Acute severe diarrhoea and hyponatremia after zoledronic acid infusion: an acute phase reaction

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Summary

Zoledronic acid (ZA), an intravenous aminobisphosphonate, is prescribed widely for postmenopausal osteoporosis. It is a relatively safe drug but may cause adverse effects including acute phase reaction. Oral non-aminobisphosphonates are known to cause diarrhoea that is usually mild and self-limited. Intravenous aminobisphosphonates are not known to cause diarrhoea. We describe a case of acute watery diarrhoea complicated by severe hyponatremia and hypotension following ZA infusion. The patient needed intensive care for four days. To the best of our knowledge, this type of acute diarrhoea complicated by severe hyponatremia, following ZA infusion, is not reported so far. Strong temporal relation with ZA administration makes it the most likely cause. Furthermore, all laboratory and imaging parameters indicate that the secretory diarrhoea may be a component of acute phase reaction. According to World Health Organization (WHO) causality scale, ZA was a probable cause of acute watery diarrhoea in our patient. Clinicians should be aware that ZA administration can cause acute watery diarrhoea and may lead to severe hypotension and hyponatremia.

KEY WORDS: zoledronic acid; acute severe diarrhoea; hypotension; hyponatremia; postmenopausal osteoporosis.

Introduction

Zoledronic acid (ZA) is used commonly for the management of post-menopausal osteoporosis. This is an effective drug and the compliance is usually good because of annual dosage. ZA is associated with short-term as well as some long-term adverse reactions. Among short-term, acute phase reaction manifest as fever, malaise, nausea, arthralgia and bone pain, is commonly seen (1). Mild diarrhoea that is self-limited has been reported with oral non-aminobisphosphonates but not with oral or intravenous aminobisphosphonates. We report a case of acute watery diarrhoea leading to severe hypotension and hyponatremia following ZA infusion.

Case report

A 62-year-old female from Afghanistan had come for annual health check-up. She had primary hypothyroidism for 2 years and was taking 200 micrograms levothyroxine. Her body mass index (BMI) was 21 kilograms per meter squared. Physical examination revealed some degree of kyphosis in the dorsal spine. Laboratory investigations revealed suppressed TSH but normal free thyroxine levels (Table 1). Bone densitometry revealed osteoporosis with T score at lumber spine (L1-L4) of -3.7. Lateral vertebral morphometry revealed anterior wedging of dorsal 8th vertebra. Other laboratory parameters were unremarkable. Her levothyroxine dose was reduced to 150 micrograms (as TSH was suppressed). She was prescribed calcium carbonate (1500 mg elemental calcium daily in divided doses) and oral cholecalciferol (2000 IU daily). She was also prescribed ZA 4 mg intravenous infusion in 200 mL normal saline over a period of 20 minutes. She was advised to take oral paracetamol 500 mg every 6 hourly for 3 days, starting from the time of ZA infusion. She received ZA in a daycare setting at 14:00 hours. On the same day, at 20:00 hours she developed fever (102 degrees Fahrenheit) and mild arthralgia. Next day, at 02:00 hours, she developed nausea, recurrent vomiting and watery diarrhoea. She had about ten episodes of watery diarrhoea till morning. She was hospitalized in the morning and was found to have hypotension (systolic blood pressure of 60 mmHg), tachycardia (pulse rate of 134 beats per minute) and hyponatremia. She had taken home-cooked food in the apartment along with her son and other three family members in the previous evening. They did not experience any problem. In the intensive care unit, she received normal saline and was investigated for any infective cause of the condition. The laboratory parameters are given in Tables 1 and 2. After initial investigations, she was put on empirical intravenous antibiotics (metronidazole and levofloxacin). However, she showed no improvement for next four days. She developed severe hyponatremia, despite giving normal saline as replacement fluids (Table 1). She was also given 100 mL of hypertonic saline for a few hours as her serum sodium dropped as low as 113 mmol/L at some point of time. Despite extensive evaluation, no cause for acute diarrhoea was evident. Stool analysis was done on four occasions during six days of hospital stay. On macroscopy, stools were greenish in color, watery in consistency and had no mucus

Table 1 - Biochemical parameters of the patient during hospital stay.

