Gabapentin Improves Oral Feeding in Neurologically Intact Infants With Abdominal Disorders

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Feeding intolerance, poor oral feeding skills, and retching are common symptoms seen in medically complex infants with a history of abdominal disorders and surgical interventions, such as gastrostomy tube placement and Nissen fundoplication. Visceral hyperalgesia may play a role in the underlying pathophysiology. We report the use of orally administered gabapentin in 3 infants with presumed visceral hyperalgesia presenting as poor tolerance of enteral and oral feeds. Retching and outward discomfort associated with feeds was resolved within 2 to 3 days of initiation of therapy. Full oral feeds were obtained in all 3 patients within 3 to 4 months of starting gabapentin without changing adjunctive medications or therapies. After attainment of full oral feeds, all patients were successfully weaned off gabapentin over a month, with no notable side effects, signs of withdrawal, or impact on ability to feed by mouth.

ABBREVIATIONS CDH, congenital diaphragmatic hernia; DOL, day of life; G, gravida; G-tube, gastrostomy tube; P, para

KEYWORDS gabapentin; infant; neonate; oral feeding; visceral hyperalgesia

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Introduction

Medically complex infants with abdominal disorders face several barriers to tolerating enteral nutrition, including delayed initiation of oral feeds and perception of discomfort or pain associated with feeds.^{1–4} Emerging data in infants suggest abnormal abdominal nociception and visceral hyperalgesia may occur with gastrointestinal injury or inflammation secondary to gastrostomy tube (G-tube) placement, Nissen fundoplication, and other surgical manipulations within the abdominal cavity. Visceral hyperalgesia results from lowered activation threshold of pain responses to normally non-painful stimuli, such as intestinal distension from enteral feeds or gas. Infants with visceral hyperalgesia may experience retching and food aversion that further activate pain receptors. Pharmacologic treatment can facilitate the return of normal nerve sensitivities in the gut and may present an option for improving enteral, and in particular oral, feeding tolerance in infants with a history of abdominal surgery.

Gabapentin is a centrally acting ligand of the alpha-2 delta subunit of voltage-gated calcium channels that has been used successfully in small numbers of infants for management of chronic neurologic irritability and difficulty tolerating enteral feeds.^{2,4} Although most published cases of gabapentin focus on infants with significant neurologic impairment, sparse data describe its use in neurologically intact infants with poor oral feeding skills secondary to presumed visceral hyperalgesia from abdominal wall disorders or surgeries. In this report, we present our experience using gabapentin

specifically to improve enteral feeding tolerance in 3 patients without significant neurologic disabilities.

Case Series

Patient 1. This 36-week–gestational age (1.84 kg) female with gastroschisis was delivered vaginally to a 22-year-old gravida 2 para 1 (G2P1) woman. A negative pressure wound device was placed on day of life (DOL) 1 for reduction of intestines, stomach, and ovaries. It was removed at 2 weeks of life. The patient failed several enteral feeding initiation attempts, clinically represented by persistent abdominal distension and bilious emesis. On DOL 45, an upper gastrointestinal series revealed dilated proximal and mid small bowel with delayed transit. The patient was given a 10-day trial of erythromycin with hopes of improving transit time; however, there was no improvement in the patient's ability to tolerate feeding advancement.

On DOL 103, the patient underwent G-tube placement and exploratory laparotomy to remove several adhesions. Postoperatively, the patient's functional intestinal failure continued to cause malabsorption and failure to thrive despite optimizing her feeding regimens and use of parenteral nutrition. The patient was noted to be uncomfortable and frequently inconsolable. Famotidine was added to her parenteral nutrition solution to provide acid suppression in the event that reflux was contributing to her discomfort.

She developed significant parenteral nutrition–associated cholestasis, with a peak direct bilirubin value of 12.4 mg/dL, limiting the ability to give adequate nutri-

tion via the intravenous route. Increasing her enteral feeding volumes beyond 100 mL/kg/day caused her to have more than 10 watery stools per day, which further limited the ability to maximize enteral nutrition. The patient was significantly malnourished, gaining only 97 g between weeks 9 and 25 after birth. A combination of parenteral nutrition and small-volume continuous feeds was given for nearly 6 months without marked improvement in clinical or nutritional status. The patient's chronic irritability continued despite non-pharmacologic comfort care measures.

