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Evaluating Gabapentin Dosing, Efficacy and Safety in Infants

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OBJECTIVE Gabapentin for management of neuropathic pain, irritability, neonatal abstinence syndrome, rescue sedation, feeding intolerance and visceral hyperalgesia in infants has grown over the past decade. There remains little guidance for indications, initiation, titration and maintenance dosing trends and assessment of outcomes. The primary objective was to describe gabapentin dosing, and the secondary objectives were to identify outcomes to assess efficacy and describe weaning practices.

METHODS A retrospective single-center study was performed in infants younger than 1 year who received gabapentin at Boston Children's Hospital between 2015 and 2021. The primary outcome was indication, initiation and maximum gabapentin dose. Secondary outcomes included mortality, adverse reactions and impact on feeding volumes, weight-for-age Z-scores and face, legs, activity, cry, consolability (FLACC) scores. Descriptive statistics were utilized.

RESULTS Sixty-six infants received gabapentin at a mean ± SD age of 5.5 ± 2.7 months (range of 0–11 months). The mean ± SD initiation dose of gabapentin was 8.6 ± 5.4 mg/kg/day with a median interval of 24 hours (8–24 hours). The maximum mean dose was 23.2 ± 14.4 mg/kg/day at a median interval of every 8 hours (8 hours). The most common indications for initiation were irritability, rescue sedation, and visceral hyperalgesia. There was a statistical improvement in weight-for-age Z scores from 24 hours prior to gabapentin initiation to 2 weeks after the maximum dose of gabapentin (−2.23 ± 1.78 to −1.66 ± 1.91, $p < 0.001$) and a reduction in FLACC scores (2.29 ± 1.64 to 1.52 ± 1.76, $p = 0.007$) from 24 hours prior to gabapentin initiation to 3 days after the maximum dose of gabapentin. Three patients experienced minor adverse events.

CONCLUSIONS Gabapentin was well tolerated in infants. Initial gabapentin dosing of 5 mg/kg/dose every 24 hours appears safe and consistent with other published studies in infants. The improvement in outcomes with few adverse events suggests a beneficial role for gabapentin.

ABBREVIATIONS BPD, bronchopulmonary dysplasia; CICU, cardiac intensive care unit; FLACC, Face, Legs, Activity, Cry, Consolability; NAS, neonatal abstinence syndrome

KEYWORDS gabapentin; infants; irritability; neonates; pain; visceral hyperalgesia

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Introduction

Gabapentin is a gamma-aminobutyric acid analog that has been used in multiple disease states in children, including neuropathic pain, irritability, visceral hyperalgesia, neonatal abstinence syndrome (NAS), rescue sedation and feeding intolerance.[1–7] Despite the increased utilization of gabapentin in neonates,[1] there remains a gap in the pediatric literature describing the initiation, titration and maintenance of gabapentin with no standardized protocols in infants. Furthermore, there is no consensus on dosing or monitoring of the potential side effect profiles. Our understanding of the literature is limited and mostly comes from small case reports and case series.[2–7] The purpose of this study was to describe the experience of gabapentin utilization at a large children's hospital in infants younger than 1 year of age with a focus on indication, dosing initiation, titration, and maintenance trends. The secondary aim was to identify outcomes to assess efficacy and describe weaning practices.

Methods

Study Design. This was a single center, retrospective study of consecutive infants on gabapentin younger than 1 year of age who were initiated on gabapentin while admitted to Boston Children's Hospital between October 1, 2015, and October 30, 2021. There were no other exclusion criteria for this study.

Primary Outcomes. The primary outcome of the study was to describe gabapentin dosing trends

based on diagnosis, ordering service, patient hospital location and gestational age.

Secondary Objective. The secondary outcomes included mortality, adverse reactions, description of feeding volumes, weight-for-age Z-scores and face, legs, activity, cry, consolability (FLACC) scores. An additional secondary objective is to describe weaning practices in the inpatient setting.

Data Collection. Patients were identified from a review of the electronic health care records (Cerner, Kansas City, MO) using an internal software program developed at Boston Children's Hospital. Data were collected from clinical documentation, medication administration records and flowsheet records. All data collected was de-identified. Baseline characteristics included gestational age (weeks), birth weight (kilograms), sex, race, chronological age when initiated on gabapentin (months), clinical service team recommending gabapentin, patient location in the hospital, and indication for gabapentin.