Parameter	OPD#(-3)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Normal Values
Sodium (mmol/L)	**137**	**120**	**118(M) 117(E)**	**113(M)* 117(N) 115(E)**	**118(M) 117(N)** 120(E)**	**124(M) 127(N) 129(E)**	**131(M) 133(N)**	**135-140**
Chloride (mmol/L)	**99**	**93**	**89**	**94**	**98**	**100**	**106**	**98-107**
Urea (mg/dL)	**39**	**11**	**8.5**	**7.0**	**4.0**	**4.0**	**4.0**	**19-43**
Creatinine (mg/dL)	**0.6**	**0.5**	**0.5**	**0.4**	**0.4**	**0.4**	**0.5**	**0.4-1.4**
Total Calcium (mg/dL)	**10.0**	**7.0**	**-**	**6.7**	**6.7**	**7.0**	**7.2**	**8.5-10.4**
Albumin (mg/dL)	**3.9**	**-**	**2.4**	**2.3**	**-**	**2.8**	**3.1**	**3.5-4.5**
Hemoglobin (g/dL)	**12.8**	**11.9**	**10.0**	**10.7**	**10.1**	**10.4**	**10.6**	**12.0-15.0**
Hematocrit (%)	**38.1**	**35.1**	**29.5**	**30.5**	**28.2**	**30.3**	**31.4**	**35-50**
Total Leucocytes (x 10^3/µL)	**7.91**	**8.5**	**5.72**	**7.57**	**6.97**	**5.86**	**7.81**	**4.0-10.0**

*#OPD = outpatient department, M = morning, N = noon, E = evening, *100ml hypertonic saline infusion was given, **Antibiotics stopped, Racecadotril and Lopamide started.*

Table 2 - Parameters of the patient during hospitalization.

Parameter	During hospitalization	Normal value
Amylase (U/L)	30.0	30-110
Lipase (U/L)	48.0	23-300
Morning Cortisol (µg/dL)	36.1	-
Hanging drop preparation (stool)	Vibrio absent	-
Clostridium difficile toxin, A & B	0.01	<0.13
TSH (µIU/mL)	0.015	0.46-4.6
Free T4 (ng/dL)	2.03	0.78-2.19
C-reactive protein (mg/L)	127.2	0.0-10.0
Anti-tTG AntibodyIgA (IU/mL)	1.0	<20.0
IgA levels (mg/dL)	202.6	70-400
Anti-HIV, I & II	Non-reactive	-
Anti-HCV	Non-reactive	-

TSH (thyroid stimulating hormone), T4 (thyroxine),

or blood. Microscopy of stools did not reveal any pus cells, red cells, ova or cysts. Stool cultures did not grow shigella, salmonella or vibrio pathogens after two days of aerobic incubation. No organisms with darting motility morphologically resembling vibriocholerae were seen. Blood and urine cultures were unremarkable. On day 4th of admission, we decided to stop antibiotics and put her on anti-secretory agents (racecadotril 100 mg 6 hourly and loperamide 2 mg 8 hourly) for diarrhoea. She showed signs of improvement after four hours of change of the treatment. Her nausea subsided and stool consistency and frequency improved. On 6th day, she had normal stools, and her serum sodium was 131 mmol/L. She was conscious and was feeling well.

Discussion

Oral bisphosphonates (alendronate, risedronate and ibandronate) may cause upper gastrointestinal tract (GI) symptoms, acute phase reactions, hypocalcemia and osteonecrosis of jaw (1). Intravenous bisphosphonates (pamidronate, ibandronate and zoledronate) do not cause upper GI adverse reactions. Furthermore, intravenous bisphosphonates have been associated with nephrotoxicity, atrial fibrillation and atypical fractures of femoral diaphysis (2). Bisphosphonates are also associated with cutaneous reactions, oral ulcerations, ocular inflammation, and esophageal neoplasia (3) in a few case reports. Acute watery diarrhoea causing pro-

found hyponatremia is not a reported adverse reaction of either oral or intravenous aminobisphosphonates.

