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EVALUATING GABAPENTIN DOSING, EFFICACY AND SAFETY IN INFANTS

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Abstract :

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. 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.

Keywords : gabapentin, infants, irritability, neonates, pain, visceral hyperalgesia

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.

Material and method :

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. 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.

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 2018 to 24 cases in 2021 . 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 . 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 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 , 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 .

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

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) . 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).

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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