Iran J Pediatr. 2018 December; 28(6):e66083. doi: 10.5812/ijp.66083.

Published online 2018 September 22. **Research Article**

The Effect of Sodium Valproate on Urinary Frequency and Enuresis Compared to Carbamazepine in Children with Epilepsy

Reza Shervin Badv [1, 2], Arash Abbasi [2, 3], Mahmoud Reza Ashrafi [1], Fakhreddin Shariatmadari [4] and Omid Bayat [1, *]

[1] Pediatric Neurology Division, Children's Medical Center, Pediatrics Center of Excellence, Tehran, Iran
[2] Department of Pediatric, Tehran University of Medical Sciences, Tehran, Iran
[3] Pediatric Chronic Kidney Disease Research Center, Children's Hospital Medical Center, Tehran University of Medical Sciences, Tehran, Iran
[4] Department of Pediatrics, Amirkabir Hospital, Arak University of Medical Sciences, Arak, Iran

[*] *Corresponding author*: Children's Medical Center, Gharib St., Keshavarz Blvd., Tehran, Iran. Tel: +98 9122868927, Email: zendegi0012@gmail.com

Received 2018 January 09; **Revised** 2018 June 14; **Accepted** 2018 June 27.

Abstract

Background: Sodium valproate is one of the widely used medications in the treatment of children with epilepsy. The aim of this study was to evaluate the possible role of sodium valproate on enuresis and urinary frequency in epileptic children in comparison to carbamazepine.

Methods: In this prospective cohort study, we enrolled epileptic children aged 5 to 14 years who met the exclusion criteria and were under monotherapy with sodium valproate or carbamazepine. All the cases were assessed for urinary complications during a period of one-year follow-up. Patients with urinary complications were tested for urinary tract infection and also for any urogenital anatomical abnormalities to avoid possible false positive results.

Results: From 290 patients who met the inclusion criteria, 254 cases were studied. It was showed that among 127 patients in sodium valproate group, 14 (11.02%) cases had enuresis while in 4 cases it was accompanied by urinary frequency. Among these 14 cases, 10 were treatment naives (new cases) (symptoms appeared after 6.1 ± 1.4 weeks) and the other four only had their medication dosage increased (symptoms appeared after 3.2 ± 0.9 weeks). In three cases, the dosage was reduced and in one case a medication was replaced with another. In all patients, however, the symptoms subsided within 10 - 30 days. On the other hand, no urinary complication was found in the carbamazepine group.

Conclusions: The results demonstrated that in children with epilepsy, enuresis and day-urinary frequency are two side effects of valproate and carbamazepine therapy that should be taken into consideration.

Keywords: Valproic Acid, Carbamazepine, Enuresis, Epilepsy

1. Background

Epilepsy is a disorder affecting the central nerves system (CNS). It has been known as one of the most prevalent neurologic disorders in children. The incidence of epilepsy in children (under the age of 16 years) is reported ranging from 41/100000 to 187/100000 (1, 2).

The aim of primary treatment in epilepsy is to prevent the possibility of occurrence of any further episodes in future. The best treatment method is one that leads to the lowest possible incidence of future episodes, minimum medication side effect(s) and provides the patient with a life as normal as possible (3). The main treatment for epilepsy is pharmacotherapy. Choosing a proper medication for these patients requires considering different parameters such as type of epilepsy, patient's age, side effect(s) of the used drug, interaction with other medication(s) the patient is on, and possibility of drug level monitoring (4, 5).

Enuresis is defined as involuntary nocturnal urination of children aged above 5 years while the toilet training has been achieved before (6).

Sodium valproate, as a wide-spectrum treatment, is one of the most prevalent medication choices in children with epilepsy. However, like other medications, it associates with different side effects such as hepatic toxicity, pancreatitis, agranulocytosis, weight gain, hyperammonemia, tremor, and hair loss (7-9). Along with the mentioned side effects, sodium valproate consumption has been shown to result in certain urinary complications such as enuresis which occurs more frequently upon the dosage increase (10-12).