Intravenous bisphosphonates cause acute systemic inflammatory reactions, characterized by fever, nausea, vomiting, myalgia, arthralgia and edema. This acute phase reaction is dose-dependent and occurs mainly after the first infusion (4). The cause of acute phase reaction is a transient rise in pyrogenic cytokines particularly interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) (5). Intravenous bisphosphonates cause disruption of the mevalonate pathway of cholesterol synthesis. The substrates of inhibited mevalonate pathway especially dimethylallyl pyrophosphate stimulate gamma/delta (γ/δ) T lymphocytes and increase production of IL-6 and TNF-α. Release of IL-6 and other pro-inflammatory cytokines occurs 24-48 hours after ZA infusion. Thus, acute phase reaction is maximally expressed 24-36 hours after ZA infusion and subsides 2-3 days later (6). We hypothesize that the type of acute watery diarrhoea and hyponatremia seen in our patient is a kind of acute phase reaction at the intestinal level. This has led to initial fever, acute secretory diarrhoea and subsequently loss of electrolytes (sodium and chloride) (Table 1). The pathogenesis of secretory diarrhoea may be analogous to the diarrhoea of systemic mastocytosis, where mast cell degranulation releases proinflammatory cytokines and lead to watery diarrhoea (7). Furthermore, hypotension in our patient does not seem to be due to fluid losses, as there was no increase in blood urea. Hypotension may be a part of vascular reaction to pro-inflammatory substances. Every effort was made to exclude infective causes of diarrhoea. The patient had fever on day first of ZA infusion and then subsided on the second day. All work-up for infective pathology was unrevealing. Her serum albumin was low which is a negative acute phase reactant. Serum C-reactive protein (CRP) levels were elevated, indicating acute phase reaction.

As the patient was evaluated three days prior to ZA infusion, her postero-anterior view of chest skiagram and ultrasonography of abdomen was unremarkable. But during the illness, her chest radiograph revealed blunting of right costo-phrenic angle suggestive of right pleural effusion. Sonography of abdomen revealed mild right pleural effusion and mild ascites. Serositis is a manifestation of acute systemic inflammatory reaction and explains mild ascites and pleural effusion in our patient. Ultrasound did not reveal pleural effusion and ascites on the 6th day of the illness. An initial acute phase reaction followed by aseptic peritonitis resulting in unnecessary laparotomy has been reported in one patient 12 days after pamidronic acid infusion (8).

Laboratory abnormalities during the acute systemic inflammatory reactions include elevated CRP, mild anemia, and transient leucopenia (9). Transient leucopenia may be detected within 24 hours and a reduction of up to 50% of CD4+ lymphocytes in peripheral blood has been observed at 3 days (10). Our patient had elevated CRP (127.2 mg/L) and dropped hemoglobin from 12.8 g/dL to 10.0 g/dL on day 2. Transient drop in total leucocytes was also seen at day 2 (TLC on day 1 = 8,500/μL and on day 2 = 5,720/μL, drop of 2,780 cells/μL). These parameters indicate the presence of acute systemic inflammatory reaction that may have led to this type of diarrhoea and hyponatremia.

Our patient also developed hypocalcemia on the 3rd day of ZA infusion (lowest total corrected calcium was 8.06 mg/dL). Hypocalcemia and hypophosphatemia are known electrolyte abnormalities following ZA infusion (11). Hyponatremia after ZA infusion is not reported. In our patient, loss of sodium and chloride from GI tract due to severe diarrhoea might have led to severe hyponatremia requiring hypertonic saline infusion.

The limitation of our report is that we could not formally exclude viral causes of the illness, although it appears least likely because all other family members had consumed the same food and had not experienced any diarrhoea. Moreover, strong temporal relation between acute diarrhoea and the administration of ZA in an otherwise normal person makes it the most likely cause. According to World Health Organization (WHO) causality scale, ZA was a probable cause of acute severe diarrhoea in our patient. According to the Naranjo's scale, the effect of ZA was scored 6 indicating a probable likelihood of causing acute watery diarrhoea and hyponatremia in our patient.

Conclusion

Short-term and long-term adverse reactions are associated with intravenous aminobisphosphonates. Among short-term adverse drug reactions, acute phase response is frequently seen. This report shows that acute watery diarrhoea leading to severe hyponatremia and hypotension may be associated with ZA administration and should be kept in mind as an uncommon adverse reaction of the drug.

Disclosure statement

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