For the primary outcome we collected the initial and maximum dose (milligram/kilogram), the initial and maximum dosing frequency (hours), and days between initiation dose and maximum dose. For secondary outcomes we documented overall study mortality. Adverse events were reviewed from initiation to 1 week after achieving maximum dose. We assessed for bradycardia, defined as a documented heart rate less than 70 beats per minute, oversedation based on clinical charting, report of nystagmus, and intolerance (e.g., emesis).[6] In addition, we captured adverse events during the weaning phase in neonates who had their dose weaned while still in the hospital. The FLACC score, a validated measurement tool used to assess pain for infants that are unable to communicate, was collected within 24 hours of starting gabapentin and 3 days after achievement of the maximum dose.[8] Per nursing instruction, they are to assess and re-assess patients' pain following pharmacologic and non-pharmacologic intervention. This assessment and re-assessment must be documented in the electronic health care record using the patients' age appropriate scale (i.e., FLACC). For most patients in this study, nursing captured the FLACC score every 1 to 4 hours (more often for the higher acuity patients, e.g., in an intensive care unit). Most patients had multiple FLACC scores documented, so the average of the scores within 24 hours of the starting gabapentin dose and within 3 days after achievement of the maximum dose were used. We captured nutritional outcomes; total volume of enteral feeding (mL/kg/day) 24 hours prior to initiation, 3 days post maximum dose, and at discharge, and weight 24 hours prior to initiation and 2 weeks post maximum dose. These nutritional outcome measures were chosen because each of the disease states for which gabapentin has been used can adversely impact the infants' metabolic demand and are commonly reported outcomes of interest in the literature.[2–9] Weight and weight-for-age Z-scores were collected 24 hours pre-gabapentin and 2 weeks after the maximum dose of gabapentin. Z-scores are a SD scale, so the goal for infant growth is to achieve scores as close to zero as possible or within 1 SD of zero. We also collected weaning practices for all infants who had their gabapentin weaned while inpatient, as well as duration of treatment for gabapentin.

We collected common neurological (e.g., intraventricular hemorrhage, periventricular leukomalacia, hydrocephalous, microcephaly, ventriculomegaly, seizures, and global developmental delay), and gastrointestinal comorbidities (necrotizing enterocolitis, emesis, gastrostomy-tube dependent, total parental nutrition dependence, constipation, feeding intolerance, gastroesophageal reflux) and other major comorbidities (e.g., chronic lung disease of prematurity, bronchopulmonary dysplasia, BPD). In addition, we collected neurology-related medications (e.g., pain and sedation medications including acetaminophen, opioids, benzodiazepines, antiepileptic drugs and skeletal muscle relaxants) and gastrointestinal related-medications (anti-reflux, promotility agents, bowel-regimen agents, antacids and proton pump inhibitors).

Statistical Analysis. Descriptive statistics of means for normally distributed data and medians for non-parametric data were used to evaluate baseline characteristics, services recommending gabapentin, common neurological and gastrointestinal comorbidities, indications for use and dosing trends. Data are presented as mean ± SD, median (IQR) or number (percentage). We have also included range where appropriate. Feeding volumes, weight gain differences and weight-for-age Z-scores were analyzed using the Wilcoxon signed rank test. The difference in FLACC scores were analyzed using the paired *T* test. The alpha priori value was 0.05. Statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC).

Results

Sixty-six patients were identified during the study period who were younger than 1 year of age and administered gabapentin for any indication. Over the 6-year study period, gabapentin use increased from 6 cases in 2016 to 24 cases in 2021 (Supplemental Figure). Baseline characteristics are summarized in Table 1. Gabapentin was initiated at a mean ± SD age of 5.5 ± 2.7 months (range of 0–11 months) and most frequently by the neurology (47%) and Pediatric Advanced Care Team (PACT; 17%) services (Table 2). The most common locations for gabapentin initiation were in the cardiac (23%), pediatric (23%), and neonatal (11%) intensive care units. The most common indications for gabapentin use were neuro-irritability (80%), visceral hyperalgesia (6%), pain (6%), and gastroesophageal reflux (5%). None of the patients had renal disease and none of the infants

Table 1. Baseline Characteristics*

Characteristic	Value, N = 66
Gestational age (wk)	34 ± 5.1
Extremely preterm (<28)	13 (20%)
Very preterm (28–31$^{6/7}$)	3 (5%)
Moderate preterm (32–36$^{6/7}$)	14 (21%)
Full term (≥37)	35 (53%)
Unknown	1 (1%)
Birth weight (kg)	2.34 ± 1.08
Extremely low birth weight (<1)	11 (17%)
Very low birth weight (<1.5)	4 (6%)
Low birth weight (<2.5)	15 (22%)
Normal birth weight (≥2.5)	29 (44%)
Unknown	7 (11%)
Sex, n (%)	
Male	42 (64%)
Female	24 (36%)
Race, n (%)	
Caucasian	29 (45%)
African American	6 (9%)
Asian	1 (1%)
Declined/unable to answer	20 (30%)
Other	10 (15%)
Chronological age upon initiation of gabapentin, mo	5.5 ± 2.7 (Range, 0–11 mo)
Weight at initiation (kg)	5.9 ± 2.2
Severe Bronchopulmonary dysplasia (BPD)	14 (21%)
Neurological comorbidity, n (%)	
Seizure disorder	22 (33%)
Global developmental delay	26 (36%)
Hypoxic ischemic encephalopathy (HIE)	10 (15%)
Hydrocephalus	12 (18%)
Intraventricular hemorrhage	9 (14%)
Mean number of neurological comorbidities	2.5 ± 2.0
Number of patients on at least 1 neurology-related medication	58 (87%)
Number of patients weaned off all neurology-related medications	31 (53%)
Gastrointestinal comorbidity, n (%)	
Feeding tube and/or parenteral nutrition dependence	58 (87%)
PN dependence	11 (17%)
Necrotizing enterocolitis (NEC)	12 (18%)
Feeding intolerance	52 (79%)
Gastroesophageal reflux	9 (14%)
Mean number of gastrointestinal (GI) comorbidities	2.8 ± 1.3
Number of patients on at least 1 GI-related medications	58 (87%)
Number of patients weaned off all GI-related medications	26 (45%)

* Data expressed as mean ± SD or number (percentage).

were started on gabapentin for in-utero exposure or as an adjuvant medication for NAS.

