

Clinical Note

Long-Term Daily Administration of Aprepitant for the Management of Intractable Nausea and Vomiting in Children With Life-Limiting Conditions: A Case Series

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Abstract

Background. Nausea and vomiting is a common symptom in children through their end of life journey. Aprepitant, a NK-1 antagonist, has become a potent weapon in the fight against chemo-induced nausea and vomiting. However, its use in palliative care for refractory nausea and vomiting has been limited due to limited experience or evidence of continuous use. Emerging evidence suggests that continuous use is not only safe, but also effective in patients with nausea and vomiting refractory to multiple lines of antiemetic therapy.

Methods. We conducted a single centre retrospective chart review of children receiving care from a specialist palliative care team who were given continuous daily aprepitant for nausea and vomiting and were unresponsive to at least two prior lines of antiemetic therapy. Parental reports of the impact of nausea on mobility and feeding were used as proxy efficacy markers. Duration of effect and toxicity was also evaluated.

Results. Ten children (eight with cancer as a primary diagnosis and two with noncancer diagnoses) received continuous aprepitant and all showed resolution of nausea and vomiting and an increased ability to mobilize and tolerate feeds. No adverse events noted.

Conclusion. Our review suggests a role for aprepitant in management of refractory nausea and vomiting, demonstrating safety and efficacy. This case series is the first report of aprepitant use in this manner in the paediatric palliative care setting. *J Pain Symptom Manage* 2021;000:1–7. © 2021 The Authors. Published by Elsevier Inc. on behalf of American Academy of Hospice and Palliative Medicine. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Key Words

Nausea, vomiting, aprepitant, paediatric, life-limiting, palliative

Key Message

This article presents a retrospective case note review demonstrating the safety and effectiveness of daily aprepitant in the management of nausea and vomiting

in children. The results suggest aprepitant may be effective in managing nausea and vomiting, proven refractory to other antiemetic therapies, potentially reducing the need for parenteral treatment.

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Background

Various studies suggest that nausea and vomiting is the third most common non-pain symptom in children and young people, through their end-of-life journey.^{1–3} Whilst commonly associated with end-of-life¹ many conditions that can limit a child's life include nausea and vomiting as a symptom throughout the disease trajectory.⁴ The impact of nausea and vomiting can be far reaching representing a physical burden as well as affecting the psychological and emotional well-being of the child and their family.^{5–7}

Pharmacological and nonpharmacological interventions play an important role in the management of nausea and vomiting. Implementation of appropriate strategies relies on an understanding of the pathophysiology of the underlying condition and how this can lead to the nausea and vomiting. Etiologies of nausea and vomiting in patients' receiving palliative care can be broadly grouped into the following: 1) due to the primary disease; 2) a side effect of therapy (either disease directed or symptom management), 3) gastrointestinal problems, 4) metabolic dysfunction, 5) infection, 6) anxiety.^{1,4} Historically medications aimed at treating and preventing nausea and vomiting targeted modulation of serotonin (ondansetron), dopamine (domperidone, metoclopramide), cholinergic (hyoscine hydrobromide), antihistamine (cyclizine) pathways. Despite utilization of these therapeutic modalities many children and young people continue to experience profound and potentially debilitating nausea and vomiting.

Substance P, a tachykinin (neuro) peptide⁸ binds to Neurokinin-1 (NK-1) receptors which are distributed throughout the central and peripheral nervous system. Substance P and NK-1 receptors are linked to the expression of a number of symptoms including pain,^{9,10} pruritus,^{11–13} depression¹⁴ and emesis.^{15–17} Therefore antagonism of NK-1 receptor activation represents an exciting therapeutic target.

High concentrations of the NK-1 receptors have been identified in areas of the brain which modulate the experience of nausea and vomiting, area postrema and nucleus tractus solitaries.¹⁸ The presence of these receptors around the areas postrema and nucleus tractus solitaries highlights the potential scope of that NK-1 antagonism to reduce emesis.

