HHS Public Access

Author manuscript

J Pediatr. Author manuscript; available in PMC 2017 February 01.

Published in final edited form as:

J Pediatr. 2016 February ; 169: 310–312. doi:10.1016/j.jpeds.2015.10.013.

Gabapentin Use in the Neonatal Intensive Care Unit

Laura Edwards, MD[1], **Stephen DeMeo, DO**[1], **Chi D. Hornik, PharmD, BCPS**[2], **C. Michael Cotten, MD, MHS**[1], **P. Brian Smith, MD, MPH, MHS**[1], **Carolyn Pizoli, MD, PhD**[3], **Julie M. Hauer, MD**[4], and **Margarita Bidegain, MD, MHS-CL**[1]

[1]Department of Pediatrics, Division of Neonatology, Duke University Medical Center, Durham NC.

[2]Department of Pharmacy, Duke University Medical Center, Durham NC.

[3]Department of Pediatrics, Division of Pediatric Neurology, Duke University Medical Center, Durham, NC.

[4]Department of Pediatrics, Children's Hospital Boston, Boston, MA.

Abstract

Gabapentin was used for the treatment of term and preterm infants with suspected visceral hyperalgesia caused by a variety of neurologic and gastrointestinal morbidities. Improved feeding tolerance and decreased irritability were seen, as well as decreased usage of opioids and benzodiazepines. Adverse events occurred with abrupt discontinuation of this medication.

Keywords

gabapentin; visceral hyperalgesia; infants; neonatal intensive care

Visceral hyperalgesia is caused by up-regulation of gastrointestinal sensory input, and has been identified as a common underlying etiology of pain, irritability, and feeding intolerance in children with severe neurologic impairment (1-4). In the newborn infant with neurologic impairment and other co-morbidities, visceral hyperalgesia presents with irritability, hypertonia, and feeding intolerance that is manifested as poor intestinal motility, gastroesophageal reflux, and constipation (3). Pharmacologic treatment options in these infants often begin with acetaminophen, opioids, benzodiazepines, or barbiturates; however, these medications may not be ideal in cases of chronic pain and discomfort.

Gabapentin has been used to treat neuropathic pain related to visceral hyperalgesia in the neonatal population (5, 6). Gabapentin, a gamma-aminobutyric acid analog, is thought to inhibit pain via voltage-dependent calcium ion channels in the central nervous system. There is minimal information on the use and side effects of initiating and discontinuing of

Corresponding Author: Margarita Bidegain, MD. 2424 Erwin Road, Suite 504, Box 2739. Durham NC, 27710. Phone: 919-668-1592. Fax: 919-681-6065. margarita.bidegain@dm.duke.edu.

The authors declare no conflicts of interest.

gabapentin in this population (3, 5-7). The objective of this study was to present a case series of neurologically impaired term and preterm infants who were treated with gabapentin for visceral hyperalgesia, and include descriptions of clinical responses and adverse events related to this medication.

Methods

This was a retrospective case series of all infants treated with gabapentin prior to discharge from a single tertiary neonatal intensive care unit from 2012-2014. We searched pharmacy records to identify patients treated with gabapentin and extracted relevant clinical data from the electronic medical record. Outcomes were extracted from nursing and physician documentation. We used standard descriptive statistics including median and interquartile range (IQR) and counts and percentages to describe the study cohort. Statistical analyses were conducted using JMP 11.0 (Cary, NC). The Duke University Institutional Review Board declared this study exempt from full review.

Results

Eleven infants were treated with gabapentin during the study period, eight of whom were born prematurely (Table I). All of the patients were medically complex with multiple secondary diagnoses, including neurologic co-morbidities (Table II). All of the patients had a gastrostomy tube (G-tube) or gastrojejunostomy (GJ tube) due to inability to feed orally, severe gastroesophageal reflux (GERD), or chronic intestinal obstruction. Five of the patients had tracheostomy tubes. One patient died due to complications from extreme prematurity. All of the infants were receiving multiple sedative and analgesic medications when gabapentin was started (Table II).

Decreased irritability was seen in the three term infants (GA, 38-41 weeks) who were treated with gabapentin. This effect was noticeable within the first two days of treatment. Infant #9 received intermittent lorazepam for persistent agitation, which caused him to be sleepy and not participate in oral feedings. Within 24 hours of initiating gabapentin, the infant no longer required lorazepam, and he was noted to have improved sleep at night and participated more consistently in oral feeding. None of the term infants had an adverse event while receiving gabapentin.