Primary Outcomes. The mean starting dose was 8.6 ± 5.4 mg/kg/day, with the median interval of every 24 hours (IQR, 8–24 hours). Fifty percent (n = 33) of infants were initiated on a dose of 5 mg/kg every 24 hours at nighttime. There were 23 (35%) patients started on a dose greater than 10 mg/kg/dose and 43 (65%) started on a dose < 10 mg/kg/dose. Gabapentin was started at an interval of every 8 hours, 12 hours, and 24 hours in 20 (30%), 13 (20%), and 33 (50%) of the infants, respectively. There were 21 (32%) infants who reached a maximum dose > 30 mg/kg/day divided every 8 hours and 13 (20%) of infants had a maximum dose > 35 mg/kg/day divided every 8 hours. The mean maximum dose was 23.2 ± 14.4 mg/kg/day (range, 4–62 mg/kg/day) with the median interval of every 8 hours (IQR, 8 hours). For 15 infants (22%), the maximum total daily dose was 15 mg/kg/day. The maximum dose in 1 patient was 62 mg/kg/day divided every 8 hours. The mean and maximum dosing and intervals by diagnosis and ordering service are presented in Table 2, with no statistical differences. The median time between initiation and achieving maximum dosing was 28.5 days (IQR, 2.75–55.5). We found no differences in the primary outcomes when we accounted for postmenstrual age at which gabapentin was initiated (Table 2).

Secondary Outcomes. Only 8 (12%) of the infants had gabapentin weaned during their hospitalization and 7 (11%) did not go home on the medication. The mean starting dose from which weaning was commenced was 18.1 ± 12.1 mg/kg/day and the median interval was 8 hours (IQR, 8 hours). All but 2 of the patients were on every 8-hour dosing when the weaning was initiated inpatient. The median time interval on the medication prior to weaning was 80 days (IQR, 13–162). For each patient, the dosing was first slowly weaned to 15 mg/kg/day while maintaining the dosing interval, and then the interval was weaned weekly from every 8 hours to every 12 hours and then daily. The median time from initiation of the weaning to off was 27 days (IQR, 14–43 days).

Nutritional Patterns. Feeding volumes, weights, and weight-for-age Z score changes can be found in Table 3. Feeding volumes (mL/kg/day) did not statistically change from 24 hours prior to gabapentin initiation to 3 days post—a maximum dose of gabapentin (63.1 ± 58.0 to 61.3 ± 55.5 mL, p = 0.804), or from 24 hours prior to gabapentin initiation to discharge (63.1 ± 58.0 mL to 76.8 ± 53.1 mL, p = 0.430). Weight (kilograms) statistically increased from 24 hours prior to gabapentin initiation to 2 weeks after the gabapentin maximum dose (5.9 ± 2.2 to 6.8 ± 2.4, p < 0.001) and at discharge (5.9 ± 2.2 to 7.1 ± 2.3, p < 0.001). Weight-for-age Z-scores approaching zero from pre-gabapentin to 2 weeks post-maximum gabapentin dose was