On DOL 183, orally administered gabapentin (250 mg/mL) was started at 5 mg/kg 3 times daily for presumed visceral hyperalgesia secondary to significant abdominal history and inability to tolerate enteral feeds. The patient was notably calmer and less agitated after the first dose. The dose was increased up to 10 mg/kg three times daily during the next 2 weeks based on clinical response and lack of sedation.

The patient was able to be advanced on enteral feeds and titrated off parenteral nutrition during the next 2 months (Figure, A). Initially, the patient could only take minimal volumes by mouth secondary to poor oral skills and occurrence of dumping. She was able to take 50% of her enteral feeds by mouth at discharge. Her weight gain markedly improved after initiation of gabapentin, increasing from 3.8 g/day in the month preceding its use to 22.5 g/day. Her direct hyperbilirubinemia was resolved by discharge (<0.2 mg/dL). She was discharged home on DOL 231 receiving gabapentin 10 mg/kg 3 times daily and was continued for 1 month after discharge. The parents elected to stop the medication after a month but reported no side effects related to discontinuation. In that time, she transitioned to full oral feeds. At 2 years of age, she is meeting normal developmental milestones and continues to feed fully by mouth.

Patient 2. A 28-week-gestational age (0.845 kg) female twin was born vaginally to a 30-year-old G2P1 female. The infant had a prenatal diagnosis of left-sided congenital diaphragmatic hernia (CDH) and ventricular septal defect. Surgical history included CDH repair on DOL 9, G-tube placement with Nissen fundoplication on DOL 100, and ventricular septal defect repair on DOL 190. Her hospital course was complicated by sepsis, feeding intolerance, failure to thrive, chronic lung disease, small left parietal intraparenchymal hemorrhage, and retinopathy of prematurity.

She was discharged home on DOL 241 with oxygen via nasal cannula, sildenafil, bumetanide, spironolactone, and famotidine. Feeds were administered exclusively via G-tube, running continuously at night and by bolus during the day. The patient displayed signs of oral aversion and retching with boluses and feeding attempts by mouth. Despite completing 9 months of speech and occupational therapy, the patient demonstrated an inability to tolerate oral feeds and continued

Figure. The percentages of total volumes of intake are shown over time in the 3 patients who received gabapentin. (A) Patient 1 was receiving IV fluids and enteral feeds. Gabapentin was started on day of life 182. The graph demonstrates the % of volume (y-axis) versus the time in days (x-axis). Day 0 represents the initiation of gabapentin. (B and C) Patients 2 (age 18 months) and 3 (age 8 months) were receiving all G-tube feeds prior to the initiation of gabapentin (day 0). The graphs demonstrate the % of volume (y-axis) versus the time in weeks (x-axis).

(A) ● Intravenous; ■ Oral; (B, C) ● G-tube; ■ Oral
G-tube, gastrostomy tube.

toretch. Based on her clinical presentation and abdominal surgical history (CDH repair and G-tube with Nissen), visceral hyperalgesia was suspected. At approximately 18 months of life, oral gabapentin (250 mg/mL) was started at 5 mg/kg 3 times daily and titrated up to 10 mg/kg 3 times daily for desired clinical response. Within 2 days of initiation, the parents reported the patient was no longer retching and was displaying more interest in oral feeds. Full oral feeds were established within 3 months (Figure, B). The gabapentin was weaned by 25% per week during the course of a month. At her 2-year neurology follow-up appointment, she was documented as achieving appropriate developmental milestones, with minor motor delays. She continues oral feeding with no noted discomfort, and her G-tube was removed shortly after her second birthday.

Patient 3. A 37-week–gestational age (3.162 kg) male with a prenatal diagnosis of left-sided CDH was born via cesarean delivery to a 26-year-old G1P0 woman. Postnatally, the left lobe of liver and stomach were found to be intrathoracic. Surgical repair of CDH occurred on the day of birth, and the patient subsequently required a 12-day course of venoarterial extracorporeal membrane oxygenation. Additional complications included a spontaneous gastrointestinal perforation diagnosed on DOL 7 requiring surgical resection of the cecum, creation of a mucous fistula, and 5 weeks of parenteral nutrition. Insertion of a G-tube with Nissen fundoplication was performed on DOL 70. The patient was discharged home on DOL 92 with bolus feeds of maternal breast milk during the day and continuous feeds at night administered exclusively via G-tube.