2. Objectives

This study intended to evaluate the effect of sodium valproate monotherapy on the enuresis and urinary frequency in children with epilepsy and also to compare it with carbamazepine as another choice of treatment for epilepsy.

3. Methods

3.1. Patients and Ethics

This prospective cohort study was conducted between August 2016 and August 2017 in the Children's Medical Center, Tehran, Iran. The study was approved by both Hospital's Medical Ethics Committee and University's Medical Ethics Committee. All the patients' guardians signed a printed consent form freely after being explained about the aims and methods of the study according to their level of knowledge.

3.2. Methodology

All the children previously diagnosed with epilepsy and on monotherapy with sodium valproate or carbamazepine were enrolled. Patients with a history of growth and developmental delay, as well as those having any past (since 3 months prior to admission) or current urinary complications or genitourinary anatomical abnormalities, were excluded. In order to evaluate the growth and developmental delay, patients' files and past medical histories were assessed. Regarding the newly diagnosed cases, clinical and para-clinical analyses such as imaging (to rule out any structural abnormalities) were performed. Moreover, patients consuming more than one type of medication for epilepsy were excluded from the study as well as other medications causing urinary complication(s) as side effect.

Patients were divided into two groups: Exposure group being the cases on sodium valproate and comparison group being those on carbamazepine. All the individuals were evaluated every three months for one year at each visit as well as by routine calls of physicians with their parents for searching for any sign(s) of urinary complications such as enuresis and day frequency. Enuresis was defined as $\geq$ 2 and $\geq$ 1 episodes of bedwetting per month in 5 to 6-year old children and older than 6 years in the absence of urinary tract infection (UTI) or genitourinary anatomical abnormalities (6). In cases with urinary sign(s)/symptom(s), a thorough history was taken and examinations were done as well as para-clinic tests such as urine analysis, urine culture and urinary system ultrasonography in order to exclude patients with UTI. Moreover, different affecting variables such as weight, age, sodium valproate dosage, and duration of the treatment were recorded for all the patients.

3.3. Statistical Analyses

All the information from patients' files as well as direct and indirect evaluations were saved in a Microsoft Office Excel file which was checked multiple times by authors in order to avoid any human caused error. Finally, all the collected information was analyzed using Statistical Package for Social Sciences (SPSS) version 21.0 (SPSS, Inc., Chicago, IL, USA). P value less than 0.05 was considered statistically significant.

4. Results

Considering the inclusion criteria, 290 patients were identified eligible for joining this study. Thirty six patients did not meet the inclusion criteria and were excluded. So, a total of 254 individuals were enrolled in the study. Among all the participants, 117 (46.1%) were male and 137 (53.9%) female. The mean age of the patients was 9.37 $\pm$ 2.6 years (ranged from 6 to 14 years) with more than half of the children aging above 11 years. The results showed the mean of disease duration being 2.82 $\pm$ 3.77 years (ranged from 6 months to 9 years). Also, 66 (26%) cases had a positive family history of epilepsy. All enrolled patients had abnormal changes in their electroencephalography (EEG) while their magnetic resonance imaging was normal. As mentioned before, patients were categorized into two groups based on their anticonvulsant medication. In the sodium valproate (syrup or tablet) group, there were 127 cases with the mean age of 7.48 $\pm$ 2.64 years among whom 57 (44.9%) were male and 70 (55.1%) female. In the other group, patients consuming carbamazepine, the mean age was 8.26 $\pm$ 2.57 years among whom 61 (48%) patients were male and 66 (52%) female. The demographic and clinical features of the two groups are illustrated in Table 1.

