

Ibandronate-associated ischemic colitis – case report

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ABSTRACT

Ibandronate is considered to be a safe drug, and the few reported side-effects in the digestive system are usually related to the upper gastrointestinal tract. Large bowel lesions associated to ibandronate use in humans have not been reported. We describe the case of a 52-year-old female with two episodes of lower abdominal pain after the intake of oral ibandronate. The second pain episode was followed by hematochezia with endoscopic and histological evidence of sigmoid ischemia. No other possible causes of colonic ischemia were found. After a short hospital admission, there was a complete clinical, endoscopic and histological recovery. Ibandronate was withdrawn and the patient reported no further gastrointestinal complaints. This is the first reported case of colon bleeding related to the use of Ibandronate.

Keywords: Colitis ischemic; Diphosphonates; Adverse effects.

INTRODUCTION

Osteoporosis is an important morbidity condition, and may cause severe disability especially in the elder. Several treatments to prevent its progression and to decrease its complications have been developed during the last two decades¹, and a variety of drugs is currently available. Among these, bisphosphonates (BPs) are widely used to reduce excessive bone turnover and to prevent pathologic fractures^{2,3}.

However, these drugs may have side-effects, especially in the gastrointestinal (GI) tract, where they can harm the mucosa, causing inflammation and leading to ulceration and necrosis^{4,5}.

A new generation of nitrogen-containing BPs was developed aiming at a better tolerance. Being administered at larger intervals, these new molecules are associated with less GI symptoms and better treatment compliance⁶. Ibandronate is one of such drugs, its formulation allowing it to be taken orally only once a month.

In spite of the improved safety profile of nitrogen-containing BPs, recent studies showed new properties and interactions⁷⁻⁹. Furthermore, on a long-term basis, the incidence of upper GI symptoms seems to be similar with both nitrogen-containing and non-nitrogen-containing BPs¹⁰.

Ischemic colitis is a frequent result of drug-induced injuries to the colon. Iatrogenic ischemic colitis can be caused by a variety of medications, including anti-hypertensive agents, diuretics, non-steroidal anti-inflammatory drugs, digoxin, oral contraceptives, pseudoephedrine and alosetron¹¹. Despite the great number of drugs causing colonic lesions, there is a wide lack of recognition of this causal relationship, and those cases are still under-reported¹². To the best of our knowledge there are no reported cases of ischemic lesions of the colon associated to the use of Ibandronate. We report a case of ischemic sigmoiditis in a patient under Ibandronate therapy.

CASE REPORT

A 52-year-old woman presented with a two days acute history of bilious vomiting, lower abdominal cramping pain, abdominal distension and diarrhea. These complaints were followed by the emission of bright red blood mixed with stools associated with an urge to defecate.

Her medical background included non-ulcer dyspepsia, controlled with oral omeprazole 20 mg/day, mild hypertension treated with lisinopril plus hydrochlorothiazide and a recent diagnosis of osteopenia treated with Ibandronate. The patient denied smoking and

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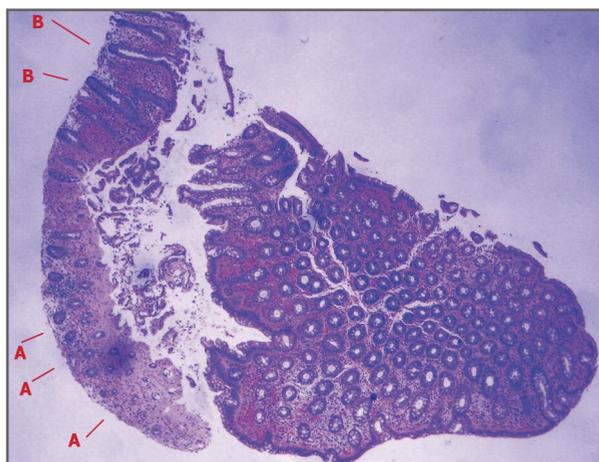


FIGURE 1. Sigmoid biopsy, haematoxylin-eosin. Severe ischemic lesions of the superficial epithelium (A) with transition to more preserved mucosa (B)

alcoholic or addiction consumptions. There was no history of hospitalizations or surgeries and no personal or family history of bleeding disorders. One month before, she had taken ibandronate for the first time, and this was followed by moderate abdominal cramping pain and diarrhea without blood; these complaints subsided spontaneously. Her second administration of ibandronate was on the day before the beginning of the present complaints.

