2019

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Matthew J. Miller
Wayne State University School of Medicine, mamiller@med.wayne.edu

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MATTHEW J. MILLER, B.S., Wayne State University School of Medicine, mamiller@med.wayne.edu

ABSTRACT   A critical appraisal and clinical application of Itou K, Fukuyama T, Sasabuchi Y, et al. Safety and efficacy of oral rehydration therapy until 2 h before surgery: a multicenter randomized controlled trial. *Journal of Anesthesia*. 2012;26(1):20-27. doi: 10.1007/s00540-011-1261-x.

Keywords: *bisphosphonates, nephrotoxicity, safety, renal insufficiency, renal failure, multiple myeloma, pamidronate, ibandronate, zaledronic acid*

Clinical Context

An 83-year-old African-American female with a history of multiple vertebral compression fractures and gastritis presented for the second time in two weeks with symptoms of hypercalcemia. At her first hospitalization, her hypercalcemia was attributed to dehydration and poor oral intake secondary to gastritis. After treatment with IV fluids alone, her calcium level improved from 13.0 mg/dL at admission to 11.3 mg/dL before discharge. Two weeks later, she was readmitted with a calcium level of 14.0 mg/dL. The patient's daughter noted a decline in her mother's cognition, and reported recent complaints of nausea, abdominal pain, and continued poor intake. The patient was diagnosed with hypercalcemia-induced pancreatitis and IV fluids were resumed. Endocrinology was consulted for management of hypercalcemia. Given a recent decline in the patient's kidney function (creatinine increased to 1.74 mg/dL from 0.86 mg/dL last admission), hemoglobin of 7.9 g/dL, and the history of fractures, a diagnosis of multiple myeloma (MM) was highly suspected. Serum and urine protein electrophoresis were ordered. In the interim, serum calcium levels were not adequately controlled with IV fluids alone, and endocrinology recommended a single dose of IV pamidronate, the standard of care for acute hypercalcemia.[1] Pharmacy declined to dispense pamidronate without the approval of nephrology, noting the patient's acute kidney injury. While awaiting nephrology consultation, the patient's mental status continued to decline and serum calcium levels spiked to 16.0 mg/dL. This case raises the question of whether bisphosphonates can be safely given for hypercalcemia in patients with impaired renal function.

Clinical Question

Can bisphosphonates be safely given to patients with hypercalcemia and renal insufficiency secondary to multiple myeloma?

MATTHEW J. MILLER, B.S., *is a 3rd year medical student at Wayne State University School of Medicine.*

Research Article

Bergner R, Henrich DM, Hoffman M, et al. Renal safety and pharmacokinetics of ibandronate in multiple myeloma patients with or without impaired renal function. *Journal of Clinical Pharmacology.* 2007 Aug;47(8):942-950. doi: 10.1177/0091270007301801

Related Literature

The literature search began with an UpToDate search using "bisphosphonates" and "renal failure" as keywords, with review of current recommendations regarding their use and safety. Several articles discuss the variability of bisphosphonates with respect to toxicity and effectiveness for treatment of hypercalcemia of malignancy (HCM). One cited article included a randomized controlled trial which showed ibandronate and pamidronate to be at least equally effective in the treatment of HCM.[2] Another retrospective study from 1999 compared renal tolerability of the various bisphosphonates, and concluded that ibandronate, pamidronate, and zoledronic acid were among the three least nephrotoxic bisphosphonates.[3]

The search for an article to address the clinical question more directly was conducted on PubMed. Keywords used were "bisphosphonates", "hypercalcemia", and "renal failure" which yielded 153 results. Six articles were found to be highly relevant to the clinical question, including three review articles about the management of hypercalcemia and bisphosphonate nephrotoxicity,[4-6] and three retrospective analyses.[3,7-8] Although there were numerous case reports of nephrotoxicity of these medications, only retrospective analyses and clinical trials were considered for appraisal. A 1996 retrospective study by Machado et al which examined 33 patients given pamidronate for hypercalcemia of malignancy showeda transient decline in renal function which was unrelated to drug administration.[7] Similarly, a 2006 study by Henrich et al. showed that in at least seven cases, ibandronate was well tolerated in patients with MM and acute renal failure.[8] While both studies help support the conclusion of this clinical appraisal, their small sample size and retrospective nature limit their generalizability.