The patient received home speech and occupational therapy to help develop oral feeding skills. He was noted to have significant feeding aversion and retching with bolus feeds. At 6 months of life, a trial of antacids and metoclopramide showed no benefit. At 8 months of life, the patient was taking less than 10% of feeds by mouth, and visceral hyperalgesia was suspected based on the history of CDH and his lack of response to previous therapies. A trial of gabapentin solution (250 mg/mL) was initiated at 5 mg/kg twice daily and increased up to 10 mg/kg 3 times daily based on clinical response. Retching resolved and feeding was successfully increased by mouth within 3 days of starting gabapentin (Figure, C). By treatment day 105, the patient achieved full oral feeds. The gabapentin was weaned by 25% per week during the next month, with no decrease in oral feeding noted. The G-tube was subsequently removed. At this time, the patient is nearly 2 years old, achieving normal developmental milestones, and continues to eat fully by mouth.

Discussion

Visceral hyperalgesia may be an important source of unrecognized pain and discomfort in infants with a history of abdominal disorders. It is often a diagnosis of exclusion made after failure to control other causes

of pain or discomfort. Because neonates and infants are unable to verbalize pain, diagnosis is difficult and is often made after response to neuropathic pain treatment.¹ Symptoms include feeding intolerance, abdominal burning/discomfort, and retching. Feeding intolerance secondary to visceral hyperalgesia can present as poor intestinal motility, gastroesophageal reflux, and constipation.⁴ Up to 70% of premature or medically complex infants experience some degree of feeding difficulty, such as food refusal, early satiety, oral discomfort, and dyspepsia.^{5–7}

Neonatal animal models suggest that early stress contributes to the development of functional pain disorders persisting beyond infancy.^{8–10} Long-term follow-up of patients with a history of gastroschisis revealed up to 40% report weekly abdominal pain, nearly one third of whom require hospitalization for this pain.¹¹ A study of children and young adults with CDH showed up to one third report chronic abdominal pain, and 50% report that it takes them longer to eat than their non-CDH peers.¹² Many adult patients with chronic abdominal disorders, such as irritable bowel syndrome, also report burning pains associated with abdominal distension and eating that are successfully managed with alpha-2 delta ligands, such as gabapentin. Although the exact mechanism is unknown, it is thought gabapentin inhibits pain via the voltage-dependent calcium ion channels in the central nervous system.^{13–15} Although not extensively described in the literature, gabapentin may be a reasonable treatment option for neonatal/infant visceral hyperalgesia.

Data describing the dosing and safety of gabapentin in the neonatal/infant population are relatively sparse. One of the largest series, published by Edwards et al,² describes its use for presumed hyperalgesia in 11 neonates/infants with diagnoses including neurologic impairment, chronic irritability, reliance on G-tubes, and gastroesophageal reflux. All patients were on neuroactive medications at the time of initiation, including benzodiazepines, antiepileptics, and opioids. Gabapentin was started at 5 to 10 mg/kg every 8 to 12 hours and appeared to be well tolerated and effective for improving irritability. Gabapentin use prompted weaning off of previously prescribed sedatives and opioids. Two patients experienced withdrawal symptoms with abrupt discontinuation. Three experienced bradycardia after initiation, but all were receiving concomitant medications associated with known risk of bradycardia. When challenged on a smaller dose, bradycardia resolved. It is unclear whether the occurrence of bradycardia was due exclusively to the addition of gabapentin, or if the incidence was confounded by the presence of concurrent medications. Based on this series, it appears that gabapentin doses up to 10 mg/kg every 8 hours are well tolerated for chronic irritability related to visceral hyperalgesia, and abrupt discontinuation should be avoided.

Although the Edwards et al² series focuses mostly on behavioral responses and pain control to presumed visceral hyperalgesia in infants with significant neurologic findings, our case series focuses specifically on the impact of hyperalgesia treatment on feeding tolerance. The patients in our series displayed persistent signs of visceral hyperalgesia despite other feeding-related therapeutic interventions. All 3 patients were given antacid therapy for discomfort with feeds, originally attributed to possible reflux. Patients 1 and 3 were also trialed on metoclopramide to facilitate faster gastric emptying time. After failure to respond to traditional therapies, gabapentin was initiated at 5 mg/kg 3 times daily in all patients. Doses were titrated up by 2.5 mg/kg per dose, starting with the nighttime dose in case sedation occurred, although we did not appreciate this in any of the patients. The maximum dose used was 10 mg/kg 3 times daily. Doses were increased based on the patients' clinical responses that prompted initiation of treatment (symptoms of pain/fussiness with feeds, retching, enteral intolerance, interest in oral feeding).