In the preterm population (GA, 23-32 weeks) decreased irritability was also appreciated, and three infants were weaned off opioids and/or benzodiazepines while receiving gabapentin. Three of the eight preterm infants were started on gabapentin due to gastrointestinal manifestations of visceral hyperalgesia, and all three of these infants tolerated full enteral feedings via G or GJ tubes with less reflux-related discomfort (restlessness during feedings and emesis). Only one of these infants fed orally, and she participated in more oral feeding attempts. Infant 7 was unique because she received gabapentin for episodic tachycardia, fever, and limb trembling attributed to sympathetic hyperactivity. These episodes did not recur after initiation of gabapentin.

Adverse events were reported in five of the 11 patients, and three were related to abrupt discontinuation of gabapentin due to NPO status, suggesting the existence of a gabapentin

withdrawal syndrome in infants. Three of these infants experienced episodic tachycardia, emesis, and increased irritability, and their symptoms resolved after reinitiation of gabapentin. The remaining two adverse events occurred in twin infants and consisted of episodes of bradycardia within the first 24 hours of starting gabapentin, with one twin restarting gabapentin at a lower dose with no further bradycardia.

Discussion

Gabapentin is increasingly being used as a treatment for pain secondary to visceral hyperalgesia in the pediatric population because of its mild reported side effect profile: apparent lack of drug-drug interactions, due to its predominantly renal route of excretion; and the ability to escalate doses quickly (8-11). In adults, pain, seizures, irritability, and autonomic instability may develop acutely with abrupt discontinuation of gabapentin (9). These reported adverse effects have not been described in infants. We used gabapentin for the treatment of term and preterm infants with refractory visceral hyperalgesia caused by neurologic and gastrointestinal morbidities. Symptom relief for chronic irritability and feeding intolerance occurred in both populations, as was a reduction in the use of opioids and benzodiazepines. Additionally, we discuss side effects of gabapentin not previously highlighted. Clinicians should be aware that abrupt discontinuation of gabapentin may result in adverse events related to autonomic instability.

A study of gabapentin single-dose pharmacokinetics and safety in healthy children found that children under five require approximately 30% higher daily doses of gabapentin, presumably due to age-related changes in pediatric renal function (10). Six of the eight preterm infants were started on a dose of 5 mg/kg every 12 hours (4). Assuming increased glomerular filtration at older gestational ages, two of the three term infants received an initial dose of 5 mg/kg every 8 hours. Further studies are needed to elucidate the pharmacokinetics, safety, and efficacy of gabapentin in infants.

Abbreviations

IQR	Interquartile range
CNS	central nervous system
NPO	nil per os
GERD	gastroesophageal reflux disease
GJ tube	gastrojejunostomy tube

References

1. Mertz H. Role of the brain and sensory pathways in gastrointestinal sensory disorders in humans. Gut. 2002; 51(suppl 1):i29–i33. [PubMed: 12077061]
2. Delgado-Aros S, Camilleri M. Visceral hypersensitivity. Journal of clinical gastroenterology. 2005; 39(5 Suppl 3):S194–203. discussion S10. [PubMed: 15798485]
3. Hauer JM. Treatment of persistent pain and irritability in children with neurological impairment. Neuropadiatrie. 2011; 10(1):7–14.

4. Hauer JM, Wical BS, Charnas L. Gabapentin Successfully Manages Chronic Unexplained Irritability in Children With Severe Neurologic Impairment. Pediatrics. 2007; 119(2):e519–e22. [PubMed: 17272610]
5. Haney AL, Garner SS, Cox TH. Gabapentin Therapy for Pain and Irritability in a Neurologically Impaired Infant. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2009; 29(8):997–1001.
6. Behm MO, Kearns GL. Treatment of Pain With Gabapentin in a Neonate. Pediatrics. 2001; 108(2): 482–4. [PubMed: 11483821]
7. Mackey, JHaD. Treatment with Gabapentin Associated with Resolution of Apnea in Two Infants with Neurologic Impairment. Journal of Palliative Medicine. 2013; 16(4):3. [PubMed: 23317317]
8. Morris GL. Gabapentin. Epilepsia. 1999; 40(Suppl 5):S63–70. [PubMed: 10530696]
9. Norton JW. Gabapentin Withdrawal Syndrome. Clinical Neuropharmacology. 2001; 24(4):245–6. [PubMed: 11479399]
10. Haig GM, Bockbrader HN, Wesche DL, Boellner SW, Ouellet D, Brown RR, et al. Single-dose gabapentin pharmacokinetics and safety in healthy infants and children. Journal of clinical pharmacology. 2001; 41(5):507–14. [PubMed: 11361047]
11. Vollmer KO, von Hodenberg A, Kolle EU. Pharmacokinetics and metabolism of gabapentin in rat, dog and man. Arzneimittel-Forschung. 1986; 36(5):830–9. [PubMed: 3730018]