Table 2. Primary Outcome: Gabapentin Initial and Maximum Dose and Intervals*

		Initial Dose (mg/kg/day)	Initial Interval (hr)	Maximum Dose (mg/kg/day)	Maximum Interval (hr)
Entire cohort	66	8.6 ± 5.4 Range (2–30)	24 (8–24)	23.2 ± 14.4 Range (4–62)	8 (8–8)
Diagnosis					
Irritability	53 (80%)	8.5 ± 5.5	24 (8–24)	22.0 ± 15.8	8 (8–8)
Pain	4 (6%)	9.1 ± 4.3	10 (8–21)	22.6 ± 7.4	8 (8–11)
Visceral hyperalgesia	4 (6%)	7.8 ± 5.5	16 (8–24)	24 ± 6.1	8 (8–8)
GER	3 (5%)	15.3 ± 0.6	12 (12–12)	30 ±13.1	8 (8–8)
Other	2 (3%)	5 ± 0	24 (24–24)	10.0 ± 5.0	16.0 ± 5.7
Ordering service					
Neurology	31 (47%)	8.0 ± 5.7	24 (8–24)	18.7 ± 11.9	8 (8–8)
PACT	11 (17%)	10.1 ± 5.3	8 (8–24)	31.9 ± 19.3	8 (8–8)
PMNR	5 (7%)	8.0 ± 5.3	24 (8–24)	28.9 ± 16.7	8 (8–8)
Neonatology	5 (7%)	6.64 ± 5.3	24 (10–24)	22.0 ± 13.9	8 (7–10)
Pediatric intensivist	4 (6%)	6.8 ± 3.7	24 (12–24)	32.8 ± 4.5	8 (4–8)
Gastroenterology	4 (6%)	14.2 ± 5.5	12 (12–21)	25 ± 14.5	10 (8–21)
Pain Team	3 (5%)	7.1 ± 2.2	12 (8–24)	15.8 ± 13.2	8 (8–12)
Cardiology	2 (3%)	12.5 ±10.6	18.0 ± 8.5	22.5 ± 10.6	8.0 ± 0
Unknown	1 (2%)	14	8	30	8
Patient hospital location					
Pediatric ICU	15 (23%)	7.6 ± 4.3	24 (8–24)	27.1 ± 13.0	8 (8–8)
Cardiac ICU	15 (23%)	11.9 ± 7.7	12 (8–24)	29.2 ± 15.0	8 (8–8)
Neonatal ICU	7 (11%)	6.3 ± 3.4	24 (8–24)	17.8 ± 20.3	8 (8–12)
Neurology/Neurosurgery	7 (11%)	7.8 ± 5.2	12 (8–24)	14.1 ± 9.9	8 (8–12)
General Pediatrics	6 (9%)	9.4 ± 4.9	10 (8–15)	19.4 ± 12.0	8 (8–9)
General Cardiology	6 (9%)	7.2 ± 4.6	24 (11–24)	20.9 ± 6.1	8 (8–9)
Complex Care	5 (7%)	8.5 ± 4.2	12 (8–24)	21.5 ± 15.3	8 (8–10)
Surgical	2 (3%)	12.2 ± 4.0	12 ± 0	20.7 ± 16.0	10 ± 2.8
Hematology/Oncology	3 (5%)	5.1 ± 0.1	24 (24–24)	24.3 ± 22.6	8 (8–24)
Gestational age (wk)					
Extremely preterm (<28)	13 (20%)	7.4 ± 5.2	24 (8–24)	25.0 ± 17.4	8 (8–8)
Very preterm (28–31$^{6/7}$)	3 (5%)	13.7 ± 7.8	12 (8–24)	29.3 ± 0.57	8 (8–8)
Moderate preterm (32–36$^{6/7}$)	14 (21%)	9.5 ± 4.3	12 (8–24)	19.7 ± 10.6	8 (8–8)
Full term (≥37)	35 (53%)	8.3 ± 5.6	21 (8–24)	23.0 ± 15.2	8 (8–8)

GER, gastroesophageal reflux; ICU, intensive care unit; PACT, pediatric advanced care team; PMNR, pediatric medicine and rehabilitation

* All data presented as number (percentage), mean (SD), or median (IQR). Categories with less than 2 individuals, data for interval is presented as mean (SD).

statistically significant (−2.23 ± 1.78 to −1.66 ± 1.91, p < 0.001).

Pain Scores. The mean FLACC score decreased 24 hours prior to starting gabapentin to 3 days after reaching the maximum dose of gabapentin, (n = 66, 2.29 ± 1.64 to 1.52 ± 1.76 p = 0.007).

Neurology-Related Medications. Of the 66 infants, 58 (87%) were on at least 1 other neurology-related medication while receiving gabapentin. Of note, 46 (70%) were on at least 2, 35 (53%) were on at least 3, 29 (44%) were on at least 4, 21 (32%) were on at least 5, 12 (18%) were on at least 6, 7 (11%) were on at least 7, 4 (6%) were on at least 8, and 1 (2%) was on at least 9 additional neurology-related medication while receiving gabapentin. Over half (n = 31/58, 53%) of the infants had all their neurology-related medications weaned off while receiving gabapentin. We identified 16 extremely and very preterm infants, 14 of whom had severe BPD (Table 1). These 14 extremely and very preterm infants with severe BPD were on more neurology-related medications compared with 2 extremely and very preterm infants without severe BPD (p < 0.001) and compared with the remaining 50 late and moderate preterm, term infants, and unknown without BPD (p < 0.001).

Gastroenterology/Reflux-Related Medications. Of the 66 infants, 58 (87%) were on at least 1 other gastroenterology/reflux-related medication while receiving gabapentin. Of note, 50 (76%) were on at least 2, 33 (50%) were on at least 3, 15 (23%) were on at least 4, 8 (12%) were on at least 5, and 3 (5%) were on at least 6 additional gastroenterology/reflux

Table 3. Nutritional Outcomes*

Nutritional measures	Value	p value
Enteral volumes (mL/kg/day)		
24 hr prior to gabapentin initiation	63.1 ± 58.0	
3 days post maximum dose of gabapentin	61.3 ± 55.5	0.804 †
Discharge	76.8 ± 53.1	0.43 ‡
Weight (kg)		
24 hr prior to gabapentin initiation	5.9 ± 2.2	
2 wk post maximum dose of gabapentin	6.8 ± 2.4	<0.001 §
Discharge	7.1 ± 2.3	<0.001 ‡
Weight-for-age Z-scores		
24 hr prior to gabapentin initiation	−2.23 ± 1.78	
2 wk post maximum dose of gabapentin	−1.66 ± 1.91	<0.001 §

*All data are presented as mean ± SD.
† Comparison between 24 hr prior to gabapentin initiation and 3 days post-maximum dose.
‡ Comparison between 24 hr prior to gabapentin initiation and discharge.
§ Comparison between 24 hr prior to gabapentin initiation and 2 wk post maximum dose.

medication while receiving gabapentin. Forty-five percent (n = 26/58) of the infants had all their gastroenterology medications weaned off while receiving gabapentin.

