Comment

While pamidronate has been well established in double-blind controlled studies as a treatment for the symptoms and skeletal complications of metastatic bone disease, no studies have dealt with the problem of breakthrough pain, incident in nature. A lack of evaluation of incident pain in all the studies is surprising, as most bone pain presents with incident characteristics.

The case reported is quite impressive, because an extraordinary recovery in the patient’s functionality and activity was observed. While a decrease in opioid dose while maintaining acceptable baseline pain relief would be expected, such a relevant effect on pain associated with physical activity was really dramatic. Several open-label studies suggested improvements in symptoms and on radiography with a variety of doses and treatment schedules with pamidronate. However, in this case report there was no change in the radiological findings after pamidronate.

Metastatic bone pain is traditionally attributed to various factors, notably the release of chemical mediators, increased pressure within the bone, microfractures, stretching of the periosteum, nerve root infiltration and/or compression. The bisphosphonates may have the potential to reduce pain on movement, which is commonly attributed to the stretching of periosteum on a weakened bone.

Pamidronate presumably contributes to bone sclerosis in patients receiving concomitant tamoxifen and radiotherapy. An accumulation of radioligand was observed in the case here reported. However, it is difficult to interpret whether this corresponds to an increase in bone mineral density. An alternative and independent effect of pamidronate may be hypothesized. The effects of pamidronate on incident pain due to bone metastases should be assessed in future prospective studies to better explain the possible mechanisms in clinical situations.

Efficacy of Haloperidol in the Treatment of Nausea and Vomiting in the Palliative Patient: A Systematic Review

To the Editor:

Nausea and vomiting are common in patients with terminal illness, even in the absence of treatment with chemotherapy or radiotherapy. Studies report that between 50–62% of patients with terminal malignant disease suffer from nausea and vomiting at some point during their illness. Clinicians often prescribe haloperidol as an antiemetic and antinauseant in these situations and textbooks of palliative care routinely suggest this therapy. We performed a systematic review to determine the evidence upon which this recommendation is based.

The review followed criteria proposed by the Cochrane Collaboration. Studies were included if they met the following criteria: any design, published in any country, in any language; data on humans of any age with cancer or a terminal or palliative condition, experiencing nausea or vomiting not induced by chemotherapy or radiotherapy; use of haloperidol, droperidol, or butyrophenone, by any route, following any regimen, for the relief of nausea or vomiting or both; and availability of data on

References


the response of nausea or vomiting to the interventions listed above.

We identified the articles through searches of MEDLINE (1966 to May 2000); HealthStar (1975 to April 2000); Cinahl (1982 to February 2000); Cancerlit (1983 to June 2000); and the Cochrane Controlled Trials Register Issue 4 of 2000. The search strategy is available upon request. We complemented this with manual search of the reference lists of all eligible articles and citation lists in palliative care textbooks, handbooks, and the personal libraries of the authors. Data were extracted independently by five of the authors, who agreed on a common data set by consensus. Meta-analysis was not performed because of the quality and quantity of the data available.

Of 80 articles identified, a total of 74 were excluded. Fifty-eight excluded articles described chemotherapy (53), radiotherapy (1), animal studies (2), patients with nonmalignant low back pain (1), and sedation (1). Seven articles were excluded because they did not specifically describe nausea and/or vomiting. Six descriptive articles, 1 letter and 2 medication utilization surveys were also excluded. Six studies met the inclusion criteria (Table 1).

![Table 1: General Characteristics of the Studies Included](image)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Diagnosis</th>
<th>No. of Patients</th>
<th>Baseline Symptoms Described</th>
<th>Intervention Described</th>
<th>Evaluation Method Described</th>
<th>Outcomes Described</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventafridda</td>
<td>1990</td>
<td>Case Series</td>
<td>Cancer patients with inoperable gastrointestinal obstruction</td>
<td>22</td>
<td>Yes</td>
<td>Not Clear</td>
<td>Not Clear</td>
<td>Vomiting controlled in 12/15 patients.</td>
<td></td>
</tr>
<tr>
<td>Turner</td>
<td>1996</td>
<td>Case Series</td>
<td>Cancer and AIDS patients referred to palliative care service</td>
<td>50</td>
<td>Not Clear</td>
<td>Not Clear</td>
<td>Not Clear</td>
<td>Not clearly reported.</td>
<td></td>
</tr>
<tr>
<td>Athanassiadis</td>
<td>1992</td>
<td>Case Report</td>
<td>Adenocarcinoma of lung</td>
<td>1</td>
<td>Not Clear</td>
<td>Not Clear</td>
<td>Not Clear</td>
<td>Symptom resolution within 48 hours after administration of Droperidol 2.5mg epidurally.</td>
<td></td>
</tr>
</tbody>
</table>

Marder et al. reported retrospectively on 25 adult cancer patients with bowel obstruction.
tion. These patients were treated with a combination of medications including haloperidol in a dosage range of 2–5 mg subcutaneously, intramuscularly, or sublingually. Baseline symptoms of nausea and vomiting, duration of drug interventions, and evaluation methods were not reported clearly.

