UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

September 15, 2022 Vol. 2, No. 15

Palliative Care Pharmacy Team:

Clinical Pharmacy Specialist:

Maria Felton Lowry, PharmD, BCPS, BCGP
Assistant Professor
University of Pittsburgh School of Pharmacy, Department of Pharmacy and Therapeutics
Palliative Care Clinical Pharmacy Specialist
UPMC Palliative and Supportive Institute

Cell: 412-627-8473
Office: 412-864-2899
Email: lowrymf@upmc.edu

If you have a topic you would like the pharmacy team to answer, please send your suggestions to: lowrymf@upmc.edu

TODAY'S TOPIC:

Aprepitant (Emend®) for Refractory Nausea

Background:

Nausea is one of the most common symptoms among seriously ill patients. The pathophysiology of nausea is multifactorial and numerous antiemetic classes exist to target different receptors based on proposed etiology of the nausea. Substance P can induce nausea and vomiting by binding to specific receptors called neurokinin-1 [NK-1] receptors. Aprepitant (Emend®) is a substance P/neurokinin 1 receptor antagonist. It is FDA-approved for the prevention of chemotherapy-induced nausea/vomiting (CINV) and recommended as part of the American Society of Clinical Oncology (ASCO) Guidelines for highly emetogenic chemotherapy regimens and is commonly used within the oncology setting. It has been used off-label for the management of refractory nausea outside the setting of chemotherapy.

Importance:

Aprepitant is commonly used in oncologic practice, although its role is unclear outside of its indication for prevention of CINV. Palliative care clinicians should be aware of the available evidence for its off-label use and implications for clinical practice.

The Literature:

Gastroenterology. 2018 Jan;154(1):65-76.

Aprepitant has mixed effects on nausea and reduces other symptoms in patients with *gastroparesis and related disorders*

Methods: 4-week, multicenter, double-masked placebo-controlled trial of patients with at least 6 month history of chronic nausea/vomiting of presumed gastric origin

- Oral aprepitant (125mg/day) daily versus placebo
- See full text for full inclusion/exclusion criteria

Outcomes:

- Primary: reduction in nausea, defined as decrease of 25mm or more, or absolute level below 25mm on a 0-100 visual analog scale (VAS) of nausea severity
- Secondary: reduction in symptom severity (0-5 Gastroparesis Clinical Symptom Index GCSI and Gastrointestinal Symptom Rating Scale GSRS) for nausea, vomiting, and overall symptoms and Quality of Life (Patient Health Questionnaire PHQ15)

Results: n=126, n = 63 aprepitant and n=63 placebo; 57% delayed gastric emptying and 43% with chronic unexplained nausea and vomiting

- No significant difference in reduction of nausea symptoms between groups: 46% reduction in VAS score in aprepitant group versus 40% reduction in placebo group (RR 1.2 [0.8-1.7])
- Sensitivity analysis showed nausea improvement in defined as meeting both conditions (listed under primary outcome above) in a significantly higher proportion of patients in aprepitant group 37% versus placebo 17%
- Percent of patients with substantial symptomatic improvement of ≥ 1 on GCSI was 60% in aprepitant and 32% in placebo (p=0.002)
- Adverse events more common in aprepitant group, most commonly characterized as mild or moderate severity with only 1 serious adverse event reported in this group

Conclusion: Aprepitant did not reduce severity of nausea on VAS, but had varying effects on secondary outcomes of symptom improvement

J Pain Symptom Manage. 2021 Sep;62(3):e225-e231.

Long-term daily administration of aprepitant for the management of *intractable nausea and vomiting* in *children with life-limiting conditions:* A case series

Methods: Case Series, maximum dose used: 2mg/kg (80mg/day: adult dose)

Objective: Examine acceptability, tolerability, and efficacy of long-term use of aprepitant in children with life-limiting illness

Results:

Table 2

Summary of Clinical Effectiveness of Aprepitant Use, Including Best Objective Response, Duration of Response Total Duration of Continuous Aprepitant Use and Adverse Events Observed

Pt	Primary Diagnosis	Previous Antiemetics Used	Aprepitant Dose (mg/kg)	Concomitant Antiemetic (dose)	Best Response	Adverse Events	Response Duration	Aprepitant Course Length
1	ATRT	Ondansetron Cyclizine Metoclopramide	25mg (2 mg/kg)	Metoclopramide (100 mcg/kg three times a day, converted to IV 19 days post start of aprepitant)	CR Reduce number and volume of vomits. Increase feed volume	Nil	Until end of life.	24 days
2	DIPG	Cyclizine Levomepromazine Metoclopramide	40 mg (2 mg/kg)	Levomepromazine (68 mcg/kg twice a day increased to 80 mcg/kg twice a day, 11 days post starting aprepitant)	CR	Thickened Secretions	1 vomit 11 days post aprepitant start. Until end of life.	18 days
3	DMD	Cyclizine Ondansetron Metoclopramide	80 mg (adult dose)	None	CR Significant increase in oral intake	Nil	Until end of life	41 days
4	DMD	Cyclizine Metoclopramide Ondansetron	60 mg (2 mg/kg)	None	CR Significant increases in oral intake	Nil	Until end of life	84 days
5	Metastatic Yolk Sac Tumour	Ondansetron Cyclizine Metoclopramide Levomepromazine	60 mg (2 mg/kg)	Levomepromazine (50 mcg/kg twice a day) then Metoclopramide 150 mcg/kg three times a day	CR	Nil – blockage of gastrostomy due to formulation	Until end of life	35 days
6	Metastatic Medulloblastoma	Ondansetron Levomepromazine	35 mg (2 mg/kg)	Levomepromazine (100 mcg/kg twice a day)	CR Able to wean levomepromazine Increased oral intake.	Nil	Until end of life	19 days
7	Choroid Plexus Carcinoma	Ondansetron	16 mg (2 mg/kg)	Metoclopramide (150 mcg/kg three times a day	Tolerated increasing oral intake and feeds. 400 g weight gain	Nil	Aprepitant weaned 48 days post start then used as required for BT	48 days continuous then as required
8	ATRT	Dexamethasone Cyclizine	20 mg (2 mg/kg)	Cyclizine (1 mg/kg three times a day, weaned down once a day)	CR Tolerated increasing feeds. Able to wean cyclizine	Nil	Until end of life	38 days
9	Osteosarcoma with lung mets (high grade)	Metoclopramide Levomepromazine	80 mg (2.5 mg/kg)	Levomepromazine (100 mcg/kg twice a day)	CR	Nil	Until end of life	6 days
10	DIPG	Metoclopramide Levomepromazine	50 mg (2 mg/kg)	Metoclopramide (150 mcg/kg three times a day)	CR Tolerated increased feed	Nil	No further reports of nausea and vomiting until end of life	50 days