Adverse Events. Of the 66 patients, 2 infants (both term and initiated on gabapentin for irritability) experienced over-sedation (9 and 15mg/kg/day, respectively) and 1 infant (late preterm initiated on gabapentin for visceral hyperalgesia) had bradycardia defined as a documented heart rate less than 70 beats per minute (maximum dose 21.4 mg/kg/day divided every 8 hours) within 7 days of the maximum dose. The 2 term infants were initiated on gabapentin at 7 and 11 months, respectively. The preterm infant was initiated on gabapentin at 1 month of age and experienced the bradycardia at the maximum dose, which was also within 7 days of initiation of gabapentin. There were no observed adverse events during the weaning phase for the 8 infants weaned off gabapentin while in the hospital. Sixteen (24%) of the infants died prior to discharge but none were related to gabapentin. Two patients were not on gabapentin at the time of death, and 1 had been off of it for 3 months and the other for 3 weeks. Of the remaining 14 deaths, the total median time on gabapentin at the time of death was 90 days (IQR, 51–265). Causes of death included cardiac arrest (n = 3), heart failure (n = 2), multiorgan failure (n = 6), terminal cancer (n = 2), progressive lung disease (n = 2), and ischemic brain injury (n = 1).

Discussion

There is growing use of gabapentin in infants younger than 1 year of age with neuropathic pain, irritability, NAS, feeding intolerance, rescue sedation and visceral hyperalgesia.[1–7] In this retrospective single center study, the mean gabapentin dose at initiation was 8.6 mg/kg/day at an initial median interval of every 24 hours and a maximum mean dose of 23.2 mg/kg/day at a median interval of every 8 hours. The most common indications for initiation were agitation, visceral hyperalgesia, pain and gastrointestinal reflux. There was improvement in weight gain, weight-for-age Z-score, a reduction in FLACC scores, and ability to wean off neurology-related medications with minimal adverse events. Gabapentin was well tolerated in infants younger than 1 year old and should be considered in certain patients that do not respond to standard analgesia and sedative regimens.

Recent literature has shown an increased use of gabapentin in neonates and infants with similar indications to what we observed in our study.[1–7,9] Abdi et al[1] identified gabapentin use over an 11-year period from the Pediatric Health Information System (PHIS) at 0.13% (374/278,403) with 0% in 2005, 0.07% use in 2010, and 0.39% in 2016. In our study we also showed an increase usage of gabapentin from 2015 (6 cases) through 2021 (24 cases) (Supplemental Figure). Abdi et al[1] showed that infants diagnosed with chromosomal abnormalities, necrotizing enterocolitis, periventricular leukomalacia, congenital brain abnormalities, and seizures had higher likelihood of receiving gabapentin. Abdi et al[1] also observed a higher likelihood than expected of gabapentin treatment for infants with severe BPD. Although there is no associated mechanisms or disorders supporting a neuropathic origin of pain in BPD, these extremely high-risk neonates have multiple comorbidities and are often on multiple neuropathic medications. In our study we identify 16 extremely and very preterm infants, 14 of whom had BPD. Compared with the late preterm and term infants without BPD, these 16 infants were on more neurology-related medications, and all had additional neurological comorbidities. We agree with Asaro et al[6] that the indication for gabapentin use in the premature infant with BPD should only be considered when they are coupled with pre-existing neurological impairments (e.g., intraventricular hemorrhage, periventricular leukomalacia, microcephaly, ventriculomegaly, seizures).

In our study, gabapentin was most often initiated in the cardiac intensive care unit (CICU). Allen et al[9] observed from a case series of 4 infants with congenital heart disease younger than 1 year of age in a CICU, that 3 of 4 patients showed improvement within 48 hours of starting gabapentin. Interestingly, 1 of the 4 patients did not show improvement within 7 days of initiation and the gabapentin was discontinued without adverse

effects. Anecdotally, we have had the same experience and we advocate for not continuing the medications if the desired outcome (e.g., decrease in FLACC score, improvement in nutritional measures, etc.) is not obtained within 3 to 7 days of reaching the dose of 15 mg/kg/day divided every 8 hours.

Gabapentin is often used as an adjunctive medication in infants with chronic neurologic and gastrointestinal comorbidities. Abdi et al[1] showed that of the 374 infants on gabapentin, 370 (98.9%) were also simultaneously prescribed opioids or anxiolytic sedative medications. In our study, 87% of the infants were on 1 or more neurology related medication. Over 50% of our cohort received 3 or more neurology-related with 10% were receiving 7 or more neurological medications. Similarly, 87% of the infants were also on 1 or more gastrointestinal related medication and 10% of infants were receiving 5 or more gastrointestinal related medications. In our study, 47% of the infants started on gabapentin were able to wean off all the neurological medications prior to discharge and 39% were able to wean off all the gastrointestinal medications prior to discharge. Allen et al[9] also demonstrated in a small case series that 50% of infants initiated on gabapentin were able to also wean off other neurology related medications within 3 to 7 days, and 1 child did not need escalation of the current pharmacological support. This is an important, yet underappreciated, potential secondary outcome of gabapentin use in infants younger than 1 year of age. Beyond tracking the impact on nutritional and pain outcomes, our results coupled with the PHIS[1] study and Allen et al[9] demonstrates the importance of how gabapentin could be useful in weaning neurology-related medications, or at the very least prevent escalation.

