Heterotopic bone formation in abdominal incisions

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Heterotopic bone formation in vertical abdominal wounds is a not infrequent and sometimes disabling complication of abdominal surgery, occurring predominantly in males. Excision of the bone is indicated only for marked discomfort or pain, usually produced by an active lifestyle. Under these circumstances, recurrence of bone following excision, would be highly undesirable and the prophylactic use of etidronate disodium may well be indicated to prevent new bone formation, as demonstrated by one of our cases (Case 8).

Introduction

Heterotopic bone formation in scars of abdominal incisions is not a rare occurrence, yet few reports are present in the literature**. We report 8 recent cases, all males, in one of whom the bone recurred after excision; in another, prophylactic treatment was given to prevent recurrence of bone formation in the surgical wound, using etidronate disodium (EHDP: Didronel). We present a review of the literature regarding heterotopic bone formation in abdominal wounds, indications for surgery and possible uses of EHDP.

Case reports

Case 1
A 53-year-old white male health professional underwent a subtotal gastrectomy for adenocarcinoma of the stomach, through a vertical incision. Two years later the patient died from metastatic disease. At autopsy, heterotopic bone formation was present in his abdominal scar.

Case 2
A 72-year-old retired white man underwent a partial colectomy for adenocarcinoma of the colon, through a vertical incision. Four months later bone formation was discovered in the scar and was surgically excised.

Case 3
A 45-year-old disabled white male laborer underwent vagotomy and pyloroplasty for intractable duodenal ulcer, through an upper midline incision. At the postoperative visit, induration was noted in the wound, which progressed to radiologically proven bone. His lifestyle was not hindered by the bone, which was thus left alone and has not changed in 3 years.

Case 4
A 69-year-old retired white man underwent palliative esophagectomy for advanced adenocarcinoma arising in Barrett's esophagus, through an upper midline and a separate right thoracic incision. Six weeks later bone 5 cm long was noted in the upper part of the vertical midline incision. This did not hinder him and was left alone.

Case 5
A 44-year-old white truck driver underwent a vagotomy, pyloroplasty and fundoplication for severe acid-pepsin disease, plus esophagitis. After several months, he was noted to have a piece of bone 3 x 2 cm in size at the upper end of his wound, near the xiphoid process. This did not progress nor interfere with his activities and was left alone.

Case 6
A 70-year-old retired white man underwent a high partial gastrectomy for gastric lymphoma. Two months later, in follow-up, he was noted to have a piece of bone about 5 cm long by 2-3 cm wide in the upper part of his abdominal scar. His main activity was walking and the bone did not hinder him, so it was left alone.

Case 7
A 40-year-old white laborer underwent drainage of a pancreatic pseudocyst through an upper midline incision. Bone formation was noted 3 weeks later in the scar. The bone was 10 cm long and bowed anteriorly, extending from xiphoid to umbilicus. As he became more active, it hindered his activities and was excised. The bone recurred but was only about 5 cm in length and no further surgery was performed.

Case 8
A 49-year-old white male plasterer underwent a cholecystectomy, appendectomy and repair of an umbilical hernia through an upper midline incision. Bone formation was noted 3 weeks later in the scar. The bone was large (6 x 4 x 3 cm), bowed forward, and continuous with the xiphoid process. The bone interfered mechanically with movement and was painful

Received for publication March 1, 1991.

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Of all the H₂-receptor antagonists, only Axid heals and relieves reflux esophagitis at its standard duodenal ulcer dosage. Axid, 150 mg b.i.d., relieves heartburn in 86% of patients after one day and 93% after one week.¹

¹ Data on file, Lilly Research Laboratories. See accompanying page for prescribing information. © 1991, ELI LILLY AND COMPANY.
AXID
nizatidine capsules

Summary. Consult the package insert for complete prescribing information.

Indications and Usage. 1. Active duodenal ulcer — for up to 6 weeks of treatment at a dosage of 300 mg. orally b.i.d. or 150 mg b.i.d. Most patients heal within 4 weeks. 2. Maintenance therapy — for healed duodenal ulcers at a dosage of 150 mg b.i.d. at bedtime. The consequences of therapy with Axid for longer than 1 year are not known.

Geotrophic/gastric reflux disease (GERD) — for up to 12 weeks of treatment of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn at a dosage of 150 mg b.i.d. 

Contraindications: Known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, β-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other β-receptor antagonists.

Precautions: General — 1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy. 2. Dosage should be reduced in patients with moderate to severe renal insufficiency. 3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is not altered.

Laboratory Tests — False-positive tests for urinalysis with Multistix® may occur during therapy. Drug interactions — No significant interactions have been observed with aspirin, aminosalicylate, lidocaine, phenylpropanolamine, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system. Therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility — A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a large increase in the density of reticulohistiocytoid (LIS) cells in the gastric antral mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic lymphoid follicles were present in the high-dose males and placebo. Female mice given the high dose of Axid (2,500 mg/kg/day, about 150 times the human dose) showed marginally statistically significant increases in hepatic carcinomas and hepatic nodular hyperplasia with no increase in the number of any of the other dose Groups. The rate of hepatic tumors in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a daily water intake that was much lower than the maximum tolerated (MTD), as indicated by hematology and clinical observations, compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal trend (a low-dose dose at which the animals given an excessive and unusual amount of hepatocellular dose) with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose) is a negative mutagenic finding that is not considered evidence of a carcinogenic potential for Axid. Axid was not mutagenic in a battery of tests performed to evaluate its potential genotoxic toxicity, including bacterial mutagenicity tests, uncharged DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and an in vivo test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine to 1,500 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy — Sympathetic Effects — Pregnancy Category C — Oral reproduction studies at doses up to 500 mg/kg/day (about 80 times the maximum recommended daily therapeutic dose) and in pregnant rabbits at 20 mg/kg/day, the highest dose to which rabbits can be exposed, showed no evidence of impaired fertility or teratogenic effect. No differences were observed in offspring outcomes between Axid and placebo at the incidence of any of the adverse reactions (one package insert for complete information).

