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Case Report

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A Case Report of Continuous Subcutaneous Infusion of Hydromorphone, Metoclopramide and Ondansetron Used To Treat Refractory Pain and Nausea in an Ambulatory Palliative Clinic

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ABSTRACT

Background: This case report describes a patient with advanced breast cancer with both refractory pain related to metastatic skeletal lesions and nausea who was successfully managed during the last nine months of her life with a continuous subcutaneous infusion of hydromorphone, metoclopramide and ondansetron in one chemically compatible mixture.
Case presentation: A 56-year-old woman with widespread metastatic breast cancer to bone who was followed in an ambulatory palliative care clinic for pain management and nausea. As her disease progressed and she was in the last year of her life, her pain and nausea had become very difficult to manage despite multiple modalities of treatment.
Case management: A continuous subcutaneous infusion of hydromorphone, metoclopramide and ondansetron was started and titrated to achieve relief of her intolerable and refractory pain and nausea. All three medications were chemically compatible, and provision for bolus was ensured.
Case outcome: The patients ultimate goals of care were achieved, including nine months of excellent relief of both nausea and pain, while enhancing quality of life due to ease of administration of one mixture.
Conclusion: The combination of hydromorphone, metoclopramide and ondansetron is a potentially useful regimen for the targeted treatment of concomitant refractory pain and nausea in the palliative care setting. This represents the first time the triad mixture has been reported successfully in case studies.

KEYWORDS: Palliative care; Subcutaneous; Hydromorphone; Metoclopramide; Ondansetron; Refractory pain; Nausea.

BACKGROUND

Pain and nausea are very common occurrences in advanced oncological states, and well described in the palliative care literature.[1-5] There are an abundance of publications dedicated to addressing various refractory symptoms and possible therapeutic options, whether nausea or pain. When concomitant symptoms exist, however, the likelihood that expert opinion is required rises.[6] Moreover, if poorly managed, the implications on not only quality of life, but also quantity of life become more apparent.[7-8] Pharmacological strategies for the management of both pain and nausea have an abundance of research dedicated to the parenteral delivery of these agents.[9-12]

For various reasons patients with advanced cancer may experience a reduction or a complete loss of the oral route, potentially severely compromising the ability to deliver evidence-based the rapeutics in a timely fashion. When it happens earlier in the disease trajectory, the concern for prolonged unnecessary suffering comes to the forefront. For a combination of the

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aforementioned reasons, including refractoriness of symptom management and limitations in the oral route, we arrived at a chemically compatible mixture of subcutaneous hydromorphone, metoclopramide, and ondansetron that dramatically improved both severe pain and nausea in a patient with advanced breast cancer. This mixture was administered as a continuous infusion with the provision for bolus doses, which not only optimally managed physical suffering but further enhanced quality of life by ensuring simplicity of delivery.

Case Presentation

A 56-year-old woman with metastatic breast cancer was assessed in an ambulatory palliative care clinic for pain and symptom management in association with widespread skeletal lesions. There had been disease progression despite completion of adjuvant treatment with chemotherapy and radiation as well as 5 years of Tamoxifen and 3 years of Letrozole. The patient presented with excruciating hip pain radiating down her left leg that inhibited her mobility, and was described as constant and "intense". Direct correlation was made with lesions seen on imaging such as bone scan and X-ray. Later, several other sites of bony metastases resulted in similar excruciating pain. Initially, pain management started with a hydromorphone based regime, moving from a short-acting formulation to a longer acting agent. Several upward titrations were then pursued, as well at the addition of co-analgesia described below. Despite various trials of oral opioids and increasing doses, along with numerous adjuvants such as gabapentin (600 mg po three times daily), methadone (10 mg po three times daily), and dexamethasone (8 mg po twice daily), the patient's pain continued to escalate. Transdermal analgesia (fentanyl 100 mcg patch every 48 hours) and further opioid rotations were no longer effective for pain relief. After experiencing a severe pain crisis, the patient was transitioned to a continuous hydromorphone subcutaneous infusion of 1.5 mg/hr with 1.5 mg bolus every 30 minutes as needed. After titration of both basal and bolus doses (2.5 mg/hr and 2.5 mg every 30 minutes as needed), her pain had eventually improved dramatically. It should be noted that the patient had previously developed severe radiation-induced enteritis, which limited the role of further palliative radiotherapy for pain management.