The clinical trial selected for appraisal in this manuscript was found by searching PubMed with keywords "nephrotoxicity of bisphosphonates" while filtering for 'clinical trials'. This search yielded eight results, only one of which was relevant to multiple myeloma. While the patient in question did not have a confirmed diagnosis of MM, clinical suspicion was high enough to warrant including this as a key parameter. The study ultimately chosen was conducted by the same authors as the Henrich, et al. case review. In the discussion of that article, they noted that further investigation was warranted in randomized prospective trials. This study is the follow-up for that statement; it is a prospective study stratifying 40 patients by their degree of renal impairment and comparing outcomes after treatment with ibandronate. The authors' primary outcome of interest correlated well with this manuscript's clinical question – will treatment of patients with multiple myeloma with a bisphosphonate (ibandronate) lead to nephrotoxic damage in patients with pre-existing renal impairment? Other articles pertaining to the usage of bisphosphonates for treatment of hypercalcemia of other malignancies were not chosen, as the mechanisms behind renal dysfunction in these patients are likely to be far too diverse compared to renal failure in MM. Additionally, the chosen article cites a similar study conducted in 1997 with pamidronate as the administered bisphosphonate. This article was not chosen because of the smaller sample size in study groups, lack of focus on MM, and lack of analysis of objective markers of renal tubular damage (i.e. β-N-acetyl-glucosaminidase (βNAG), α-glutathione-S-transferase (αGST)).[9]

Critical Appraisal

This study is an open-label study examining the nephrotoxicity and pharmacokinetics of ibandronate in 40 patients with multiple myeloma. Ibandronate was chosen over other bisphosphonates as it had been shown in previous trials not to cause worsening of renal impairment in patients with pre-existing severe renal impairment. The study was conducted at Medical Department A of the City Clinic of Ludwigshafen, Germany. The recruitment strategy for study subjects was unclear, making it difficult to rule out selection bias. Inclusion criteria were adults aged 18 years or older, confirmed diagnosis of MM, and an indication for bisphosphonate treatment (bone lesions, osteolysis, or hypercalcemia). Patients were divided into four groups based on their baseline creatinine clearance (CrCl) determined by the average of three accepted criteria. All four groups received ibandronate treatment, with the highest CrCl group serving as the primary control for comparing to patients with decreased renal function. No blinding or randomization was utilized because all subjects received the same treatment allocation; the outcomes of interest, kidney function markers, were drawn by routine laboratory protocol unlikely to be influenced by measurement bias. The primary

pharmacokinetic endpoints in this trial included ibandronate area under the curve (AUC), serum ibandronate t1/2, ibandronate peak serum level, renal clearance, total body clearance, and nonrenal clearance. Tubular damage endpoints included change in serum creatinine, αGST, and βNAG measured at baseline, 24, and 72 hours. All subjects completed the study, with one subject not screened for markers of renal toxicity due to lack of availability of urine samples.

Despite a statistically significant increase in the ibandronate AUC over 24 hours in the lowest CrCl group relative to the highest CrCl group, no significant difference was found in peak serum ibandronate levels. Furthermore, there was no difference found between the stratified groups in markers of tubular damage at 24 and 72 hours post-infusion compared with pre-infusion. These data suggest that ibandronate can be used safely in MM patients across the entire range of kidney function.

Strengths of this study include the range of subjects with respect to kidney function, and the detailed measurement protocol with multiple fail-safes to control for variance in individual measurements. However, there are several limitations which prevent simple external generalizability. These include relatively small sample size, arbitrary groupings of kidney function, and lack of racial diversity in the sample. With a sample of only 40 subjects, the study may lack the statistical power needed to detect small but significant changes in serum creatinine or tubular damage markers. Variance for these markers was high, with the reported standard error of the αGST and βNAG being larger in magnitude than the reported mean in all cases. Furthermore, no rationalization is provided for CrCl cutoffs for stages of renal insufficiency. As a result, it can be assumed that cutoffs were chosen to allow a roughly equivalent number of subjects in each group (~10). It is unclear if statistical significance would still be found if more recently validated CKD staging definitions were used (i.e. category 1 renal insufficiency being defined as CrCl >90, category 2 as CrCl 60-89, etc).[10] Lastly, all 40 study subjects were Caucasian, limiting external validity to the African-American population, which is known to have different kidney function parameters.[11]

In addition to these study-specific limitations, it is also difficult to ensure that the lack of renal toxicity shown with ibandronate proxies well for other bisphosphonates shown to be less nephrotoxic. Although zoledronic acid and pamidronate were previously shown to be less nephrotoxic than other bisphosphonates,3 their pharmacokinetics are not perfectly analogous. For instance, the authors note that the AUC of pamidronate has been shown to increase 3-fold in patients with a CrCl <30 mL/min, which has an uncertain effect on the most severely renally impaired patients with multiple myeloma.

