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Research Paper

Efficacy and Safety of Repetitive Intravenous Sodium Valproate in Pediatric Patients With Refractory Chronic Headache Disorders: A Retrospective Review

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ABSTRACT

Background: Chronic headache disorders can cause substantial disability and be treatment refractory. Often, these patients are excluded from clinical trials with leaving little evidence to guide treatment. In adults, divalproex sodium is an effective preventive migraine treatment.
Methods: All pediatric patients admitted for first-time sodium valproate infusions to treat refractory, chronic migraine (CM), new daily persistent headache, or persistent headache attributed to head trauma from January 2017 to October 2020 were identified for review. Each patient underwent a standardized, 4-day protocol. A new preventive was started one week after discharge. Data on headache frequency, severity, and acute medication use were collected through preadmission and postadmission clinic notes. Safety and tolerability were evaluated. Results were evaluated using descriptive statistics and compared with paired *t*-tests.
Results: Forty-five patients were identified for review. Patients with CM had a median of 7 previous preventive trials, and 85% had previously received alternative intravenous treatment for headache. Baseline headache pain significant decreased from 6.9/10 to 5.4/10 by 7-week postadmission follow up, (95% confidence interval = −0.7 to −2.4), $P < 0.001$. Use of medications for acute headache treatment decreased significantly from 2.1 days/week to 1.5 days/week, (95% confidence interval = −0.3 to −1), $P < 0.001$. Baseline headache frequency did not significantly change. At postadmission follow-up, 26 of 39 (67%) patients saw improvements in headache frequency, headache intensity, and/or acute pain medication usage. There were no serious adverse events.
Conclusions: Repetitive sodium valproate infusions were well tolerated and significantly reduced baseline headache intensity and acute medication usage in pediatric patients with refractory, chronic headache disorders.

Conflict of Interest: In the last 12 months, Dr. Pavitt received honoraria from Theranica for meeting of their scientific advisory board. In the last 12 months, Dr. Gelfand has received honoraria from UpToDate (for authorship) and *JAMA Neurology*. She receives payment from the American Headache Society for her role as Editor of *Headache*. She received grant support from the Duke Clinical Research Institute and the UCSF Resource Allocation Program. Her spouse reports research support (to UCSF) from Genentech for a clinical trial, honoraria for editorial work from Dynamed Plus, and personal compensation for medical-legal consulting. N. Zorrilla reports no disclosures relevant to the manuscript. In the last 12 months, Dr. Allen has received honoraria from Gilead Sciences for meetings of their Science Advisory Board, from Sonomotion as part of their Data Safety Monitoring Committee, and from Audentes as a biostatistics advisor. Dr Riggins received research support from Eli Lilly & Company, Electrocore, Miles for Migraine, and TheraSpecs for her role as a Principal investigator.

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Introduction

Headache is common among the pediatric population. According to the 2019 Global Burden of Disease report, headache is the second leading cause of disability worldwide in people 10-24 years old.[1] Pediatric patients with migraine often miss school and have their ability to participate in daily activities impacted, with increasing disease burden directly related to increase in headache frequency.[2,3] It has been estimated that within adults in the United States, 4% of females and 2% of males have chronic daily headache disorders and the highest burden of disease.[4]

Pharmacologic treatment of primary headache disorders includes acute and preventive treatment. Acute treatments are taken as needed at the onset of pain or increasing severity of pain (in patients with daily/continuous pain). Some examples include nonsteroidal anti-inflammatory drugs, triptans, and gepants. Preventive treatments are given at scheduled intervals, often daily or monthly, to prevent headache attacks. Common preventive medications include antiseizure medications, antihypertensives, mood stabilizers, and calcitonin gene–related peptide pathway monoclonal antibodies. It is not uncommon for chronic migraine (CM), new daily persistent headache (NDPH), and persistent headache attributed to headache trauma (PHHT), hereafter referred to as chronic headache disorders, to become refractory,[5] that is, unresponsive to multiple preventive trials. However, patients with refractory headache disorders are often excluded from clinical trials,[6-8] leaving clinicians with little evidence to guide management. One strategy is to bring patients into the hospital for treatment with intravenous (IV) medications. IV administration of dihydroergotamine (DHE) is often used to abort acute exacerbations of headache,[9-11] but it has also been shown to be effective as a preventive with improvement in medium-term (6-8 weeks) outcomes in adults with chronic headache disorders.[12,13] However, given the vasoactive properties and potential bothersome side effects (e.g., nausea), many patients have contraindications or do not tolerate repetitive DHE infusions and alternative therapy is needed.

