

# Narrative Review: Furosemide for Hypercalcemia: An Unproven yet Common Practice

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Although primary hyperparathyroidism is the most common cause of hypercalcemia, cancer is the most common cause requiring inpatient intervention. An estimated 10% to 20% of all patients with cancer have hypercalcemia at some point in their disease trajectory, particularly in advanced disease. Aggressive saline hydration and varying doses of furosemide continue to be the standard of care for emergency management. However, a review of the evidence for the use of furosemide in the medical management of hypercalce-

mia yields only case reports published before the introduction of bisphosphonates, in contrast to multiple randomized, controlled trials supporting the use of bisphosphonates. The use of furosemide in the management of hypercalcemia should no longer be recommended.

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**B**efore the advent of bisphosphonates, the medical management of hypercalcemia was frustrating, particularly in patients with cancer. Because patients with hypercalcemia cannot concentrate urine and therefore become significantly dehydrated, saline hydration is important but rarely sufficient in moderate to severe cases. Common treatments included tumor excision when possible, steroids, plicamycin, intravenous phosphate, sulfate, or ethylenediamine tetra-acetate. These treatments were not benign, which made furosemide seem to be an attractive alternative. Beginning in 1970, reports on the use of furosemide to increase calciuresis were published (1–9). Forced saline diuresis subsequently became the standard of care; however, physicians did not use the methods described in these articles. Studies of etidronate, the first bisphosphonate released in the United States, began in 1980, and randomized, controlled trials found it efficacious with few side effects (10, 11). In 1991, a randomized, controlled trial of gallium nitrate and etidronate found gallium to be superior (12). Pamidronate and zoledronic acid followed; both were demonstrated to have improved efficacy (13, 14). Nonetheless, most current textbooks continue to recommend first-line management with saline and furosemide. Although many comment that adequate hydration is needed before the use of furosemide, our anecdotal experience is that this recommendation is not routinely followed. We therefore sought evidence to support the use of furosemide as primary therapy for hypercalcemia.

## METHODS

We identified articles related to the use of furosemide for hypercalcemia by searching Ovid MEDLINE from 1950 to 2007 using the terms *hypercalcemia*, *hypercalcemia of malignancy*, *furosemide and hypercalcemia*, and *treatment of hypercalcemia*. We limited the search to English-language studies involving adults. Because of the paucity of articles, we repeated the search with the terms *furosemide*, *hypercalcemia*, and *hypercalcaemia*; widened the search period from

1950 to April 2008; and limited the search to only human trials. A reviewer translated the French-language articles.

We identified articles related to bisphosphonates by searching Ovid MEDLINE for articles from 1950 through April 2008 using the terms *bisphosphonate*, *diphosphonates*, *hypercalcemia*, and *hypercalcaemia*. We limited the search to English-language studies of human adults. We then reviewed articles to identify prospective single-group trials; randomized, controlled trials; and systematic reviews or meta-analyses. Although we did not limit the search by underlying cause, we identified only case reports and uncontrolled case series for nonmalignant causes. We also searched the Ovid database Evidence-Based Medicine Reviews, which includes *ACP Journal Club*, the Cochrane Database of Systematic Reviews, and the Database of Abstracts of Review of Effects, but identified no additional articles.

A reviewer also searched online full textbooks available via the McGraw-Hill AccessMedicine and AccessEmergency Medicine, ACP Medicine, MD Consult, and Books @Ovid as of April 2008 for hypercalcemia treatment recommendations.

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## RESULTS

### Furosemide

We found only 14 articles documenting the use of furosemide in hypercalcemia, with the last article published in 1983. Of these 5 were excluded: 1 on the induction of

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**Key Summary Points**

There is no evidence to support the common practice of using furosemide for hypercalcemia of any cause.

Hydration with normal saline and immediate institution of bisphosphonate therapy is the treatment of choice.