Table 1

Characteristics of study cohort

	<37 weeks	**≥37weeks**
	n=8	**n=3**
Birth weight (g), median (IQR)	875 (700-1900)	2940 (2920-3500)
Gestational age (weeks), median (IQR)	25 (24-32)	39 (38-41)
Male, n (%)	5 (63)	2 (66)
Age at start of treatment (days), median (IQR)	143 (98-253)	131 (48-182)
Mortality, n (%)	1 (12)	0 (0)
Experienced adverse event, n (%)	5 (62)	0 (0)

Abbreviations: g-grams, IQR-interquartile range

Table 2

Diagnoses and Outcomes

Infant	GA (weeks)	BW (g)	Diagnoses	Indication	Concurrent neurological medications	Starting dose[1]	Died	Discharge dose[1]	Outcome
1	23	670	IVH with shunt, seizures, tracheostomy, GJ-tube	feeding intolerance/seizures	levetiracetam	5 q8	No	5 q24	Improved feeding tolerance. Tachycardia, emesis, and agitation with abrupt discontinuation when NPO
2	24	430	IVH with shunt, seizures, tracheostomy, G-tube	visceral hyperalgesia/agitation	clonidine, diazepam, acetaminophen PRN	10 q12	No	10 q8	Improved feeding tolerance
3	24	860	CLD, G-tube, GERD, hypertonia	visceral hyperalgesia/seizures	phenobarbital, diazepam, methadone, morphine PRN, lorazepam PRN	5 q12	Yes	Died	Decreased irritability and reduced use of benzodiazepines and morphine
4	24	790	CLD, G-tube, GERD, hypertonia	visceral hyperalgesia/agitation	baclofen	5 q12	No	5 q12	Decreased irritability, improved oral feeding and toleration of G-tube feeds. Tachycardia, emesis, and agitation with abrupt discontinuation when NPO
5	26	890	CLD, hypertonia, G-tube, bowel obstruction, twin	visceral hyperalgesia/agitation	baclofen, lorazepam	5 q12	No	2.5 q12	Bradycardia: resolved with lower dose; weaned off of benzodiazepines
6	26	890	CLD, hypertonia, G-tube, twin	visceral hyperalgesia/agitation	baclofen, lorazepam	5 q12	No	N/a	Bradycardia: discontinued without trial of lower dose
7	27	1003	Congenital intestinal atresia, microcephaly, lissencephaly, seizures, tracheostomy, GJ-tube	visceral hyperalgesia/agitation	diazepam, phenobarbital, topiramate, baclofen, lorazepam PRN	5 q24	No	7.5 q12	Decreased sympathetic hyperactivity; weaned off of benzodiazepines
8	32	1900	Pulmonary hypoplasia with tracheostomy, joint contractures, G-tube	visceral hyperalgesia/agitation	baclofen, clonidine, lorazepam PRN	5 q12	No	5 q8	Bradycardia which resolved at lower dose; weaned off of benzodiazepines and methadone
9	38	3500	HIE, hypertonia, GERD, G-tube	visceral hyperalgesia/agitation	baclofen, lorazepam PRN	5 q8	No	7.5 q12	Decreased irritability and improved oral feeding
10	39	2940	CDH, history of ECMO, tracheostomy, GJ-tube, NAS, seizures	visceral hyperalgesia/agitation/seizures	clonidine, lorazepam, methadone, phenobarbital	5 q12	No	N/a	Decreased irritability and use of benzodiazepines
11	41	2921	VATER syndrome, pulmonary hypoplasia with tracheostomy, chromosomal abnormality, G-tube, NAS, seizures	agitation/seizures	clonidine, diazepam, levetriracetam, oxcarbazepine, phenobarbital, dexmedetomidine gtt, midazolam gtt	5 q8	No	5 q8	Decreased irritability

Abbreviations: CDH- congenital diaphragmatic hernia; CLD-chronic lung disease; ECMO- extracorporeal membrane oxygenation; EEG- electroencephalogram; GERD- gastroesophageal reflux disease; G-tube- gastrostomy tube; GJ tube-gastro-jejunostomy tube; HIE-hypoxic ischemic encephalopathy; IVH-intraventricular hemorrhage; NAS- neonatal abstinence syndrome

[1] mg/kg weight dosing with hourly dosing