After careful evaluations in the mentioned period, 17 (6.7%) out of 254 patients reported enuresis and/or day frequency. The incidence of urinary complications in sodium valproate group was 16 and in carbamazepine group 1, which decreased to 14 and 0, respectively, after the mentioned evaluations in the methods. The differences between cases with and without urinary complications in sodium valproate group are shown in Table 2. Statistically significant difference was found between age and treatment duration (P values are bolded in Table 2). Moreover, among 14 cases in the sodium valproate group with urinary complications, 12 had isolated enuresis and the other two had enuresis accompanied with day frequency. Among

Table 1. Demographic and Clinical Data of Both Groups

Demographic and Clinical Features	Sodium Valproate Group	Carbamazepine Group	P Value
Gender, No. (%)			0.2
Male	57 (44.9)	61 (48)	
Female	70 (55.1)	66 (52)	
Age, y	7.48 ± 2.64	8.26 ± 2.57	0.23
Weight, kg	26 ± 7.07	25.69 ± 6.74	0.79
Disease duration, y	3.96 ± 3.01	3.59 ± 2.62	0.09
Treatment duration, mo	12.5 ± 6.55	12.37 ± 6.58	0.12
Positive family history	33 (26)	29 (22.8)	0.34

the mentioned 14 cases, 10 had started sodium valproate for the first time, while the others experienced dosage increase. Among 10 sodium valproate naive cases (new cases), the mean time within which the urinary complication(s) were observed was 6.1 ± 1.4 weeks. Moreover, for those four individuals who had dosage increase, the mean time for expression of urinary complication(s) was 3.25 ± 0.95 weeks. If required, changes were made in the medication type or the dosage of sodium valproate. Accordingly, three cases needed their dosage decreased and in the other one the treatment was changed to carbamazepine. In these three cases both interventions led to vanishing of urinary complications in a time period of 10 - 30 days. Among other 10 cases, seven were symptom-free after 183.7 ± 31.5 days while in other three individuals the urinary complications remained untreated.

5. Discussion

During the childhood, two of the most common medications in the treatment of epilepsy are sodium valproate and carbamazepine (7-9). Therefore, the aim of the current study was to investigate the role of sodium valproate monotherapy on urinary complications especially enuresis in children with epilepsy and to compare the results with carbamazepine monotherapy as well as investigation of those factors which are related to the complications. Also, some other questions including effectiveness of changing the medication or other interventions for these complications were tried to be answered.

According to Table 1, there was no statistically significant difference found between the two groups. Our results showed an incidence of 11.02% for urinary complications including enuresis and polyuria in sodium valproate group while this incidence was 0% in carbamazepine group. The statistical analysis on urinary complications showed a statistically significant difference between these two groups ($P < 0.001$). Moreover, the results demonstrated that among all the demographic and clinically evaluated parameters from patients with and without urinary complication in sodium valproate group, only age ($P = 0.003$) and treatment duration ($P = 0.029$) were statistically significant.

Recent studies have shown that there might be a relation between consumption of sodium valproate and urinary complications such as enuresis, polyuria, and urine incontinency. According to the literature, these side effects are more likely to occur in patients who require dosage increase. Despite these reports, there is a lack of solid evidences on association of urinary complications with sodium valproate and thus these complications are not known as side effects of this drug (11, 13, 14). Egger and Brett performed a retrospective study on the side effects of sodium valproate on epileptic children focusing on weight gain, they showed that among 100 cases, only 7% exhibited enuresis as a side effect (15). Also, Herranz et al. found an incidence of 5.6% (5 out of 88 cases) for enuresis and 6.8% (6 of 88 cases) for polyuria in epileptic children under monotherapy with sodium valproate (10). In 2015, Yamak et al. performed a perspective study on 72 epileptic children aged 8 years and 7 months (range 5 - 12 years) consuming sodium valproate (as monotherapy). The enuresis caused by sodium valproate was present in 24% of their cases in a mean time period of 19.8 days after exposure (13). This study, which is more similar to results from the current study, showed a higher range of enuresis rate that might be due to different factors such as genetic and/or epigenetic variations. However, the authors have not evaluated the UTI or genitourinary abnormalities in the cases with urinary complications that may be another reason for the higher prevalence of enuresis and/or day urinary frequency. According to their results, no statistically significant relation was found between enuresis and any of the studied parameters such as positive family history of epilepsy or disease duration which is in agreement with

Table 2. Differences in Demographic and Clinical Data in Patients with and Without Urinary Complication(s) in Sodium Valproate Group

