*Palliative Care Rounds*

# Intractable Nausea and Vomiting Due to Gastrointestinal Mucosal Metastases Relieved by Tetrahydrocannabinol (Dronabinol)

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***Abstract***
*Four years following resection of a Clark's level IV malignant melanoma, a 50-year-old man developed widespread metastatic disease involving the liver, bones, brain, gastrointestinal mucosa, and lungs. One week after whole brain radiation therapy, he was admitted to the hospital for nausea, vomiting, and pain. He was treated with several antiemetic drugs, but it was not until dronabinol was added that the nausea and vomiting stopped. Dronabinol was an effective antiemetic used in combination with prochlorperazine in nausea and vomiting unresponsive to conventional antiemetics.*
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***Key Words***
*Antiemetic, dronabinol, gastrointestinal mucosal metastases, melanoma, nausea, tetrahydrocannabinol, vomiting*

## *Introduction*

Dronabinol (Marinol®, Roxane Laboratories, Columbus, OH) better known as delta-9-tetrahydrocannabinol (THC) is recommended in the United States as antiemetic prophylaxis for chemotherapy induced nausea and vomiting when other antiemetic medication are not effective.[1,2] Another recognized use of dronabinol is for anorexia cachexia in the acquired immunodeficiency syndrome (AIDS).[3,4] There is some information in the literature about other indications, including nausea and vomiting related with anesthesia,[5] and spasticity associated with multiple sclerosis.[6,7] It may also have a role in anorexia due to cancer.[8,9] Tachyphylaxis and tolerance to some effects of dronabinol develop with chronic use.[1]

There is no information about the use of dronabinol as an antiemetic in patients with vomiting that is not chemotherapy related but is associated with advanced cancer. We present a patient with metastatic malignant melanoma in whom the main problem was intractable nausea and vomiting unresponsive to conventional antiemetics (metoclopramide, prochlorperazine, or dexamethasone). We believe that the main cause of the nausea and vomiting was diffuse gastrointestinal mucosal tract

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metastases. It was not until we added dronabinol that these symptoms resolved.

## *Case History*

The patient was a 50-year-old white male Vietnam War veteran with a history of two malignancies. In June 1990, a left shoulder subcutaneous malignant fibrous histiocytoma was removed, and he received local radiotherapy and adjuvant chemotherapy, and this tumor apparently remained in remission until his death. The second primary cancer was a Clark's level IV malignant melanoma in the skin of his right posterior midthoracic region. This tumor was widely excised in May 1991, and investigations (chest radiography, bone scintigram, and computerized tomography of the liver) at that time were negative for metastasis. One week later, right axillary lymph node dissection was done, and all 16 nodes dissected were free of tumor.

He remained well until March 1995, when he experienced nausea, anorexia, abdominal pain, and weight loss. Liver metastases were detected, and an ultrasound-guided biopsy was positive for malignant melanoma. The same month he noted headaches, and a computed tomographic scan of the brain with contrast showed a right parietal lesion. He received whole brain radiation therapy (30 Gy) from March to April 1995.

On April 12, 1995, 6 days after he completed whole brain radiotherapy, he was admitted to the palliative care unit in the Cleveland Clinic with a 3-day history of chills, diaphoresis, anorexia, weight loss, insomnia, dehydration, pain in the right posterolateral lower costal area, constipation, and severe nausea and vomiting. He was unable to take anything by mouth except small amounts of liquid. The vomiting was uncontrolled by prochlorperazine at 10 mg by mouth every 6 hr as needed. He appeared clinically ill and in mild distress. He was afebrile, but had a dry mouth and oral thrush, and was moderately dehydrated. Lungs and heart were unremarkable. The abdomen was soft with mild tenderness in the right upper quadrant. Bowel sounds were normal; rectal examination was normal, with a negative test for occult blood in the stool. Laboratory results on admission revealed the following; white blood cells 14,390, hemoglobin 13.6, hematocrit 39.7, platelets 234,000, calcium 8.5, albumin 3.2, total bilirubin 0.5, glucose 207, sodium 132, potassium 3.9, chlo-

Fig. 1. Gastric mucosal metastasis from malignant melanoma.