Aprepitant (Emend[®]), available since 2003, is an oral NK-1 receptor antagonist¹⁷ licensed for use to treat and prevent chemotherapy-induced nausea and vomiting (CINV). When used to prevent and/or modulate the impact of CINV secondary to highly emetogenic chemotherapy aprepitant is commonly prescribed in a three-day regime (once a day for 3 days).¹⁹ However 5-day regimens have been reported,

off license, to manage nausea and vomiting associated with longer chemotherapy courses.^{15,20}

Prolonged continuous use of aprepitant in paediatrics, for nausea and vomiting, has only recently been described. *Jacobse* et al published the successful management of three children with refractory nausea and vomiting post haematopoietic stem cell transplantation (HSCT) using aprepitant.²¹ However, this paper reports on the use of aprepitant exclusively in children with cancer diagnoses. Our case series is the first to report on the use of prolonged continuous aprepitant use to treat nausea and vomiting in children and young people with life-limiting conditions both cancer and noncancer who are receiving palliative care and whose nausea and vomiting remained uncontrolled despite multiple lines standard antiemetic therapy.

Practice Challenge

The aim of this retrospective case series was to examine our clinical experience using aprepitant in children and young people with life-limiting conditions who had intractable nausea and vomiting, considering the acceptability, tolerability and efficacy of prolonged continuous use.

Methods

A retrospective case note and medication review of children and young people (0–18 years) with intractable nausea was conducted between August 2017 and January 2019. The project was registered with the trust R&D department and an opinion sought from NHS Health Research Authority (NHSRA) to ensure that further ethical approval was required prior to commencing the review. All children had been referred to and accepted by the Louis Dundas Palliative Care team at Great Ormond Street Hospital for Children. Children with cancer and non-cancer diagnoses were included and had to have experienced intractable nausea and vomiting. Included children had to have: 1) been prescribed aprepitant, 2) failed standard antiemetic regimes and³ not receiving aprepitant for the management of chemotherapy induced nausea and vomiting (CINV). Children receiving aprepitant, for management of CINV as per institutional antiemetic policy, were excluded from this review. Choice of initial antiemetic therapy that was employed prior to the use of aprepitant for intractable nausea and vomiting was based on the pathophysiology thought to be responsible for causing the nausea and vomiting rather than based on specific protocols. Where these initial measures failed to illicit adequate response escalation of therapy was rationalized based on pharmacological activity of antiemetic medications. This ensured minimization of the risk of pharmacokinetic and

pharmacodynamics interactions and maximized the potential for synergistic activity. The first author (B.P.) screened both electronic patient records and electronic pharmacy records to identify all eligible children.

Data for each patient was collected and captured using an Excel spreadsheet, with patients deidentified to maintain confidentiality. Baseline line data included sex, age at initiation of aprepitant, weight and diagnosis. Previous anti-emetic strategies were also recorded. The starting dose, duration of aprepitant episode, response, response duration and adverse effects were recorded through assessment of the patients' electronic notes. Response was categorised as complete response, partial response or no response, based on history from care-givers or patients themselves, ability to restart and/or tolerate increasing enteral feeds and/or weight gain. Complete response was defined as less than 1 breakthrough episode of nausea and vomiting post start of aprepitant, whilst partial response was defined as more than 1 episode of breakthrough nausea and vomiting that required addition, rotation or dose escalation of concomitant antiemetics. Response scores were based on patient reported (where the child was deemed competent to do so by healthcare professionals) or proxy-reported feeling(s) or sensation(s) of nausea at the time of assessment. Unfortunately validated scoring tools such as a visual analog scale (VAS) or an index of nausea, vomiting and retching (INVR) are not used to measure nausea by the palliative care team within current clinical practice, at the time of this study. Adverse events were assessed through spontaneous patient or proxy reported unexpected symptoms that may have occurred whilst children were receiving aprepitant. Electronic notes were reviewed with response classified by the primary author (BP) and classification verified by a second author (J.D.). No differences in classification of effectiveness occurred between reviewers.