Finally, this stratified controlled trial meets criteria for level 3 evidence using the SORT Criteria, due to the focus on disease-oriented evidence (creatinine clearance, tubular necrosis markers) as opposed to patient-oriented evidence (morbidity, mortality, symptoms, or quality of life).[12]

Clinical Application

When treating patients with osteolytic and hypercalcemic manifestations of multiple myeloma, renal insufficiency has remained an important consideration before administration of bisphosphonate therapy. In our 83-year-old female with mild renal insufficiency but severe altered mental status secondary to hypercalcemia, a rapid treatment decision was needed. Based on the results of this study, ibandronate can be safely used to treat hypercalcemia secondary to MM in patients with renal insufficiency. However, the application of this study to our patient was imperfect, as confirmed diagnosis of MM was required for study inclusion and the study did not include any African-American patients. Furthermore, as is commonplace, availability of specific medications in the hospital formulary was limited, forcing clinicians to choose between other less nephrotoxic bisphosphonates such as pamidronate or zoledronic acid. Ultimately, an informed discussion with the patient's daughter was needed regarding proceeding with treatment. Given that the patient was too altered to communicate and the evidence for its safety, the daughter agreed that it was worth risking possible further nephrotoxicity from pamidronate. The decision was made to administer renally-dosed pamidronate, and the patient's hypercalcemia and mental status rapidly improved without evidence of further kidney injury.

Learning points:

1. Renal insufficiency is not an absolute contraindication to bisphosphonate therapy for multiple myeloma, and symptomatic treatment need not be delayed on this basis.

2. The highest degree of evidence for renal safety exists for ibandronate, but pamidronate and zoledronic acid have also shown less renal toxicity than other bisphosphonates.

3. Clinical trials may have limited external validity if the study group chosen is not particularly diverse, even despite adequately broad inclusion criteria.

References

1. Wood AJJ, M.D., Bilezikian JP, M.D. Drug therapy: Management of acute hypercalcemia. *N Engl J Med.* 1992;326(18):1196-1203. doi: 10.1056/NEJM199204303261806

2. Pecherstorfer M, Steinheuer EU, Rizzoli R, et al. Efficacy and safety of ibandronate in the treatment of hypercalcemia of malignancy: a randomized multicentric comparison to pamidronate. *Supportive Care in Cancer*. 2003;11(8):539-47. doi: 10.1007/s00520-003-0477-1

3. Zojer N, Keck AV, Pecherstorfer M. Comparative tolerability of drug therapies for hypercalcaemia of malignancy. *Drug Safety.* 1999;21(5):389-406. doi: 10.2165/00002018-199921050-00004

4. Assadi F. Hypercalcemia: an evidence-based approach to clinical cases. *Iranian Journal of Kidney Disease.* 2009;3(2):71-9

5. Perazella MA, Markowitz GS. Bisphosphonate nephrotoxicity. *Kidney International*. 2008;74(11):1385-93. doi: 10.1038/ki.2008.356

6. Tanvetyanon T, Stiff PJ. Management of the adverse effects associated with intravenous bisphosphonates. *Annals of Oncology*. 2006;17(6): 897-907. doi: 10.1093/annonc/mdj105

7. Machado CE, Flombaum CD. Safety of pamidronate in patients with renal failure and hypercalcemia. *Clinical Nephrology*. 1996;45(3):175-9

8. Henrich D, Hoffmann M, Uppenkamp M. Ibandronate for the treatment of hypercalcemia or nephrocalcinosis in patients with multiple myeloma and acute renal failure: Case reports. *Acta Haematologica*. 2006;116(3):165-72. doi: 10.1159/000094676

9. Berenson JR, Rosen L, Vescio R, et al. Pharmacokinetics of pamidronate disodium in patients with cancer with normal or impaired renal function. *Journal of Clinical Pharmacology.* 1997;37:285–290. doi: 10.1002/j.1552-4604.1997.tb04304.x

10. Delanaye P, Glassock RJ, Pottel H, et al. An age-calibrated definition of chronic kidney disease: rationale and benefits. *Clin Biochem Rev*. 2016;37(1):17-26

11. Levey AS, Berg RL, Gassman JJ, et al. Creatinine filtration, secretion and excretion during progressive renal disease. Modification of Diet in Renal Disease (MDRD) Study Group. *Kidney Int Suppl.* 1989;27:S73-80

12. Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *J Am Board Fam Pract*. 2004;17(1):59-67. doi: 10.3122/jabfm.17.1.59