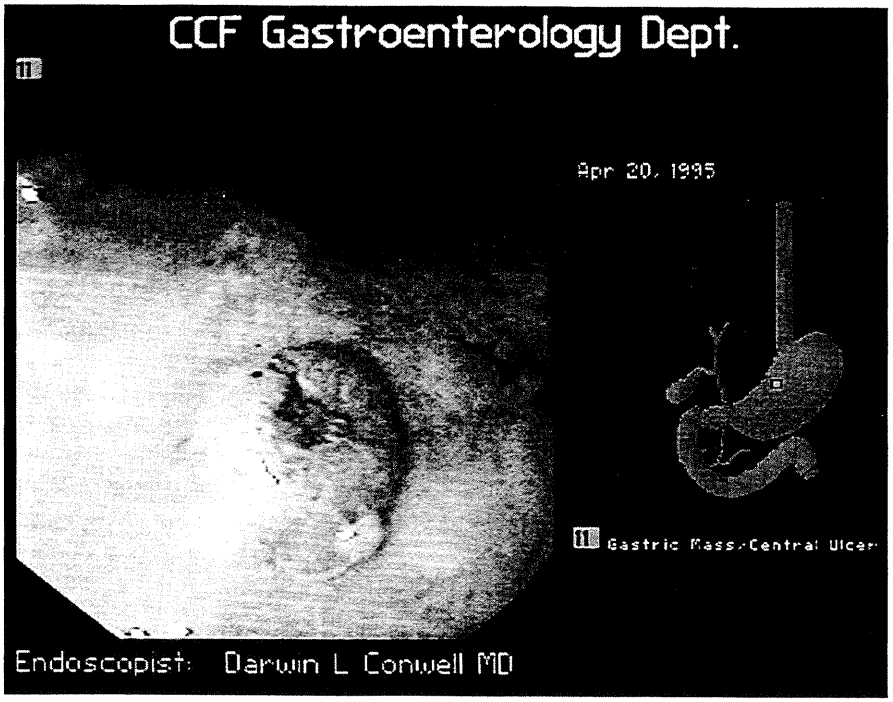

*Table 1*
**Antiemetics, Dosage, and Schedule**

| Day | Date | Drug | Dose | Route and schedule | Status/comments |
|---|---|---|---|---|---|
| 1 | 4/12 | Prochlorperazine | 10 mg | IV Q 6 hr PRN | Severe nausea and vomiting. |
| | | Dexamethasone | 8 mg | IV twice daily ATC | Continued throughout. |
| 2 | 4/13 | Prochlorperazine | 5 mg | IV Q 6 hr ATC | Vomited twice. |
| | | Metoclopramide | 10 mg | IV AC and HS ATC | Added. |
| 5 | 4/16 | | | | Severe nausea continues. |
| 6 | 4/17 | Metoclopramide | 10 mg | PO AC and HS ATC | Route changed. |
| 7 | 4/18 | Prochlorperazine | 10 mg | IV Q 6 hr ATC | Severe nausea, dose increase. |
| 9 | 4/20 | Prochlorperazine | 10 mg | IV Q 8 hr ATC | Dose reduced for sedation. |
| | | Dronabinol | 5 mg | PO PC and HS ATC | Added; severe nausea. |
| 10 | 4/21 | | | | No nausea, vomited once. |
| 11 | 4/22 | | | | No nausea, vomited once. |
| 12 | 4/23 | Dronabinol | 5 mg | PO AC and HS ATC | Mild nausea. |
| | | Metoclopramide | 10 mg | | Discontinued. |
| 13 | 4/24 | Prochlorperazine | 10 mg | PO Q 8 hr ATC | No nausea, vomited once. |
| 14 | 4/25 | | | | No nausea or vomiting. |
| 15 | 4/26 | Prochlorperazine | 10 mg | PO Q 6 hr ATC | Discharged, no nausea or vomiting, eating normal diet. |
| | | Dexamethasone | 8 mg | PO twice daily | |
| | | Dronabinol | 5 mg | PO AC and HS | |