Aprepitant dosing, as per the licensed dosing for CINV, usually suggests a loading dose of 3mg/kg (maximum 125mg) on day 1 before continuing with a 2 mg/kg (maximum 80 mg/dose) daily from day 2.¹⁹ In order to simplify the dosing regimen, our patients were only dosed at 2 mg/kg/day (max. 80 mg/day) given once a day. This decision was based on available PK data suggesting 90% NK-1 inhibition was achieved from a blood concentration of 100 ng/mL.¹⁶ PK analysis suggest that standard dosing achieve a plasma level in excess of 200 ng/mL to 500 ng/mL.¹⁹

Results

A keyword search of the electronic health record using "aprepitant" as the search term identified 14 children receiving palliative care. Four children were excluded from analysis. Of those four children, one

Table 1
Demographic Details of Patients in Whom Aprepitant (Emend®) Was Indicated for the Management of Refractory Nausea and Vomiting, Including Primary Diagnosis for Which Referral to Palliative Care Was Required

| Patient Demographic Details (n = 10) | |
|--|-----------------------------|
| Sex | |
| Male | 6 |
| Female | 4 |
| Age (at initiation of aprepitant) | |
| Median | 7 yrs (Range: 1–13 yrs) |
| Weight | |
| Median | 21.5 kg (Range: 8–62 kg) |
| Primary diagnosis: | |
| CNS cancer | |
| Diffuse Intrinsic Pontine Glioma (DIPG) | 2 |
| Atypical teratoid rhabdoid tumor (ATRT) | 2 |
| Choroid plexus carcinoma | 1 |
| Mets medulloblastoma | 1 |
| Non-CNS cancer | |
| Mets osteosarcoma | 1 |
| Mets yolk sac tumor | 1 |
| Noncancer | |
| Duchenne's muscular dystrophy (DMD) | 2 |

child was recommended to start aprepitant, but parenteral antiemetic therapy was initiated prior to medication being available in the home and three children received aprepitant as per institutional antiemetic policies for CINV. Aprepitant use was evaluated for each of the 10 patients. Demographic and diagnoses are provided in [Table 1](#).

Prior to initiation of aprepitant children identified by this review had experienced therapeutic failure with 2.6 prior antiemetic therapies ([Table 2](#)). Eight out of 10 children treated had cancer as a primary diagnosis (six of 10 with CNS cancer). Two of 10 children treated with aprepitant for refractory nausea and vomiting had nononcological primary diagnosis with nausea and vomiting thought to be attributed to poor gastric perfusion. The mean number of days of aprepitant therapy was 36.5 days (range 6–84 days).

A complete resolution of nausea and vomiting was reported in all 10 children following the commencement of aprepitant. Nine of the 10 children demonstrated a durable response until death, seven able to tolerate increased oral intake and one experiencing weight gain. Only one child experienced significant breakthrough emesis, occurring 11 days post initiation of aprepitant. Three of the 10 children were able to wean concomitant antiemetic therapy. One of these three children was able to be weaned off all antiemetic therapy following establishment of emetic control with aprepitant and then managed on PRN antisickness medication until death. Six of the eight children with oncological primary diagnosis were able to maintain a viable oral route until end of life. Of the two children unable to, one child had to be switched to parenteral

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 Until end of life | 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.

therapy due to suspected loss of absorption five days prior to death and the other child was converted to parenteral therapy as part of inpatient hospital management, rather than necessity.²²

No significant adverse events attributable to aprepitant were reported in any of the ten children exposed to long-term administration of aprepitant. One child with diffuse intrinsic pontine glioma (DIPG) was noted to have thickened secretions whilst receiving aprepitant, however she had a history of difficulty in managing secretions throughout her illness.

Discussion

Nausea and vomiting are common symptoms in the end of life journey of paediatric patients.¹ Causative factors for nausea and vomiting during this phase of care is often multifactorial resulting from progression of the underlying condition and/or medication used as part of multi-modal symptom management (e.g. opioids, palliative chemotherapy). Strategies for appropriate management of emesis rely on having an understanding of the underlying cause and using appropriate strategies to therapeutically target aberrant signal pathways (serotonin, dopamine etc.) leading to the emetic response.

