head of the femur, which was interpreted as being premorbid. He later developed heterotopic ossification in the region of that hip. The patient was discharged home on February 8, 1996, on home total parenteral nutrition with a recommendation of weekly monitoring of calcium levels.

Case 2
A 20-year-old man was admitted to the trauma service on October 10, 1995 with multiple gunshot wounds to the left
Table 1: Laboratory Data of Case 1 (6 Weeks Postinjury) and Case 2 (7 Weeks)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal Range</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin-corrected serum calcium</td>
<td>2.2-2.6</td>
<td>2.9</td>
<td>3.2</td>
</tr>
<tr>
<td>(mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum alkaline phosphatase (U/L)</td>
<td>30-120</td>
<td>230</td>
<td>104</td>
</tr>
<tr>
<td>Parathyroid hormone (pg/mL)</td>
<td>10-65</td>
<td>&lt;7.8</td>
<td>4.2</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>3.5-5.5</td>
<td>4.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Urine hydroxyproline/creatinine</td>
<td>&lt;0.033</td>
<td>0.13</td>
<td>-</td>
</tr>
<tr>
<td>Urine calcium/creatinine</td>
<td>&lt;0.50</td>
<td>0.75</td>
<td>-</td>
</tr>
</tbody>
</table>

He was transferred to the SCI rehabilitation unit 9 weeks after injury, on December 5, 1995, with ASIA C L3-L4 incomplete paraplegia. He also had a healing right flank wound. His weight was 133 lb and his height was 69 inches.

During the 7th week after injury, the patient had symptoms of nausea, vomiting, lethargy, and irritability, with an elevated serum calcium level. His laboratory values are as shown in table 1. He was treated with intravenous fluids and diuretics, but without success. In the 11th week, on December 19, salmon calcitonin 100U subcutaneously every 12 hours was started. Initially, his calcium levels decreased, and the following week the calcitonin dose was reduced to 100U every day. The calcium levels began to increase again. On January 9, 1996 (in the 14th week after injury), the dose of calcitonin was increased to 1000U every 12 hours. Calcium levels remained elevated. Pamidronate 30mg in 500mL of normal saline was infused over a period of 6 hours on January 18. He did not have any febrile reaction. He was discharged home on January 30. Calcium levels have been normal since then, except for a slight upward trend during the 21st and 27th weeks, although the patient was asymptomatic.

DISCUSSION

Increased osteoclastic bone resorption is the main event leading to IH. The proposed pathophysiologic mechanisms are lack of mechanical stress because of absence of loading and muscle action, poor vascularity, metabolic changes in bone, and bone denervation. The increase in bone turnover with resorption is seen within the first 3 days after SCI. Onset of hypercalcemia occurs in 4 to 8 weeks and reaches maximum at 10 weeks following immobilization in most patients. It can persist for 6 to 18 months after injury.

Children and adolescents are more prone to IH than are older individuals because of an increased rate of bone turnover. The rate of bone loss is inversely related to age, decreasing from 50% in adolescents to 15% in elderly women. Another contributing factor is sepsis with release of cytokines such as interleukin-1. One of our patients (case 2) had sepsis complicated by osteomyelitis. A possible contributing factor in case 1 could have been sluit bowel syndrome, which decreases calcium absorption and possibly could have stimulated bone resorption to maintain calcium homeostasis. A nonimmobilized patient with short bowel syndrome will develop hypocalcemia without calcium supplementation. In our patient, serum calcium levels were high even after discontinuation of calcium in total parenteral nutrition, which strongly suggests that immobilization was the cause of continued hypercalcemia. Experiments in immobilized monkeys have shown increased bone turnover in axial and appendicular bone compared with peripheral cortical bone. Weight-bearing bones are more likely to react to immobilization.