Subcutaneous calcitonin may be used for emergency management in patients with severe symptoms.

hypercalcemia with furosemide, 2 duplicate reports of a series, 1 letter commenting on an earlier report, and 1 review article. Of the remaining 9 articles, Suki and colleagues' study (1) is the most commonly cited reference in current recommendations. The original publications comprise 37 patients in total (39 treatment episodes) and include 5 case series (8, 11, 5, 6, and 3 patients) and 4 single-case reports. **Table 1** shows details of the treatment given. We include the pediatric series in **Table 1** but not in the following summary.

We calculated the average of the reported furosemide dosages used in adults to be 1120 mg over 24 hours, with a dose range of 240 to 2400 mg. The dosage recommendation in 2 articles (6, 7) was 100 mg/h. Normalization occurred in 14 of 39 episodes, but occurred quickly (in 6 and 12 hours) only in 2 cases (7, 8). No consistently rapid effect was reported; durations of therapy ranged from 6 hours to 12 days. The only report in which investigators administered lower doses (40 to 60 mg/d, orally) did not achieve normalization at 12 days (5). Monitoring was intense and frequently invasive, involving aggressive replacement of hourly urine output with calculation and replacement of urinary electrolyte losses every 2 to 4 hours. One patient went into a coma from severe hypernatremia, hypophosphatemia, and metabolic acidosis (5), and 2 patients had episodes of severe hypomagnesemia with altered mental status (1) and tetanic crisis (5). Current texts typically recommend doses ranging from 10 to 80 mg and make no recommendations on monitoring. We identified no studies published since 1983 that investigated the appropriate dose or monitoring for furosemide or its success as primary therapy for management of hypercalcemia of any cause.

**Bisphosphonates**

Our search for articles on bisphosphonates yielded 1 systematic review; 34 randomized, controlled trials with a combined total of more than 1000 patients; and 22 prospective single-group trials or nonrandomized case-control studies. We found an orderly progression from placebo-controlled trials to comparisons of existing therapies and from the earliest agent, etidronate, to the more potent agents pamidronate, zoledronic acid, and ibandronate. We also found dose-response and administration-method tri-

als. The systematic review (14) concluded that bisphosphonates are the drugs of choice for the treatment of hypercalcemia of cancer. This article reviewed 26 studies that examined calcium normalization with the use of intravenous bisphosphonates. The investigators cited heterogeneity among the studies as preventing meta-analysis but identified normalization of calcium in greater than 70% of patients with minimal side effects, which included fever and asymptomatic biochemical abnormalities.

Other nonsystematic reviews (15–17) have also concluded that the role of furosemide should change:

Bisphosphonates have supplanted all other drugs except corticosteroids for hypercalcemia of multiple myeloma (15).

The use of loop diuretics should be restricted to those patients who are in danger of fluid overload. Loop diuretics are not very effective in promoting significant renal calcium excretion, and may provoke volume depletion when used in patients whose volume deficit has not been reversed and who are not fully rehydrated (16).

Today, IV [intravenous] bisphosphonates are the standard therapy for hypercalcemia of malignancy (17).

Bisphosphonates have also been used in other causes of hypercalcemia, although the level of evidence is case reports or retrospective case series. Successful management of hypercalcemia with bisphosphonates has been reported in primary hyperparathyroidism, either in preparation for surgery or in nonsurgical candidates, although with a short duration of response (18); vitamin D intoxication (19); immobilization in patients undergoing obesity surgery, those with burns, and those with spinal cord injury (20–23); and disseminated coccidioidomycosis (24, 25).

**Current Reference Texts**

Despite the level-1 evidence for the benefit of bisphosphonates and the minimal evidence for the value of furosemide, most clinical reference texts readily available to physicians in training or in practice still recommend forced saline diuresis as first-line therapy (**Table 2**) (26–41).