PRN, as needed; ATC, around the clock; PO, oral; PC, after meals; AC, before meals; Q, every; HS, bedtime; hr, hours.

ride 98, $CO_2$ 20, creatinine 0.9, blood urea nitrogen 15, lactate dehydrogenase 2280, aspartate aminotransferase 53, alkaline phosphatase 489, and prothrombin time INR 1.05. A technetium bone scintigram showed metastases to the skull, right humeral shaft, bilateral femoral shafts, left acetabulum, fourth lumbar vertebra, anterior and posterior multiple bilateral ribs, and axial skeleton. An upper gastrointestinal endoscopy showed multiple dark lesions in the stomach (Figure 1) and duodenum. Biopsy of the lesions was positive for malignant melanoma invading the lamina propria.

On admission, in addition to prochlorperazine, he was taking dexamethasone 8 mg orally twice daily (principally for the brain metastases but also for its antiemetic effect), docusate sodium at 200 mg orally twice daily, morphine elixir (just 2.5 mg orally every 4 hr as needed), and famotidine at 20 mg orally twice daily. A radiograph of the abdomen was normal except for a large amount of stool in the colon.

He was hydrated, and the pain was controlled with intravenous morphine within 24 hr of admission. The vomiting lessened, but the nausea persisted despite multiple intravenous and oral antiemetics (the sequence of doses and schedule of antiemetic medication is in Table 1).

Dronabinol was initiated 8 days after admission on April 20, 1995. Four days later, he was evaluated by a dietitian and was tolerating a soft diet well. The intravenous fluids were discontinued. Five days after dronabinol was initiated, he was doing much better. By then, he had no pain, nausea, vomiting, constipation, or dysphoria, and no other new symptoms. The morphine was switched back to an oral liquid form. He was discharged from the hospital 6 days after dronabinol was started. There was no recurrence of the nausea and vomiting subsequently.

## *Discussion*

The absorption of dronabinol from the gastrointestinal tract is not constant, and plasma concentrations vary around a peak 2–3 hr after ingestion. Metabolite excretion is mainly biliary. Approximately 50% of the oral dose is excreted in the feces, and a small percentage is excreted in the urine. The mechanism of the antiemetic effect of cannabinoids is unknown. A central action is suspected, perhaps by indirect inhibition of the vomiting center in the medulla as a result of binding to opiate receptors in the forebrain.[10]

Nausea and vomiting are among the 20 most frequent symptoms in advanced cancer.[11] The etiology is multifactorial.[12] In this case, we believe that the main cause was diffuse metastatic disease in the gastrointestinal tract mucosa. Malignant melanoma is one of the

cancers that metastasizes more frequently to the bowel.[13] Although brain metastases and radiation therapy can cause nausea and vomiting, we do not believe that these etiologies were involved in the present case. The inefficacy of the dexamethasone in therapeutic doses[14] may argue against these etiologies.

The pharmacologic treatment of nausea and vomiting in the palliative care setting usually involves established drugs. An important principle is to use combinations of antiemetics,[15] with different modes of action. The antiemetics of choice for our service are prochlorperazine, metoclopramide, and dexamethasone. Less frequently used drugs include dronabinol, other phenothiazines, haloperidol, H1 antagonists, and benzodiazepines. More expensive drugs, such as the 5-$HT_3$ antagonists (ondansetron, granisetron), are widely used for nausea and vomiting related to chemotherapy, but there is little experience or information about these drugs in this setting.[16] We also avoid them because of the expense. We did not use haloperidol because the mechanism of action is similar to prochlorperazine and metoclopramide (that is, antagonism of $D_2$ dopamine receptors).[16] The extrapyramidal side effects of this group of antiemetics may be additive when used together.

The improvement after we added dronabinol was notable, and the clinical appreciation of the time of onset (<24 hr) led us to believe that dronabinol, in combination with the other drugs, made the difference. We therefore conclude that low doses of dronabinol may be safe and effective when used in combination with other antiemetics for intractable cancer-related nausea and vomiting with no mechanical obstruction. Dronabinol should be considered a potentially useful agent in this setting.

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