Divalproex sodium is a mood stabilizer and antiepileptic that has level A evidence as a preventative treatment of migraine in adults.[14-16] Short-term use appears well tolerated with few side effects, although special considerations should be taken in people of childbearing potential given its teratogenic effects. The mechanism of action in headache is not fully understood but believed to be through modulation of neuroinflammation and inhibition of release of calcitonin gene–related peptide.[17] While sodium valproate (VPA) may be used in treatment of acute headache exacerbations, small studies have reported that repetitive VPA infusions are an effective and well-tolerated preventive strategy in the treatment of refractory, chronic headache disorders in adults and may be an alternative to IV DHE.[18,19]

At our institution for preventive treatment, we conduct elective, planned hospital admissions for pediatric patients with refractory, chronic headache disorders to undergo a standardized treatment protocol of repetitive VPA infusions in combination with the start of a new preventive medication (one week after discharge). We hypothesized that this treatment protocol would be well tolerated and reduce headache frequency and/or severity, as well as decrease acute medication use within 6-8 weeks of discharge.

Methods

We conducted a retrospective chart review of all pediatric patients from January 2017 to October 2020 who were admitted for VPA infusions for preventive treatment of a chronic primary headache disorder under the care of the University of California–San Francisco pediatric headache team. All patients received the same standardized 4-day protocol of repetitive IV VPA infusions (Fig 1).

This protocol was adapted from previous work by Schwartz et al.[18] Laboratory investigations on admission included a complete blood count, ammonia, basic metabolic panel, and liver function tests in all patients; a urine pregnancy test was completed for postmenarche patients with female reproductive organs. Patients were treated with our standardized protocol: a 15 mg/kg IV VPA load (max of 3000 mg) followed by 5 mg/kg IV every 6 hours for a total of 13 doses. VPA levels are not collected given there is currently no specific VPA level to target for headache treatment. During admission, patients generally continued their current preventive medications, but did not receive medications for acute headache treatment. One week after discharge, a new preventative treatment was generally started. These preventatives included riboflavin, melatonin, amitriptyline, propranolol, candesartan, venlafaxine, memantine, gabapentin, erenumab, galcanezumab, fremanezumab, and neuromodulation devices such as single-pulse transmagnetic stimulation or the supraorbital nerve stimulation device.

All patients aged 18 years and younger who met International Classification of Headache Disorders − 3 criteria for CM, NDPH, or PHHT and were admitted for VPA from January 2017 to October 2020 were included for review. All patients were seen and assigned a diagnosis by pediatric headache specialists. Patients had refractory headache disorders, defined as unresponsive to at least 2 adequate preventative trials—that is, at least 6-week trials on appropriately dosed treatments. To avoid positive selection bias, if patients were admitted multiple times during the study period, only the first admission was included for review.

Seventy-three patient encounters were initially identified; 26 were excluded given they were repeat VPA admissions, with 2 additional patients excluded for alternative diagnosis (idiopathic intracranial hypertension and cyclic vomiting syndrome) (Fig 2).

Chart review was completed by one author (S.P.). Clinical notes from before, during, and after admission were reviewed. All included patients had a postadmission clinic follow-up (mean was 7 weeks after discharge). A standardized abstraction form was used, and data were entered in a Research Electronic Data Capture (REDCap) database.[20] Demographics and clinical data regarding headache frequency, severity, and acute medication usage were collected before and after admission. At each clinic visit, our headache clinicians use similar note templates to assess the number of headache days per month (out of 30), severity of pain (on a scale of 0-10), and frequency of acute medication use. During extraction, if a range was given within the chart (i.e., headache pain ranged 5-6/10), the higher number was used. Headache variables were only included for analysis if missing data were 20% or less.

At our center, as the anticipated timing of headache benefit in this clinical situation is not during the hospitalization, but rather weeks after discharge,[12,13,19] we generally do not ask about headache intensity during admission.

Safety and tolerability were evaluated by reviewing admission data and the postadmission notes including laboratory data, reported side effects, and unexpected required interventions. Abnormal labs were discussed by three authors (S.P., A.G., and R.N.) to determine clinical significance.