Turner et al. described the last 3 days of life of 50 consecutive adult patients (49 with malignancy and 1 with AIDS) on a palliative care service. Two of the 6 patients who had nausea and vomiting had good control using unreported drug interventions.

Lichter described 100 consecutive episodes of nausea and vomiting in 86 terminally ill patients. The author concluded that nausea and vomiting in terminal illness could be controlled within 48 hours in 95% of cases using a special protocol. Baseline symptoms, intervention, evaluation, and outcome data were not reported clearly.

One of the case reports suggested that combined blockade of dopamine (D2) and serotonin receptors in the chemoreceptor trigger zone, with haloperidol and ondansetron, respectively, is sometimes required to relieve intractable nausea and vomiting. The other case report suggested that droperidol given epidurally may be effective in patients with nausea and vomiting secondary to epidural morphine.

Comment

Three of six studies included in this review which provided enough information on baseline symptoms, interventions, outcome measures and evaluation tools suggest that haloperidol may be effective in patients diagnosed with a variety of different cancers (lung, breast, metastatic disease) who experience nausea and vomiting due to bowel obstruction, epidural morphine and unknown causes. Any conclusions from the studies available are limited by their lack of control groups.

A limitation of our study is that our search strategy did not include specific terms for terminal illnesses other than cancer. As a result there may be relevant studies that were not identified. We welcome feedback from readers.

This systematic review underscores the paucity of well-designed and clearly reported studies evaluating the treatment of nausea and vomiting in palliative patients. Until further research can be completed and adequately reported, the clinical use of haloperidol for treatment of patients with cancer or terminal or palliative conditions not receiving chemotherapy or radiotherapy must continue to be guided by clinical experience and judgment, inferences from basic research on its putative antiemetic effects, the limited information provided by case reports and case series, and the opinion of experts in major textbooks of palliative care.

Future studies should provide a detailed and replicable description of the patient population, specific interventions used, including medication doses, routes, schedule and duration of treatment. Authors should provide data on clinically relevant outcomes, including severity and frequency of nausea and vomiting, onset of antiemetic effect and side effects. Given the variety of antiemetics currently available, it would be of great interest to see comparative studies of antiemetics either alone or in combinations. We need objective evaluations of the cost-effectiveness of different agents and their effect on patient satisfaction and quality of life. Future studies, which address these issues, will advance our knowledge of the most effective palliative therapies and ultimately lead to improved evidence-based end of life care.

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References


Postural Hypotension Blamed on Epidural

To the Editor:

In normovolemic young patients, postural hypotension following surgery is an uncommon complication. However, postural hypotension is frequently seen with severe hypovolemia, alpha-blocking drugs, and with epidural local anesthetics. When it occurs, it restricts early ambulation of the patient and increases morbidity. We are presenting a case in which a patient developed postural hypotension initially believed to be due to an epidural placed for pain relief following thoracoabdominal dissection. However, the hypotension persisted for many days despite discontinuation of the epidural local anesthetics. We believe this was a result of coincidental sympathectomy that was not apparent in the early postoperative period.

Case Report

A 28-year-old male was scheduled to undergo a left-sided thoracoabdominal retroperitoneal lymph node dissection for testicular cancer. The metastatic involvement extended in the left retroperitoneal area to the crux of the diaphragm and laterally to the renal hilum presenting as multiple masses. Preoperatively he had a thoracic epidural placed at T9-10 level for postoperative pain relief. He was induced with propofol and muscle relaxation was achieved with vecuronium. Fentanyl and isoflurane were used for maintenance. The surgical dissection was difficult and the procedure lasted 10 hours. He received 6 L of intravenous solution consisting of 5 L crystalloid and 1 L colloid. His blood loss was 350 cc. His anesthesia was uneventful and he was extubated the following morning. He was tachycardic and hypotensive and required 2 L of intravenous fluid in the immediate postoperative period. On the second postop day, efforts were made to ambulate him and he developed severe postural hypotension with HR varying from 135 to 150 and BP in the 70–90 range. The postural hypotension recurred in spite of rehydration with 1 L of fluid, after which recumbent CVP was 10. The patient was receiving an epidural solution of 1% lidocaine with fentanyl 5 µg/cc at 6 cc/hr. On the third day, the epidural local anesthetics were discontinued and 5 mg preservative-free morphine was injected. Still the patient continued to develop postural hypotension. He also complained of slight weakness and numbness of the left leg. The left lower extremity was found to be warm with dilated veins. Ultrasound of the left lower extremity revealed no thrombosis. Venodilation was