Symptoms of IH are vague and nonspecific, including nausea, vomiting, anorexia, lethargy, depression, irritability, and abdominal pain and discomfort. A high degree of suspicion in the correct setting is necessary for prompt diagnosis and proper treatment. The laboratory findings include increased serum and ionized calcium levels, increased excretion of calcium and hydroxyproline in the urine, and suppressed intact parathyroid hormone and 1-25(OH)2 vitamin D3 levels. Primary hyperparathyroidism as a cause for hypercalcemia should be ruled out.
because hypercalcemia can be induced in mild primary hyperparathyroidism by immobilization. Complications of IH are renal stones (in more than 50% of children immobilized because of SCI), nephrocalcinosis causing renal failure, and osteoporosis with its associated morbidity.

Early institution of effective treatment is very important in IH to prevent secondary complications, morbidity, and to facilitate rehabilitation. Conventional therapy with intravenous fluids and diuresis can only increase renal excretion of calcium without affecting the main underlying process. The effects are short-lived and the process is cumbersome in rehabilitative settings. Active range of movements, as in ambulation, with muscles pulling on the bones, is important in maintaining homeostasis in the bone milieu. Hence, passive range of motion, sitting, and passive weight-bearing do not prevent IH. Dietary restriction of calcium was not shown to have significant results on serum calcium levels, and may even be detrimental in III.11 Other modalities of treatment for IH, such as oral phosphates, corticosteroids, and mithramycin, have been studied. Their beneficial effects are variable and are limited by their adverse effects. Calcitonin has been used to treat IH, but its effects are not long-lasting because of the "escape" phenomenon.10 Calcitonin has been combined with corticosteroids19 and etidronate (a bisphosphonate), however, to prolong its effect. The combination of calcitonin and etidronate has been successful. The administration of both of these agents for the recommended period may be inconvenient, however, and may be limited by the adverse effects of etidronate.

The advent of a newer generation of bisphosphonates has revolutionized the treatment of Paget's disease, osteoporosis, and hypercalcemia caused by malignancy and immobilization. The older bisphosphonate etidronate, the first in this class of drugs, was introduced in 1971 for the treatment of Paget's disease, and has been used for hypercalcemia of malignancy and immobilization.12 It is also used to prevent heterotopic ossification and bone loss in osteoarthritis. Etidronate is unsuccessful in initiating the treatment of hypercalcemia because of its slow onset of action, but it is useful in maintenance therapy. The adverse effects of etidronate include asymptomatic hyperphosphatemia, metallic taste, nephrotoxicity, and osteomalacia.19 The new bisphosphonates are aminobisphosphonates that have different mechanisms of action. Pamidronate, 100 times more potent than etidronate, is a new non-nitrogen-containing aminobisphosphonate with a novel mechanism and response to pamidronate.7

Pamidronate is chemically aminohydroxypropylidene diphosphate (APD). The modes of action of pamidronate are (1) adsorption onto the surface of hydroxyapatite crystals in mineralized bone matrix, thereby reducing the solubility of the mineralized matrix and rendering it more resistant to osteoclastic resorption, and (2) impairment of the attachment of osteoclast precursors to the mineralized matrix, thereby blocking their subsequent transformation into mature, functioning osteoclasts. This also accounts for its sustained activity. In a study conducted in Europe that compared intravenous bisphosphonates for use in hypercalcemia of malignancy, pamidronate produced normocalcemia for a mean of 4 weeks, compared with 2 weeks for clodronate and 1.5 weeks for etidronate.3 The most common side effect is a transient, self-limiting, and asymptomatic pyrexia typically occurring in the first 48 to 72 hours after the drug administration and observed in 10% to 20% of cases.22 In some cases, this is paralleled by transient leukopenia and lymphopenia. These are thought to be "first dose" effects. Other side effects are malaise, and gastrointestinal symptoms like nausea and epigastric discomfort with oral administration. Symptomatic hypercalcemia with high-dose pamidronate has been reported.14 Newer aminobisphosphonates like alendronate and risedronate are better tolerated orally and can be considered for use in IH, but further clinical evaluation is necessary.

CONCLUSION

Although IH is more common in patients with complete high-level injuries, it also should be considered in patients with low-level incomplete SCI when other contributing factors are present. It should be treated promptly. Pamidronate appears to be the most suitable agent for the treatment of IH in rehabilitation settings. It is very effective in a single intravenous dose, its effects are long-lasting and well tolerated, and it induces minimal adverse reactions.

References