Several small case series and reports have previously documented the indication and initial dosage regimen of gabapentin for infants.[2,4–7,9,12,14–16]Table 4 includes a summary of these reports. Initial dosing in these reports is variable and ranges from 5 to 20 mg/kg/day with dosing intervals ranging from every 8 to 24 hours. The mean dose of 8.6 mg/kg/day noted in this study is consistent with these previous reports. The maximum dose in the previous reports ranged from 15 to 35 mg/kg/day, which is consistent with the mean maximum dose in our study of 23.2 mg/kg/day. In our study, we not only documented similar initial and maximum dosing and intervals for infants, but we also compared the dosing regimens by indication, ordering service, and gestational age. Although we found no statistical difference with practice amongst these different classifications, we also demonstrated no adverse effects with dosing regimens > 35 mg/kg/day at intervals of every 8 hours.

The impact that gabapentin has on nutritional outcomes has not been fully explored in the literature. A few studies report that gabapentin was beneficial to mitigate the feeding intolerance associated with visceral hyperalgesia, refractory pain, and irritability.[6,7,9] Specifically, Asaro et al[6] reported poor weight gain prior to initiation of gabapentin due to feeding tolerance, but a significant increase in total feeding volume with enhanced weight gain while on gabapentin. While Allen et al[9] reported no improvement in feeding volumes within 48 hours of gabapentin initiation, 1 patient did improve oral intake. In our study we did not find statistical increases in feeding volumes from before initiation through discharge while on gabapentin. Recognizing that there are many variables that could contribute to weight gain in these patients, we chose to also assess Z-score for age to analyze growth. Weight-for-age Z-scores collected 24 hours pre-gabapentin and 2 weeks after the maximum dose of gabapentin statistically increased in our study. These findings suggest that infants were gaining appropriate weight for their age after initiation of gabapentin and during the maintenance phase.

Adverse events need to be considered with each phase of initiation, maintenance and weaning (Figure). We identified 3 patients with adverse events within 7 days of the maximum dose during the maintenance phase, but there was no relationship between interval or maximum dose. We did not find any adverse events during the initiation or weaning phase. Of the existing literature, only Edwards et al[7] report adverse effects from their case series; 3 infants had adverse effects (tachycardia, emesis, and agitation) due to abrupt discontinuation of the drug due to nil per os (NPO) status, and 2 infants had adverse events due to bradycardia. In our study 16 infants expired prior to discharge, but there was no evidence that mortality was attributed to gabapentin and there was no association between death and length of time on the medication. Two of the patients had been weaned off of gabapentin between 3 weeks and 3 months before they expired.

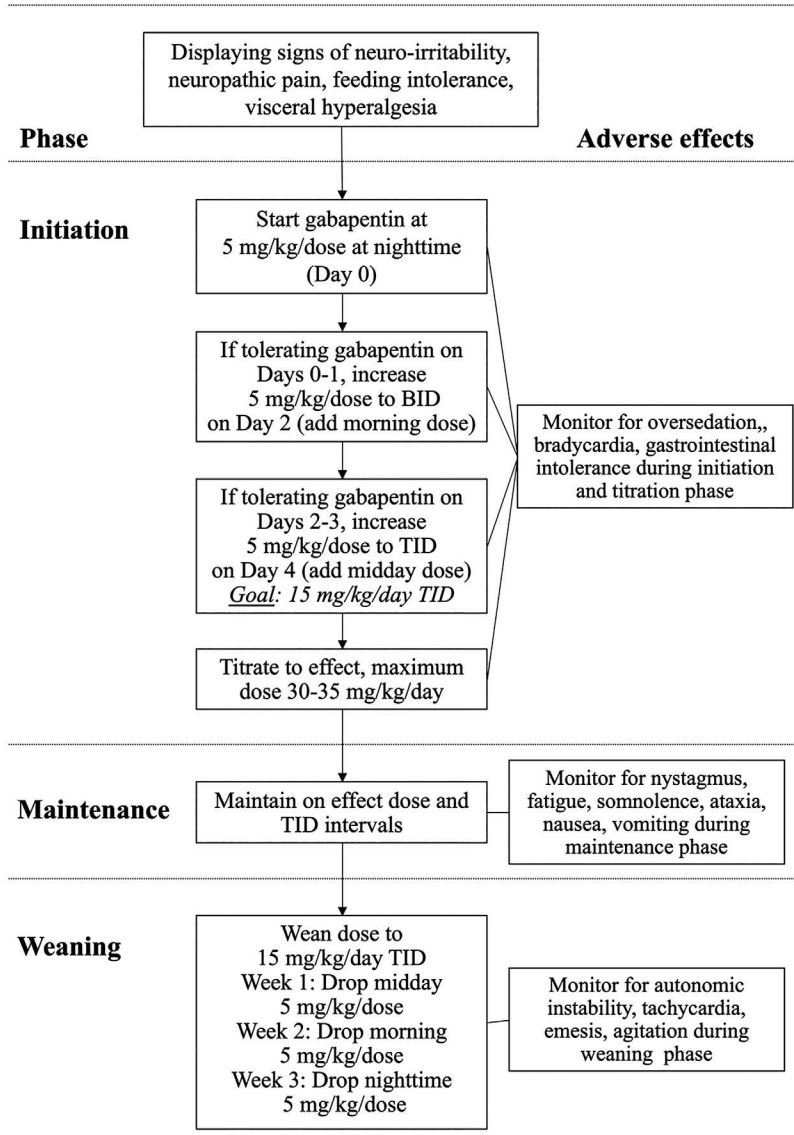
A Suggested Reference Tool for Initiation, Maintenance, and Weaning. Currently, there is no standardized guideline for prescribing, titrating and monitoring gabapentin in infants. The intent of this retrospective study was to aid in the development of such a reference tool for providers caring for neonates or infants requiring gabapentin (Figure). The proposed reference tool takes into the account potential side effects during each phase.