In addition to her rapidly escalating pain, the patient also developed refractory nausea. As with strategies aimed at managing her pain, numerous oral anti-emetic agents of differing mechanistic action were trialed with little success. This in turn depleted her quality of life. Not until parenteral formulations (subcutaneous) of both ondansetron (8 mg subcutaneous three times daily) and metoclopramide (10 mg subcutaneous four times daily) were instituted did the patient begin experiencing excellent relief of her nausea. This of course raised the suspicion that the patient was, in addition to all the aforementioned, experiencing poor GI absorption of medications given a previous history of chemotherapy-induced enterocolitis and partial small bowel obstruction with resection. This is outside the scope of this article.

Case Management

Given the evolution and escalation of therapeutic options described above, and in particular the triad of parenteral hydromorphone, metoclopramide, and ondansetron being effective for this patient's symptom control, the clinical team confirmed that the three medications were compatible in one mixture.[13] We desired greatly to simplify the patient's regime in order to enhance quality of life. Our clinical pharmacist established that the three agents could indeed be mixed together without crystallization and degradation of the product. The initial mixture reflected both the basal and bolus rate of her hydromorphone infusion, as well as the required doses of ondansetron and metoclopramide used to mitigate nausea. As such, the initial mixture consisted of 250 mg of hydromorphone, 90 mg of metoclopramide, and 72 mg of ondansetron in a 500 ml minibag of normal saline. This was run at 5 ml/hr, with the provision for a 5 ml bolus every thirty minutes with lockout. Ultimately titration reached a final mixture that included 500 mg of hydromorphone in 500 ml of normal saline with the aforementioned anti-emetic doses. This equated to roughly a basal rate of 5 mg/hr of hydromorphone and equivalent bolus dose (5 ml/hr and 5 ml every 30 minutes). Similarly, metoclopramide, according to these ratios, equates to approximately 0.9 mg/hr (21.6 mg/day) and ondansetron at 0.72 mg/hr (17.3 mg/day).

Case Outcome

The patient's pain and nausea improved dramatically. Very much consistent with the patient's wishes, she was able to enjoy a fairly high quality of life without restriction to several hours of nursing in the home that would otherwise have been encountered had the medications been administered separately *via* the parenteral route. As such she could for example, maintain high levels of functioning, such as driving and taking longer trips away from home, given the mixture cassette size allowing for changing every fourth day.

It can be seen from Table 1 above that shortly after institution of the pump on May 27, and in close follow-up, the patient's nausea improved dramatically, which remained a sustained effect throughout the remainder of the her journey. When the patient's pain escalated on September 12, it was found to be secondary to a new bony metastatic lesion. This new disease site responded quite well to palliative radiotherapy.

DISCUSSION

A mixture of subcutaenous hydromorphone, metoclopramide, and ondansetron was deemed compatible and safe to administer as a continuous infusion with the provision for bolus dosing. The combination of hydromorphone, metoclopramide, and ondansetron aligned with the patient and family wish to achieve excellent pain and symptom management, while simplifying the

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Table 1: Sequential ESAS Scores after Institution of Patient's Pump, a Chemically Compatible (Singular) Mixture of Subcutaneous Hydromorphone, Metoclopramide, and Ondansetron.

ESAS	May 27	June 30	July 29	Aug 30	Sept 12	Oct 5
Pain	5	4	2	2	6	1
Fatigue	8	8	5	9	9	5
Drowsiness	8	8	4	8	8	4
Nausea	7	2	0	1	0	0
Appetite	8	2	0	5	7	2
SOB	0	5	0	0	0	0
Depression	5	6	3	5	5	4
Anxiety	6	6	4	5	5	4
Well-being	6	5	3	5	5	4

regime as much as possible. This represents the first case report documentation of this combination of medications used in such a long-term fashion.

CONCLUSION

The combination of subcutaneous hydromorphone, metoclopramide, and ondansetron is a compatible mixture that could be a valuable addition to the palliative care armamentarium. This mixture was found to be significantly beneficial in the management of intractable pain and nausea in a patient with advanced metastatic disease.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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