**DISCUSSION**

We show that despite more than 20 years of careful phase I to III research supporting saline hydration with bisphosphonates as the preferred first-line therapy in hypercalcemia and the lack of significant supporting evidence for furosemide, this medication continues to be routinely recommended for emergency management. As recently as 2005, a review (42) recommended 20 to 40 mg of furosemide after adequate hydration; the author acknowledged that this was based on “historical precedent and common practice” (42).

**Table 1. Published Reports of Furosemide for Hypercalcemia**

Study, Year (Reference)	Study Design	Patients, <i>n</i>	Monitoring	IV Fluid	Furosemide Dose	Results
Suki et al., 1970 (1)	Case series	8	Hourly urine output and urinary electrolyte losses	1–2 L normal saline, then hourly	80–100 mg every 1–2 h for 6–47 h	3 normal, 3 near-normal, 2 reduced
Fillastre et al., 1973 (2)	Case series	11	Arterial pressures and central venous pressure, urinary output, urinary electrolyte losses	Corrected dehydration first	7 patients, 125 mg every 3 h; 4 patients, 100 mg/h	6 normalized in 37 h–7 d, 1 unrelated death
Helzberg et al., 1983 (3)	Case report	1	Swan–Ganz catheter	Up to 39.5 L/d	160 mg/d IV, without response; 40 mg IV × 2 after massive fluids	Normalization on day 13; could not wean from fluids, died
Latos and Valentine, 1973 (4)	Case report	1	Urinary output and urinary electrolyte losses	Replaced hourly fluid and electrolyte output	80 mg every 2 h for 24 h, then 80 mg/h for 14 h, then 80 mg every 6 h	Normalized in 50 h; also given methylprednisolone, 80 mg, every 4 h
Caron, 1975 (5)	Case report	1	Not stated	Not stated	160 mg over 4 h	Improved calcium, severe electrolyte imbalance, death
	Case series	3	Not stated	Normal saline, 3.5–8 L/d	40–60 mg/d orally	Gradual decrease over 12 d (none normalized), 1 tetanic crisis from low magnesium
Baguet et al., 1972 (6)	Case series	5	ICU, hourly central venous pressure measurement, weight checked every 6 h	1–2 L normal saline, then replacement of hourly losses	4–160 mg every 4 h, 2–100 mg/h, 6–144 h	Only the patient with lowest initial level normalized
Le Gall et al., 1971 (7)	Case report	1 (3 episodes)	Urinary output and urinary electrolyte losses	1 L normal saline, then hourly replacement and 15 mg/h magnesium	60–100 mg IV hourly	Episode 1, patient normalized after 12 h; episodes 2–3, levels improved but did not normalize
Humbert et al., 1972 (8)	Case series	6	Central venous pressure, urinary output every 3 h, urinary electrolyte losses every 6 h	Normal saline, then replacement of losses	125 mg every 3 h	3 of 6 patients normalized; furosemide doses in responders, 625–5000 mg
Najjar et al., 1972 (9)	Case series	3 infants (age <2 y) with vitamin D intoxication	Hourly urinary output, urine electrolyte losses every 2–4 h	20 mL/kg, then replacement of hourly losses	20–140 mg; 24 h treatment in 2, 48 h in 1	2 patients improved with rebound after 72 h—re-treated 4 times over 38 d (normalized) and twice in 7 d (not normal); 1 normalized with no rebound

ICU = intensive care unit; IV = intravenous.

Reliance on historical precedent is not limited solely to the management of hypercalcemia; many therapies have become habit, often without supporting evidence. We may not know where such a habit came from and may struggle to find its origin; however, that search may be informative and practice-changing. Such a search may have several possible outcomes: No evidence is found to support the current recommendations, leading to a new standard of care; limited but supporting evidence is found that argues for additional studies; or adequate evidence is found to support the existing precedent. We argue that our search of furosemide studies is an example of the first outcome.