Initiation. In our study the mean initiation dosing of 8.6 mg/kg/day at a median interval of 24 hours did not result in any adverse events. Fifty percent of infants were initiated on a dose of 5 mg/kg every 24 hours at nighttime. Previous studies also suggest that the initial dose be started at night.[3,6,10] Accordingly we recommend a starting dose of 5 mg/kg administered once daily at nighttime. Since gabapentin is excreted by the kidneys, we also felt that a more conservative

Table 4. Summary of Current Literature on Initial Gabapentin Dosing in Infants

Author	Number	Gestational Age at Birth (wk)	Chronological Age at Initiation	Indications for Initiation	Initiation Dose and Interval	Maximum Dose and Interval
Behm[15]	1	36	3 wk	Pain	7 mg/kg once daily	10 mg/kg once daily
Haney[14]	1	39	98 days	Pain and irritability	5 mg/kg at nighttime	5 mg/kg am/ 10 mg/kg pm
Hauer[4]	2	25, 31	2 mo, 5 mo	Pain, hypertonia	20 mg/ kg/day divided every 8 hr	20 mg/kg divided every 8 hr
Brzenski[16]	1	Term	2 wk	Extreme irritability and poor sleep	10 mg/ kg/day divided every 8 hr	20 mg/kg divided every 8 hr
Carrasco[12]	1	35	6 days	Maternal Gabapentin exposure	2.5 mg/ kg/day divided every 12 hr	10 mg/kg/day divided every 12 hr
Edwards[7]	11	23–41	Not recorded	Agitation Seizures Visceral hyperalgesia Feeding intolerance	10 mg/ kg/day divided every 12 hr	Not recorded
Asaro[6]	1	29	3.5 mo	Visceral hyperalgesia agitation	5 mg/kg/ day at nighttime	15 mg/kg/day divided every 8 hours
Sacha[2]	22	28	87 (51.5–147.8) days	Refractory pain and agitation	10 mg/ kg/day divided every 8 hr	16.4 mg/kg/ day (range, 9–25.5 mg/ kg/day)
Burnsed[5]	16	31	44 wk corrected age (range, 36.2–75 wk).	Pain agitation	2.5–5 mg/ kg/day every 24 hr	17 ± 10 mg/ kg/day, (range, 5–35 mg/kg/ day)
Allen[9]	4	35–39	1–16 mo	Feeding intolerance irritability	5 mg/ kg/day divided every 8 or 12 hr	Not recorded
This study Fleser et al	66	34 ± 5.1	5.5 ± 2.7	Neuro-irritability Pain Visceral hyperalgesia Gastroesophageal reflux	Mean 8.6 ± 5.4 mg/ kg/day Median 24 (8–24) hours	23.2 ± 14.4 Median 8 hr

Figure. Reference tool for gabapentin dosing in infants under 1 year of age.



Preparation: Commercially-available gabapentin 50 mg/mL suspension. BID, 2 times a day; TID, 3 times a day

starting dose (5 mg/kg/dose) and interval (every 24 hours) regimen will be suitable for children with acute kidney injury without having to decrease the dose or the interval by 50% (since the initial starting dose can be as high as 10 mg/kg/day).

Maintenance. The goal with titration to maintenance dosing is to optimize the dose and interval to relief of symptoms while minimizing adverse effects. Once symptoms prompting initiation of gabapentin are stabilized with no observed side effects from the medication, the dose should be maintained and followed accordingly.[6] We suggest increasing the dose and frequency every 1 to 2 days to an initial goal of 15 mg/kg/day divided every 8 hours. If the initial dose is provided at night, then a morning dose is next added to the regimen followed by a midday dose in carefully spaced 8-hour intervals.[3,6,10] In our study the mean maximum dose was 23.2 mg/kg/day, with 50% reaching a maximum dose that ranged from 5 mg/kg/day to 20 mg/kg/day divided every 8 hours. One-third of the infants had a maximum dose > 30 mg/kg/day divided every 8 hours and 20% of infants had a maximum dose > 35 mg/kg/day divided every 8 hours without reported side effects. As such, we feel that

a maximum dose of 30 to 35 mg/kg/day would be safe in infants, which is in-line with previous reports.[3,6] Finally, it is important to discuss the need for weight adjustments with the dose to ensure its full efficacy once in the maintenance phase.