On examination the patient was prostrated and clammy. The temperature was 36°C, the blood pressure 128/65 mmHg, the pulse 78 beats per minute. The cardiopulmonary examination was unremarkable and the abdomen was soft but with a tender area in the left and lower quadrants. Bowel sounds were present; the digital rectal examination showed traces of blood without stools or palpable masses. The sequential blood tests were all normal (hemoglobin 148 > 136 g/L, leucocytes 10000 > 5100 /L, neutrophils 81.8% > 65.2%, C-reactive protein 0.6 > 0.6 mg/dL). The ECG was normal, with no cardiac rhythm abnormalities.

A fibrosigmoidoscopy was performed. The rectal mucosa was normal, but at 30 cm from the anal margin there was an abrupt and irregular transition to a segment of congestive mucosa, with friability and easy bleeding when touched. Biopsies disclosed mucosal and submucosal hemorrhage with some hemosiderocytes, superficial destruction of crypts and fibrin. Crypt distortion, pathologic inflammatory infiltration or goblet cell depletion were absent (Figure 1). The

patient was admitted and put on iv fluids and metronidazole. Her outpatient anti-hypertensive medication was maintained and she showed a good tolerance to oral feeding, resuming her usual dietary pattern. She kept normal bowel movements, was discharged after her tolerance to solid foods was confirmed. A recommendation was made to avoid ibandronate treatment.

The laboratory coagulation study was within normal range, including thrombin, fibrinogen, TTPa, prothrombin time, V Leiden factor, Protrombin-G20210A and von Willebrand factor. A left-side colonoscopy two months later showed a normal colonic mucosa, which was confirmed by the biopsy.

DISCUSSION

The common presentation of non-gangrenous ischemic colitis (disease contained within colonic wall) is consistent with the clinical, endoscopic and laboratory patterns described in this case and the recommended treatment is mainly supportive^{11,13}.

This patient was on anti-hypertensive medication, and this was continued during her hospital admission and there was no evidence of hypotension or any other transient circulatory impairment leading to ischemia of the colon. The age of the patient and the absence of clinical history or signs suggestive of atherosclerotic disease, together with her prompt complete recovery, argue against that etiology. The coagulation studies were helpful in excluding the major prothrombotic conditions. Also the rapid recovery without specific medication helps to exclude other conditions, namely infectious causes. On the other hand, there were two similar episodes of cramping abdominal pain and diarrhea both immediately after the oral intake of ibandronate: these could be viewed as a rechallenge test and suggests a causal relationship between the ibandronate use and the colonic injury. The evidence of acute ischemic sigmoiditis precluded the progression to the cecum, and the patient declined a total colonoscopy after her symptoms improved – but she had no previous or further bleeding episodes.

Ibandronate and other related nitrogen-containing BPs inhibit the enzyme farnesyl pyrophosphate (FPP) synthase in the mevalonate pathway. This inhibition breaks protein prenylation, which leads to instability in osteoclast's cytoskeleton, reducing its activity and bone resorption⁹.

Besides the bone effects, other systemic reactions

such as the mevalonate pathway blockage can occur and result in an acute-phase reaction mediated by tumor necrosis factor alpha which is promoted by a precursor called isopentenyl pyrophosphate (IPP) which accumulates during the FPP synthase disruption⁹.

Another property of nitrogen-containing BPs is to induce apoptosis or to inhibit proliferation of a laboratorial model of gut epithelial cells (Caco-2 human epithelial cells), which explain what could be happening on GI tract in vivo⁷.

Moreover, recent studies have shown that is a protective effect of BPs on inflammatory bowel disease in rats model as a consequence of inhibition of Cyclooxygenase-2 (COX-2) and induced-Oxid Nitric synthase (iNOS) production in the colon cells⁸. However, not only are COXs and NOS effects important to inflammatory phases, but they are also key enzymes in the regulation of vascular permeability in response to hypoxia and angiogenesis stimulus (by mediators such as, VEGF/VPE, bFGF, TGF-beta, PDGF, and endothelin-1)^{14,15}.

Furthermore, it is well-known the protection against ischemia promoted by the COX-2 and iNOS in other organs. In fact, several studies showed its benefits in decreasing myocardial ischemic injury¹⁶.

Overall, a better knowledge of nitrogen-containing lower GI effects BPs is necessary to determine its potential properties to cause ischemic colitis.

We believe that this ischemia of the colon was related to the ibandronate use and to the best of our knowledge no previous reports of this association are found in the medical literature. We hope that this report will contribute to a raised awareness of medications as a potential cause of large bowel lesions.

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