All 3 patients successfully transitioned to oral feeding, although patient 1 was unique in that her initial indication for use was enteral feeding intolerance. Gabapentin was continued until full oral feeds were achieved and maintained for at least 2 weeks, at which point the patient was weaned. None of the patients in our case series experienced withdrawal after discontinuation of treatment. Patient 1 was electively stopped per the parents, but patients 2 and 3 tolerated 25% weans during 4 weeks. We did not observe any adverse effects necessitating discontinuation of treatment in our patients. Timing of initiation of visceral hyperalgesia treatment is an important clinical consideration. Although some patients may benefit from inpatient initiation, having the ability to safely initiate therapy in the outpatient setting is an attractive option for patients who have already been discharged home.

Treatment for visceral hyperalgesia as part of an outpatient multimodal approach to improving oral feeding skills in medically fragile toddlers has been shown to help transition patients to oral feeding.¹⁶ Patients were given gabapentin 10 mg/kg 3 times daily or amitriptyline 1 mg/kg/day for 8 weeks. Although Davis et al¹ do not specifically detail which medication the patients received, the authors describe criteria for the use of each. Gabapentin was preferentially given to patients with a history of seizures or cardiac arrhythmias. Primary underlying diagnoses included prematurity, cerebral palsy, failure to thrive, and chromosomal abnormalities. A total of 8 of 9 patients exclusively feeding via G-tube were able to achieve and sustain full oral feeding and maintain appropriate weight gain. One patient with severe cerebral palsy was unable to maintain his weight with full oral feeds but was able to transition to 50% oral feeds. This small study suggests a potential for outpatient initiation and management of visceral

hyperalgesia treatment in medically complex children with poor oral intake. In our case series, gabapentin was initiated as outpatient therapy for 2 of the 3 patients described. Parents were in communication with the providers to help assess response to therapy by keeping oral feeding logs and observing for the presence or absence of previously noted feeding-related discomfort and retching. Both of these patients were successfully transitioned to full oral feedings with appropriate weight gain, which facilitated removal of their G-tubes.

Once gabapentin therapy is initiated for feeding intolerance, it is important to consider when to expect a clinical response. Bruce et al¹⁶ described their experience with gabapentin in post-cardiac surgery hospitalized infants with inadequate oral feeding thought to be secondary to hyperalgesia. Underlying congenital heart disease diagnoses were varied. Most infants were term and initiated on treatment within the first 2 months of life following cardiac repair. Gabapentin was initiated at 10 mg/kg twice daily and increased to 3 times daily if no sedation was noted. Treatment continued for 3 days and demonstrated improved oral feeding in 13 of 15 patients. Average oral intake volumes nearly doubled in the study period (401 ± 451 mL/day to 781 ± 586 mL/day), with 9 of the 13 responders experiencing more than a 50% increase in oral volume intake within 72 hours. There were no notable adverse effects documented, and gabapentin appeared to be well tolerated. Although a limitation of this study is the relatively short duration of treatment, it is encouraging that relatively young infants demonstrated a favorable response to therapy in a short time frame. In our patients, we used this as a guide for expectations of timing of initial response to treatment. In our case series, all 3 patients responded in terms of improved discomfort with feeds within the first 48 to 72 hours of treatment initiation. Our patients were older than most included in this case series, but all were able to achieve full oral feeds within 3 months. Patients 2 and 3 were treated exclusively at home without access to daily feeding therapies, which may help explain the length of time needed to transition to full oral feeds.

Conclusions

Use of gabapentin in neurologically intact infants with abdominal disorders may present a novel method to facilitate tolerance of enteral feeds and attainment of full oral feeding. Gabapentin has relatively few drug interactions, and its use in infants appears to have minimal side effects. Caution should be used when initiating in infants receiving concurrent medications with the potential to cause bradycardia. Abrupt discontinuation should be avoided. Although our experience suggests that gabapentin improves oral feedings and enteral feeding tolerance, larger prospective studies are needed to evaluate the efficacy and long-term safety of gabapentin use in this vulnerable population.

ARTICLE INFORMATION

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