Weaning. Only 2 case series discuss a weaning regimen for infants,[9,13] and 1 case series reports adverse events with abrupt cessation.[7] Loudin et al[13] observed that any attempt at weaning gabapentin more than 25% every 4 days was associated with increasing adverse events. Allen et al[9] reports that gabapentin was able to be weaned off within 3 to 7 days in 3 cardiac infants without side effects. Edwards et al[7] reported that 3 preterm infants had adverse events following abrupt discontinuation of the drug due to nil per os status. These reports coupled with the fact that only 12% of the infants in our study had their gabapentin weaned while in-patient, lead us to suggest a more cautious approach to allow for proper monitoring of the side effect profile during the weaning phase. Based on our data and experience, we currently wean gabapentin slowly with weekly changes. We initially wean the dose to 15 mg/kg/day divided every 8 hours from the maximum dose. This can be done by decreasing the total gabapentin dose by 5 mg/kg/day divided every 8 hours on a weekly basis. Once we reach the 15 mg/kg/day divided every 8 hours we then discontinue the midday 5 mg/kg dose on Week 1, followed by discontinuation of the morning 5 mg/kg dose on Week 2, and then the nighttime 5 mg/kg dose on Week 3.

Limitations. The strengths of this study need to be interpreted within the framework of its limitations. The retrospective, single center nature, may limit the generalizability of these data. However, besides the report by Abdi et al[1] exploring the PHIS database, all of the published literature is in case reports or small case series. Our study represents the largest report with over 6 years of clinical experience and 66 infants younger than 1 year of age. This is the first report to present an algorithm based on data for initiation, titration, and maintenance of gabapentin in an inpatient setting. Although our data relied heavily on medical documentation, this study covered a large range of primary outcomes related to dosing and intervals, and secondary clinical outcomes based on nutritional, pain, adverse events and the ability to wean off other neurological and gastrointestinal-related medications. We chose to monitor FLACC scores because of existing literature that suggests improvement of irritability with gabapentin use,[6] but recognize outcomes likely need to depend upon the indication for use of gabapentin.

There was variation in the time to achieve the maximum dose (IQR of 2–55 days) and this could have impacted some of the outcomes we evaluated pre-gabapentin and post-maximum dose. Minimal adverse events were observed in this study, but missing documentation could have led to an underreporting of gabapentin adverse events. Although there appears to be minimal adverse effects in the short-term, long-term neurodevelopmental effects were not explored in this study, but may be challenging to parse out with certain comorbidity conditions (e.g., prematurity, congenital heart disease, etc.). Pediatric data suggest a favorable profile for long-term neurodevelopment.[11] None of the patients in our study were initiated on gabapentin for withdrawal from in utero exposure or as an adjuvant medication for NAS. As such, we could not comment on its use in this population of neonates but recognize its potential role.[12,13] We attempted to account for as many indications as reported in the literature in our descriptive analysis, but recognize that further research is needed into dosing, dose titration, and ability to monitor response based on indication. Although Edwards et al[7] used longer intervals (every 12 hours vs 8 hours) for preterm infants, we found no difference in the starting or maximum dosing based on the degree of prematurity. However, we recognize that this area may need to be further explored, especially with the developing renal system. Finally, gabapentin toxicity in infants with acute or chronic kidney disease has not been described and likely remains underrecognized. In this study, none of the infants (including the premature infants) had reported kidney disease. Although an initiation dose of 10 mg/kg/dose was found to be safe in our study, we still advocate for starting at 5 mg/kg/dose to prevent any infant from receiving inappropriately high gabapentin dosage for their kidney function. Gabapentin is excreted solely by the kidney and plasma levels will rise as renal clearance falls. In infants, 50% dose adjustment may be recommended in patients with renal failure. Future work is needed to investigate the impact of gabapentin on kidney function in infants and identify additional risk factors that can heightened awareness of such preventable risk.

Conclusion

In this large retrospective study of infants younger than 1 year of age who received gabapentin, dosing was consistent with other published small studies in the neonatal and infant population. There was a significant improvement in weight-for-age Z scores and reduction in FLACC scores from 24 hours prior to initiation of gabapentin to 2 weeks and 3 days after reaching maximum gabapentin dose, respectively. Gabapentin appears to be well tolerated in neonates and infants with minimal adverse events. With publication of a reference tool for initiation, maintenance, and weaning of gabapentin in infants younger than 1 year of age this study will aid in the understanding of how to monitor these children and follow different outcomes. There remains a need for future randomized, placebo-controlled studies to determine the short and long-term safety and efficacy of gabapentin in infants.

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