Demographic and Clinical Features	With Urinary Complication(s)	Without Urinary Complication(s)	P Value
Gender, No. (%)			0.61
Male	7 (50)	48 (43.2)	
Female	7 (50)	63 (56.8)	
Age, y	6.7 ± 1.3	8.9 ± 1.4	0.003[a]
Weight, kg	22.44 ± 7.25	27.79 ± 7.06	0.07
Disease duration, y	4.9 ± 3.31	3.82 ± 2.9	0.18
Treatment duration, mo	1.18 ± 0.06	12.37 ± 6.58	0.029[a]
Dosage, mg/kg/day	28.5 ± 7.59	27.2 ± 7.6	0.73
Positive family history, No. (%)	5 (45.4)	29 (26.1)	0.92

[a] Indicated by small letters.

our study. Moreover, they found that there is a statistically significant relation between age and enuresis (P = 0.03) which was also confirmed by the current study (P = 0.003).

So far, no exact pathway(s) have been introduced as the mechanism of enuresis as a result of consuming sodium valproate. However, different hypotheses have been suggested such as an increase in sleep depth and the inability of waking up after taking sodium valproate (16-18). Unfortunately, due to the lack of polysomnography in this study, it is not possible to evaluate this hypothesis with the results. The other hypothesized pathway is that sleep apnea which also causes weight gain (one of the major side effects of sodium valproate) could be considered a risk factor for this condition, although it was showed that there was no statistically significant difference between patients with urinary complications and symptom free cases in sodium valproate group regarding this particular factor.

Lack of some evaluating tools such as polysomnography could be considered as a imitation to this study. Also lack of healthy controls may be another one but there are different studies which previously evaluated the incidence of enuresis in healthy children (6).

Taken together, the current study showed that enuresis is a prevalent side effect of sodium valproate in children with epilepsy where the younger patients are more prone to present this phenomenon. Moreover, results indicated that dose reduction or changing the medication might be a proper choice for the mentioned patients with enuresis if their adherence to the medication seems to be poor due to the side effects. However, it was showed that in more than half of the cases with enuresis, this phenomenon may vanish by time and trying the wait and watch theory is highly recommended as a proper action. Although authors strongly hope that these findings help clinicians, it is necessary to carry out further complementary studies in this field. We recommend evaluating the possible relation between urinary complications and plasma levels of sodium valproate in children with epilepsy as well as performing polysomnography.

Acknowledgments

Authors are grateful for participation of all the patients and their guardians in this study.

Footnotes

Funding/Support: This study was supported by Tehran University of Medical Sciences.

Ethical Considerations: IR.TUMS.MEDICINE.REC.1395.1840. https://research.tums.ac.ir/user_new/letter_list.phtml.

References

1. Camfield P, Camfield C. Incidence, prevalence and aetiology of seizures and epilepsy in children. *Epileptic Disord*. 2015;**17**(2):117–23. doi: 10.1684/epd.2015.0736. [PubMed: 25895502].
2. Preux PM, Druet-Cabanac M. Epidemiology and aetiology of epilepsy in sub-Saharan Africa. *Lancet Neurol*. 2005;**4**(1):21–31. doi: 10.1016/S1474-4422(04)00963-9. [PubMed: 15620854].
3. Ventola CL. Epilepsy management: Newer agents, unmet needs, and future treatment strategies. *P T*. 2014;**39**(11):776–92. [PubMed: 25395820]. [PubMed Central: PMC4218673].
4. Goldenberg MM. Overview of drugs used for epilepsy and seizures: Etiology, diagnosis, and treatment. *P T*. 2010;**35**(7):392–415. [PubMed: 20689626]. [PubMed Central: PMC2912003].
5. Johannessen SI, Landmark CJ. Antiepileptic drug interactions - principles and clinical implications. *Curr Neuropharmacol*. 2010;**8**(3):254–67. doi: 10.2174/157015910792246254. [PubMed: 21358975]. [PubMed Central: PMC3001218].
6. Norgaard JP, van Gool JD, Hjalmas K, Djurhuus JC, Hellstrom AL. Standardization and definitions in lower urinary tract dysfunction in children. International Children's Continence Society. *Br J Urol*. 1998;**81 Suppl 3**:1–16. doi: 10.1046/j.1464-410x.1998.00025.x. [PubMed: 9634012].