Despite having an understanding of the pathophysiology of causes of nausea and vomiting, management can still be hit and miss with therapeutic failure occurring despite the availability of numerous classes of antiemetic therapies. Failure to appropriately manage emesis can have a significant impact on the child and family including the inability of health professionals' ability to manage other symptoms such as pain as well as significant distress for family.^{5,6}

When existing enteral therapeutic options fail, palliative care professionals can often rely on parenteral antiemetic therapy. However parenteral administration may, only be deliverable in a hospital inpatient environment owing either to lack of community service or drug availability.^{23,24} When parenteral therapy can be delivered in a home setting delivery may be extremely labour intensive and invasive for patients and families, necessitating daily visits (as a minimum) from community nursing teams. In addition, whilst ambulatory pump technology has developed tremendously over the last decade even the smallest ambulatory pump may seem unwieldy and cumbersome to some paediatric patients, restricting physical movement as well as being aesthetically unpleasing, influencing potential quality of life during the end of life journey.²⁴

Substance P, has been shown to modulate a number of biological processes including nausea and vomiting through interaction with the NK-1 receptor.^{25,26} There is a lack of data on the long-term use of aprepitant in children. It is, however used off-label, in pediatric gastroenterology to manage cyclical vomiting syndrome.²⁷

Current studies include investigation for efficacy in patients with symptoms of nausea and vomiting associated with gastroparesis and related disorders.²⁸ Jacobse et al demonstrated the safety and efficacy of aprepitant in helping alleviate intractable nausea vomiting in a small case report of children, as young as five months old, post hematopoietic stem cell (HSC) transplant suggesting the potential safety and efficacy of prolonged continuous aprepitant.²¹

Aprepitant is known to interact with liver cytochrome P450 enzymes, specifically inhibiting cytochrome 3A4 and inducing the activity of cytochrome 2C9. Aprepitant's inhibition of cytochrome 3A4 is of particular concern owing to the potential for drug-drug interactions, such as with opioids or benzodiazepines commonly used in symptom management and how these interactions alter drug handling of concomitant medications during long-term use¹⁹ have been cited¹⁹ as rationale for not trialling long term administration of aprepitant.

Given these actions, concern over potential for drug-drug interactions following long-term administration of aprepitant may appear well founded. However, two systematic reviews of the literature looking specifically at reports of interactions of aprepitant with other medications demonstrate that whilst the potential for interaction exist, few are of clinical significance.^{29,30} Also arguing that knowledge of potential interactions can facilitate the safe use of aprepitant.^{29,30}

Our results demonstrate the effectiveness of aprepitant in helping to restore emetic control in those children with progressive disease, whose nausea and vomiting had remained refractory to multiple lines of prior antiemetic therapy. All children started on aprepitant were reported by the children themselves or by a parent to have had immediate resolution of nausea and vomiting.

Within our case series, of particular interest, six of 10 children had CNS malignancy as the primary presenting complaint. Nausea and vomiting is common complication associated with CNS malignancy, often relating to raised intracranial pressure. Our data suggests aprepitant may provide a significant benefit in this cohort of patients. Evidence is emerging of the role neurokinins may play in neuroinflammation, blood brain barrier permeability and edema formation,³¹ thus reduction of intracranial pressure may play a secondary role in treating nausea and vomiting associated with CNS cancer.

Whilst objective measuring and scoring of nausea and vomiting using validated tools such as a nausea visual analogue scale would have been ideal, the retrospective nature of this chart review meant that this was not possible. Subjective reporting of feeding and feelings of nausea from notes had to be relied upon, as

well as parental/carer/patient reporting of number, volume and intensity of vomiting.³²

Subjective self or proxy reporting of efficacy may have also contributed to conformation bias, with those evaluating interventions at the time seeking to correlate the intervention with a positive rather than negative outcome.³³ In addition, lack of repeated probing and questioning around adverse effects, may have contributed to attribution of symptomology associated with disease progression to the disease rather than to the addition of aprepitant.

Conclusion

This is the first study to demonstrate the efficacy and tolerability in children with life-limiting conditions receiving specialist palliative care at the end of life. Despite limitations outlined above our study suggests aprepitant can be used safely and effectively in children at the end of life with nausea and vomiting; particularly in children with CNS cancer.

Future Research

It is imperative that this body of work not stand in isolation, but serve as a building blocks for further study leading on to randomised controlled trial of safety and efficacy of aprepitant in children with refractory nausea and vomiting at the end of life.

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