No statistical power calculation was conducted before the study. The sample size was based on the available data. Results were evaluated using descriptive statistics as the number (percent), mean (standard deviation), and median (range) and changes from preadmission to postadmission follow-up with Student's paired *t*-tests. Differences from preadmission to postadmission were determined to be statistically significant if $P < 0.05$ in the paired analyses. Given the low number of patients admitted with diagnosis

Sodium Valproate use for Pediatric Headache Treatment

Indication: Chronic migraine, new daily persistent headache, persistent headache attributed to head trauma

Contraindications and Warnings
- Hypersensitivity to valproic acid, divalproex, derivatives or any component of the formulation
- Hepatic disease or significant impairment
- Inborn errors of metabolism such as mitochondrial or urea cycle disorders
- Pregnancy or lactation

Pre-initiation work up
- Vital signs
- Obtain labs: complete blood count, complete metabolic panel, magnesium, phosphorus, calcium, and urine pregnancy test (for post-menarche patients with female reproductive organs)

Treatment course
- Loading dose: 15mg/kg (max 3000 mg) intravenously over 30 minutes. Dosage form: 10 mg/ml.
- Thereafter: 5mg/kg every 6 hours for 12 additional doses (total of 13 doses)
- Total duration of treatment: 4 days

Adverse effects & Management

Common and generally mild
- Drowsiness
- Nausea

Major
- Symptoms of anaphylaxis such as shortness of breath, swelling, and/or pruritus: Immediately STOP infusion
- Lethargy, vomiting, or changes in mental status: Immediately stop infusion and check serum ammonia level.
- Hepatic disease, pancreatitis, thrombocytopenia

FIGURE 1. Four-day standardized protocol of sodium valproate infusions for patients with refractory, chronic headache disorders.

of NDPH or PHHT, preadmission and postadmission analyses were not conducted for these groups. Patterns of missing data were examined using the missingness command in Stata, no patterns were identified, and data were classified as missing at random. All analyses used Stata 16.1 (StataCorp, College Station, TX).

This study was approved by the UCSF Institutional Review Board (IRB), and written informed consent was waived (IRB 296291).

Results

Forty-five patients were included for review, 39 with CM, 5 with NDPH, and 1 with PHHT. Demographics are shown in Table 1.

The majority of patients were adolescent and female. Patients with CM had a median of 7 (range = 2-15) previous preventive trials, patients with NDPH had a median of 9 (range = 2-14) previous preventive trials, and the patient with PHHT had 6 previous trials. Of the patients with CM, 90% ($n = 35$) had daily, continuous headache. The vast majority of patients (CM: 84% [$n = 33$]; NDPH: 100% [n = 5]; PHHT: 100% [n = 1]) had been previously admitted for IV preventive headache treatment with a different medication (DHE, chlorpromazine, or lidocaine) with continued headache resistant to these treatments. All patients completed a follow-up appointment (average = 7 weeks after discharge; range = 3-52 weeks).

In patients with CM, the average pretreatment baseline head pain intensity was 6.9/10. By postadmission follow-up, mean pain intensity decreased to 5.4/10, $P < 0.001$, with mean difference of -1.5 (95% confidence interval = -0.7 to-2.4). Acute medication usage for headache significantly decreased from 2.1 days/week before treatment to 1.5 days/week after treatment, $P < 0.001$, with a mean difference of -0.6 (95% confidence interval = -0.3 to -1.0). There was no statistically significant change in mean headache frequency (29.6 days vs. 27.5 days, mean difference -2.1, $P = 0.054$) (Table 2).

Four patients (10%, 2 male and 2 female) reported decreased headache frequency (30 days to 16 days per month, 30 days to 8 days per month, 20 days to 3 days per month, and 30 days to 0 days per month). A greater percentage of patients whose headache frequency responded were male, did not have continuous headache at baseline, and had CM as their diagnosis compared with the group whose headache frequency did not decrease; however, given the small numbers, statistical testing of these comparisons was not performed (Table 3).

At postadmission follow-up in patients with CM, 26 of 39 (67%) patients saw improvements in either baseline headache frequency,

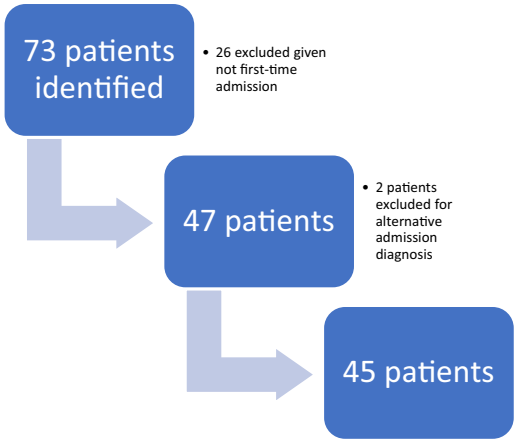

FIGURE 2. Flow diagram of patient inclusion. The color version of this figure is available in the online edition.

headache intensity, and/or frequency of acute pain medication usage, whereas 9 of 39 (23%) had no changes and 4 of 39 (10%) had worsening in one domain.