ATRT = Atypical Teratoid Rhabdoid Tumour; BT = Breakthrough; CR = Complete Response; DIPG = Diffuse Intrinsic Pontine Glioma; DMD = Duchenne's Muscular Dystrophy; kg = kilograms; mcg = micrograms; mg = milligrams; PT = patient.

J Pain Palliat Care Pharmacotherapy. 2014 Jun;28(2):135-7.

Aprepitant for the management of *refractory emesis in a patient with a small bowel carcinoid tumor*

Methods: Case Report

Description:

- 88 yo F, small bowel carcinoid tumor
- HPI: 5-month history of flushing, abdominal pain, nausea/vomiting, no obstruction
- Previously trailed antiemetics: domperidone, metoclopramide, levomepromazine, cyclizine; combination of ondansetron/prednisolone, granisetron
- 3-day trial of oral aprepitant (125mg x1 day, 80mg daily on days 2-3)
  - Within 48 hours of commencing aprepitant, nausea resolved and resolution lasted 10 days
- Second 3-day trial of aprepitant commenced, and continued at 80mg daily indefinitely with control of nausea for 2 months until her death
  - No adverse effects reported

CLINICAL PEARL: Aprepitant seems safe to try in cases of refractory nausea and vomiting

UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

September 15, 2022 Vol. 2, No. 15

Palliat Med. 2014 Jul;28(7):990-991.

The use of aprepitant in a case of *refractory nausea and vomiting*

Methods: Case report

Description: 27 yo F, invasive lobular breast carcinoma with meningeal metastases

- HPI: s/p chemotherapy, ventriculoperitoneal shunt, 18-month history of NV
- Previously trialed antiemetics: cyclizine, haloperidol, levomepromazine, olanzapine, metoclopramide, domperidone, dexamethasone
- Aprepitant 80mg PO daily
    - Prior to initiating aprepitant, daily palliative care assessment tool (PACA) scores for nausea and vomiting were 2 or 3 and after two doses of aprepitant scores reduced to 0 (symptom absent) and remained controlled after 5 months with monotherapy
    - No definite or severe side effects reported

J Clin Pharm Ther. 2019 Oct;44(5):805-808.

Off-label use of aprepitant for *scleroderma-associated nausea and vomiting*: A case report

Methods: Case Report

Description:

- 56 yo F, cutaneous scleroderma
- HPI: C. Diff infection, treated with vancomycin, resolved. Hospital course complicated by severe nausea and vomiting. Weight declining given lack of PO intake. Obstruction, Barrett's esophagus or clear inflammatory mucosal change were ruled out
- Previously trailed antiemetics: dimenhydrinate, ondansetron, olanzapine, metoclopramide, prochlorperazine, pantoprazole, and domperidone, nabilone
- Oesophageal motility study performed and demonstrated a complete absence of peristalsis
- **Aprepitant 80mg PO daily** was trialed and had improvement in nausea on first day, and remained for following 2 weeks during hospital stay. It was discontinued prior to discharge due to lack of insurance coverage and nausea returned 2 days later. It was restarted, insurance authorization obtained and her nausea remained controlled to the point of tolerating oral intake

Bottom Line:

- There is very limited data for extended use of aprepitant beyond prevention of CINV
- One RCT examined its use for dysmotility-related nausea and unknown chronic nausea without improvement in primary outcome for nausea severity (VAS) but showed improvement in other symptom assessment outcomes
    - More patients with delayed gastric emptying in placebo group
    - Both groups had heterogeneity including patients with both normal and delayed gastric emptying… although sensitivity analysis showed no effects of gastric emptying on outcome…
    - You could still argue that nausea pathophysiology is different between individuals within the groups and patients may respond differently to the same pharmacologic treatment based on normal or delayed gastric emptying, absorption of medication, and etiology of nausea
- Case series in children with life-limiting illness showed promise although a wide range of doses were used and it is hard to extrapolate to adult dosing
- Efficacy is hard to compare, given different indications and potential for different etiologies of nausea
- It appears that long-term use of aprepitant was well-tolerated and did not have signs of severe adverse effects
- Once daily dosing is fairly simplistic from a pill burden and adherence point of view
- Average wholesale price is: $200 **per capsule**. Would first take necessary steps to ensure insurance coverage such as completing prior authorization with clear documentation if wishing to prescribe as outpatient

CLINICAL PEARL: Aprepitant seems safe to try in cases of refractory nausea and vomiting