Adverse Reactions: Worldwide, controlled clinical trials included over 6,000 patients given nizatidine in studies of varying durations. Placental complications were observed in the United States and Canada over 2,600 patients and 130 pregnancies. Among the adverse events in these placebo-controlled trials, only anemia (6.2% vs 9%) and urticaria (0.5% vs 0.1%) were significantly more common in the nizatidine group. Among the adverse events that occurred in 1% or more of these patients, there was no statistically significant difference between Axid and placebo in the incidence of any of these adverse events. No significant differences were observed in any adverse reactions (one package insert for complete information).

In a total of 320 patients, adverse events were reported, it was not possible to determine whether these events were caused by nizatidine or were probably caused by the use of the test drug or were unrelated to nizatidine. 

Hypersensitivity — Adverse reactions (reactions which may occur with the use of a drug and are not necessarily caused by the drug), including urticaria, angioneurotic edema, erythematous rash, asthma, angioedema, anaphylactic shock, and eosinophilia have been reported. Mixed cutaneous-hypersensitivity reactions have also been reported. Adverse reactions which may occur with the use of a drug and are not necessarily caused by the drug, including allergic reactions, urticaria, angioneurotic edema, erythematous rash, asthma, angioedema, anaphylactic shock, and eosinophilia have been reported. Adverse reactions which may occur with the use of a drug and are not necessarily caused by the drug, including allergic reactions, urticaria, angioneurotic edema, erythematous rash, asthma, angioedema, anaphylactic shock, and eosinophilia have been reported.

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Heterotopic bone formation in surgical wounds of the abdomen occurs only in longitudinal incisions (as opposed to horizontal ones)4, thus implicating the xiphoid process or symphysis pubis as possible progenitors in its pathogenesis. The bone is formed in the lower abdomen, and is usually attached near the xiphoid process. The bone is formed in the lower abdomen, and is usually attached near the xiphoid process. The bone is formed in the lower abdomen, and is usually attached near the xiphoid process. The bone is formed in the lower abdomen, and is usually attached near the xiphoid process. The bone is formed in the lower abdomen, and is usually attached near the xiphoid process. The bone is formed in the lower abdomen, and is usually attached near the xiphoid process. The bone is formed in the lower abdomen, and is usually attached near the xiphoid process. The bone is formed in the lower abdomen, and is usually attached near the xiphoid process.

Discussion
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ly exclusive and it is our belief that either of these modes of bone formation may occur, separately or together, keeping in mind that the linea alba is possibly a vestigial remnant of the sternum. There is no evidence linking heterotopic bone formation to any metabolic or endocrine disorder, nor to the nature of the suture material used.

The cure for heterotopic bone formation in surgical wounds has generally been surgical excision, with occasional postoperative radiation. However, we now propose a possible preventive measure with the use of etidronate disodium (EHDP). EHDP is the only drug of its class of compounds — biphosphonates (formerly diphosphonates) — currently on the market. Biphosphonates are structural analogs of pyrophosphate, a naturally occurring inhibitor of bone formation. EHDP prevents the conversion of amorphous calcium phosphate to crystalline hydroxyapatite, the mineral component of bone. Furthermore, it also binds to the hydroxyapatite present, rendering it more resistant to chemical attack by alkaline and acid phosphatases produced by the osteoblasts and osteoclasts respectively. It thus slows down both the dissolution and the accumulation of mineral. Also, it appears to interfere with the conversion of osteoblasts to osteocytes and markedly reduces the osteoclast population. Serum calcium and parathyroid hormone levels are not significantly changed, yet in Paget's Disease a marked decrease in both urinary hydroxyproline and serum alkaline phosphatase is noted, reflecting decreased osteoclastic and osteoblastic activity.

In short, EHDP inhibits both bone remodeling and mineralization.

The principal use of EHDP is in the treatment of Paget's Disease. It has also been recommended for heterotopic ossification in patients following severe head or spinal cord injury and following total hip arthroplasty. EHDP has also been used with varying success in postmenopausal osteoporosis, myositis ossificans progressiva, calcinosis universalis, the prevention of periodontosis, and the prevention of calculi in the urinary tract. On an investigational basis, it has been studied for the prevention of atherosclerosis. Recently, the intravenous administration of dichloromethylene diphosphonate (not currently on the market) and EHDP have shown great promise in lowering the serum calcium in patients with hypercalcemia of malignancy.

The side effects of EHDP therapy are usually manifested only when large or prolonged doses are administered, consisting of gastrointestinal upset, osteomalacia (with increased likelihood of pathologic fractures), hyperphosphatemia, and an increase in bone pain.

Apart from its primary use in Paget's Disease, EHDP exerts its most beneficial effect in the prevention of heterotopic bone formation before its actual onset, rather than as treatment.

Two of our patients (Cases 7 and 8) experienced severe pain and inconvenience from the large ossified fragments in their abdominal wounds. Since in each patient the heterotopic bone was attached to the xiphoid process, there was considerable limitation of their activities as construction workers. It is known that trauma and heavy physical labor can predispose to heterotopic bone formation. With these considerations in mind, and after the bone recurred in Case 7, the next patient (Case 8) received pre- and postoperative EHDP and has not had a recurrence of heterotopic bone formation after 6 years.