7. Cattaneo CI, Ressico F, Valsesia R, D'Innella P, Ballabio M, Fornaro M. Sudden valproate-induced hyperammonemia managed with L-carnitine in a medically healthy bipolar patient: Essential review of the literature and case report. *Medicine (Baltimore)*. 2017;**96**(39). e8117. doi: 10.1097/MD.0000000000008117. [PubMed: 28953637]. [PubMed Central: PMC5626280].
8. Gerstner T, Bell N, Konig S. Oral valproic acid for epilepsy–long-term experience in therapy and side effects. *Expert Opin Pharmacother*. 2008;**9**(2):285–92. doi: 10.1517/14656566.9.2.285. [PubMed: 18201150].
9. Yang CS, Zhang LL, Lin YZ, Guo Q. Sodium valproate for the treatment of Tourettes syndrome in children: A systematic review and meta-analysis. *Psychiatry Res*. 2015;**226**(2-3):411–7. doi: 10.1016/j.psychres.2014.08.058. [PubMed: 25724485].
10. Herranz JL, Armijo JA, Arteaga R. Clinical side effects of phenobarbital, primidone, phenytoin, carbamazepine, and valproate during monotherapy in children. *Epilepsia*. 1988;**29**(6):794–804. doi: 10.1111/j.1528-1157.1988.tb04237.x. [PubMed: 3142761].
11. Gosavi DD, Suman A, Jain M. Sodium valproate induced increased frequency of micturition and enuresis. *Indian J Pharmacol*. 2013;**45**(1):87–8. doi: 10.4103/0253-7613.106443. [PubMed: 23543036]. [PubMed Central: PMC3608303].
12. Kanemura H, Sano F, Maeda Y, Sugita K, Aihara M. Valproate sodium enhances body weight gain in patients with childhood epilepsy: A pathogenic mechanisms and open-label clinical trial of behavior therapy. *Seizure*. 2012;**21**(7):496–500. doi: 10.1016/j.seizure.2012.05.001. [PubMed: 22694920].
13. Yamak WR, Hmaimess G, Makke Y, Sabbagh S, Arabi M, Beydoun A, et al. Valproate-induced enuresis: A prospective study. *Dev Med Child Neurol*. 2015;**57**(8):737–41. doi: 10.1111/dmcn.12737. [PubMed: 25808512].
14. Malik AM, Usmani A. Day time urinary incontinence due to valproate in a patient with idiopathic generalized tonic clonic seizures. *J Case Re*. 2013;**3**(1):53–5. doi: 10.17659/01.2013.0013.
15. Egger J, Brett EM. Effects of sodium valproate in 100 children with special reference to weight. *Br Med J (Clin Res Ed)*. 1981;**283**(6291):577–81. doi: 10.1136/bmj.283.6291.577. [PubMed: 6790086]. [PubMed Central: PMC1506957].
16. Robert M, Averous M, Besset A, Carlander B, Billiard M, Guiter J, et al. Sleep polygraphic studies using cystomanometry in twenty patients with enuresis. *Eur Urol*. 1993;**24**(1):97–102. doi: 10.1159/000474272. [PubMed: 8365450].
17. Ehrenberg BL, Eisensehr I, Corbett KE, Crowley PF, Walters AS. Valproate for sleep consolidation in periodic limb movement disorder. *J Clin Psychopharmacol*. 2000;**20**(5):574–8. doi: 10.1097/00004714-200010000-00013. [PubMed: 11001243].
18. Schmitt B, Martin F, Critelli H, Molinari L, Jenni OG. Effects of valproic acid on sleep in children with epilepsy. *Epilepsia*. 2009;**50**(8):1860–7. doi: 10.1111/j.1528-1167.2009.02105.x. [PubMed: 19453719].