All five patients with NDPH had initial headache frequency of 30 days per month, which did not change after admission. One patient had a decrease in baseline headache intensity from 6/10 to 5/10. Two patients had decreases in reported acute medication usage. No patients reported headache worsening.

The one patient admitted with PHHT reported decreased baseline pain intensity from 9/10 before admission to 4/10 after admission. Preadmission headache frequency was 30/30 days per month which did not change after admission. Acute medication usage also did not change.

Only five patients (11%, 5/45) reported side effects during the admission; these are shown in Table 4.

There were no serious adverse events. One patient discontinued the infusion early owing to anxiety around the hospitalization and IV placement; this was thought not to be related to VPA. Two patients had mild elevations in liver function tests (less than two times the upper limit of normal) on admission, which did not change before discharge. Both patients were evaluated by gastroenterology specialists and diagnosed as having nonalcoholic steatohepatitis. There were no other clinically meaningful laboratory changes.

Ninety percent of patients were started on a new preventive medication or neuromodulation device one week after discharge from the hospital, as is the standard practice in our center.

Discussion

In this study, the preventive strategy of repetitive dosing of IV VPA significantly decreased medium-term headache pain intensity and acute medication usage in pediatric patients with CM that had been refractory to multiple previous preventive trials and alternative IV medications. In this refractory population, two-thirds of patients reported improvement in at least one outcome (headache frequency, headache intensity, and/or frequency of acute medication use) at the postadmission follow-up appointment. There was no significant change in mean headache frequency. However, it may be difficult to detect significant change in headache frequency in patients who have daily and continuous headache, as experienced by 90% of patients with CM in our study. Four patients did experience frequency reductions of ≥50%, which may be clinically meaningful in this refractory population. We did not find any specific variables that predicted treatment response in these four individuals.

Among all admitted patients, five (11%) reported side effects, all of which were considered mild and resolved before discharge. One patient discontinued the admission early. VPA is known to have the potential to cause hepatotoxicity, but this did not occur in any of our patients. No serious adverse events occurred.

Within the pediatric population, VPA has been shown to be effective in aborting status migrainosus when given either as repetitive doses,[21] or as a continuous infusion.[22] However, to our knowledge, this is the first study to examine the effect of a standardized protocol of repetitive VPA doses paired with a new preventive medication or device as a preventive treatment for refractory, chronic headache disorders within the pediatric population. Often these patients have daily, continuous headache and the highest burden of disease, requiring multiple preventive trials and treatment strategies. Yet these patients are often excluded from clinical trials, including trials in CM,[23,24] which makes evidence to base treatment decisions upon limited. Intravenous DHE has been proposed as an effective treatment strategy for refractory headache disorders in adults[12,25,26] and in pediatrics,[10,11] but a subset of patients have contraindications or do not respond. For these patients, VPA may be an effective option.

There are several limitations to this study. It was conducted at a single academic institution, which may limit its generalizability.

TABLE 1.
Demographic and Clinical Information for 44 Patients With Chronic Migraine and New Daily Persistent Headache

Demographics	Chronic Migraine ($n = 39$)	New Daily Persistent Headache ($n = 5$)
Mean age in years (SD) (range)	15.3 (1.9), (9-18)	16.2 (1.6), (14-18)
Sex, % (n)	82% (32) Female 18% (7) Male	80.0% (4) Female 20.0% (1) Male
History of medication overuse, % (n)	Yes – 15.4% (6) No – 85% (33)	Yes – 40.0% (2) No – 60.0% (3)
Number of preadmission preventative trials (median) (range)	7 (2-15)	9 (2-14)
Previous hospital infusions for headache, % (n)	Yes – 85% (33) No – 15% (6)	Yes – 100% (5)
Contraindication to other infusions, % (n)	Yes – 15% (6) No – 85% (33)	No – 100% (5)
Number with continuous pain (n)	Yes – 90% (35) No – 10% (4)	Yes – 100% (5)
Preadmission cognitive behavioral therapy, % (n)	Yes – 64% (25) No – 36% (14)	Yes – 60% (3) No – 40% (2)

Abbreviation:
SD = Standard deviation

TABLE 2.
Monthly Headache Frequency, Headache Severity, and Frequency of Acute Medication Use Before and After Admission (Mean = 7 Weeks After Discharge) in Patients With Chronic Migraine