Because bisphosphonates require 48 hours (on average) to take effect, it could be argued that furosemide still has a role in treatment of hypercalcemia during the first few days. However, furosemide did not consistently normalize calcium levels quickly, even at markedly higher

doses than those routinely prescribed. In contrast, calcitonin can effectively decrease the serum calcium level in as quickly as 2 hours (43), and although tachyphylaxis limits prolonged use, it is perfectly suited for emergency management. Case reports and at least 1 case–control trial (44, 45) have studied the use of calcitonin in combination with various bisphosphonates. Our routine approach is saline hydration and bisphosphonates with subcutaneous calcitonin (4 U/kg subcutaneously every 12 hours) for severe symptoms.

Renal failure has been a concern with bisphosphonate therapy, and some texts list nephrotoxicity as a complication (30); however, we found few reports in the literature, and most cases of renal insufficiency occurred after repeated use for bone stabilization in cancer (46). One letter examining voluntary adverse event reports at the U.S. Food and Drug Administration identified only 6 of 72 patients

**Table 2. Textbook Recommendations**

Source (Reference)	Fluid	Furosemide	Bisphosphonate
<i>Emergency Medicine Manual</i> (26)	Normal saline, 5–10 L	Yes, 40 mg	Not mentioned
<i>Tintanalli's Emergency Medicine: A Comprehensive Study Guide</i> (27)	Normal saline volume repletion	Yes, 40–100 mg every 2–4 h	Not mentioned
<i>Harrison's Principles of Internal Medicine</i> (28)	Normal saline, 4–6 L over 24 h	Yes; no dose given	Should be considered for patients with cancer
<i>Current Medical Diagnosis and Treatment 2008</i> (29)	250–500 mL/h normal saline or 1/2-normal saline	Yes, 20–40 mg every 2 h	Mainstay of treatment
<i>Clinical Anesthesiology</i> (30)	Normal saline	Yes; no dose given	Usually required if severe
<i>Principles of Critical Care</i> (31)	Normal saline	Yes; no dose given	Fifth on table of options
<i>Clinician's Pocket Reference</i> (32)	Normal saline, 250–500 mL/h	Yes, 20–80 mg or more	Second-line therapy
<i>ACP Medicine</i> (33)	Normal saline	Yes; no dose given	Drug of choice if fluids and loop diuretic are ineffective
<i>ACP Medicine</i> (34)	Normal saline	Yes; strong hydration statement	Improved and simplified therapy
<i>Cecil Medicine</i> (35)	Normal saline, 200–300 mL/h	Yes; no dose given	Standard for cancer-associated hypercalcemia
<i>Brenner &amp; Rector's The Kidney</i> (36)	Normal saline	Yes, no dose given, strong fluid statement	May be reasonable
<i>Greenspan's Basic and Clinical Endocrinology</i> (37)	Normal saline, 500–1000 mL in the first hour, then 25–500 mL/h	Yes, to avoid fluid overload	First choice for most patients after initial therapy
<i>Clinical Oncology</i> (38)	Normal saline	Reserved for fluid overload	Mainstay of therapy
<i>Washington Manual of Medical Therapeutics</i> (39)	Normal saline, 3–4 L in first 24 h	No, except for fluid overload	Administer early
<i>Hospital Medicine</i> (40)	Normal saline	"Contraindicated" unless fluid overload	Primary therapy with fluids
UptoDate (41)	Normal saline	Loop diuretic "out of favor"; use for overload	Concurrent with saline

who had an elevated creatinine level after a single dose of zoledronic acid (47). When managing hypercalcemia, a life-threatening complication, the risk–benefit ratio would certainly favor treatment because elevated creatinine levels are typically mild and reversible. Bisphosphonates have also been safely used for hypercalcemia in patients with pre-existing renal failure (48, 49).

Fluid resuscitation with normal saline and the immediate institution of bisphosphonate therapy—with or without calcitonin, depending on the severity of symptoms—is and has been the new standard for management of hypercalcemia (see **Key Summary Points**). Furosemide should be relegated to the management of fluid overload, which should be rare if one focuses on appropriate rehydration rather than trying to induce forced diuresis.

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