Clinical Characteristics	Before Admission	After Admission	Mean Difference (95% CI)	Number of Matched Pairs for Analysis
Mean headache frequency, days per month (range)	29.6 (20-30)	27.5 (0-30)	−2.1 (95% CI −0.04 to 4.3) $P = 0.054$	39
Baseline pain intensity on a scale 0-10, (range)	6.9 (4-10)	5.4 (0-10)	**−1.5 (95% CI −2.4 to −0.7) $P = 0.001$**	28
Acute medication use, days per week (range)	2.1 (0-6)	1.5 (0-5)	**−0.6 (95% CI −0.3 to −1.0) $P = 0.001$**	37

Abbreviation:
CI = Confidence interval
Bolded values are significant with $P < 0.05$.

However, large academic institutions often provide care for patients with refractory, chronic headache diseases. The sample size was relatively small. Although the providers within our headache clinic use similar templates for documentation, missing data occurred for some outcomes measures, which may have resulted in an overestimate or underestimate in our findings. To mitigate this, we only evaluated outcomes which had less than 20% of data missing. We also performed the missingness command which showed no identified patterns, so data were classified as missing at random. The patients included in this study have the most medically refractory headache diseases in our practice and have had multiple preventatives and alternative IV infusions fail them. Although this was not a placebo-controlled study, the refractory nature of their headache disorders makes placebo effect or natural history less likely, but still a possible explanation for our results. Furthermore, given approximately 90% of our population had continuous headache at baseline, acute medication usage may be a difficult variable to evaluate treatment response as patients may overutilize or underutilize these medications. During hospitalization, patients are seen daily by headache providers and have access to our integrative pain providers. Although there is no formalized education during admission, daily access to providers and counseling may have influenced our results. Lastly, patients are started on a new preventive treatment one week after discharge with the theory that the combination of repetitive VPA treatments and a new preventive, provides a synergistic effect for the new preventive to become effective. Therefore, it is impossible to untangle if the VPA, a new preventive, or the combination is driving the improvement seen in our study. The new preventive selection is determined by provider discretion which may introduce selection bias. New preventives are not started during the hospitalization given options may be limited depending on institution-specific formulary restrictions and time for device processing. Furthermore, it would be difficult to delineate side effects of VPA and the new preventive which may influence compliance with the ongoing preventive treatment.

Research is needed in patients with refractory headache diseases to give insight into effective treatment strategies. Although this retrospective review shows promising results, prospective studies are needed to confirm the findings.

Conclusion

In this small pilot study, a standardized, 4-day protocol of repetitive VPA infusions was well tolerated and reduced pain intensity and acute medication usage in pediatric patients with chronic headache disorders refractory to multiple oral and alternate intravenous therapies. Given these promising results, prospective studies are needed for further investigation.

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TABLE 3.
Characteristics of Patients With Reduction of Headache Frequency Compared With Those Without Reduction of Headache Frequency

Clinical Characteristics of Patients With Reduction in Headache Frequency After Treatment Compared With Those With No Change in Headache Frequency		
	Group Whose HA Frequency Did Not Change (n = 41)	Group Whose HA Frequency Did Change (n = 4)
Mean (SD) age, years	15.5 (1.7)	13.8 (3.2)
% female	85%	50%
ICHD-3 diagnosis - *n*	CM: 35 NDPH: 5 PHHT: 1	CM: 4 NDPH:0 PHHT: 0
History of medication overuse, % (*n*)	17% - yes (7)	24% - yes (1)
Number of preadmission preventative trials (median) (range)	7 (2-15)	6.5 (2-11)
Previous hospital infusions for headache, % (*n*)	88% - yes (36)	75% - yes (3)
Percentage with continuous pain *(n)*	91% (38)	50% (2)
Preadmission cognitive behavioral therapy, % (*n*)	63% - yes (26)	50% - yes (2)
Mean (SD) preadmission headache frequency, days per month	29.9 (0.8)	27.5 (5)
Mean (SD) postadmission headache frequency, days per month	29.9 (0.8)	6.8 (7)

Abbreviations:
CM = Chronic migraine
HA = Headache
ICHD = International Classification of Headache Disorders
NDPH = New daily persistent headache
PHHT = Persistent headache attributed to headache trauma
SD = Standard deviation

TABLE 4.
Adverse Events Reported by All Admitted Patients

Adverse Event	*n* (%)
Nausea	2 (4)
Dizziness	2 (4)
Fatigue	1 (2)
Anxiety	1 (2)

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