Original Article

Valproic Acid-induced Nocturnal Enuresis in Pediatric Patients

K Ozan, Y Coskun, CK Bora, Y Ayten

Department of Pediatric Neurology, Eskisehir Osmangazi University Hospital, Eskisehir, Turkey

Abstract

Background: Valproic acid (VPA) is one of the commonly used antiepileptic drug. It has various side effects which may be fatal, such as fulminant hepatitis. Nocturnal enuresis (NE) has rarely been reported as side effect of VPA. The aim of this study is to evaluate the frequency of VPA-induced NE and discuss the possible reasons. **Materials and Methods:** This retrospective cohort study was performed at the Department of Pediatric Neurology, Eskisehir Osmangazi University Hospital, in Eskisehir, Turkey, between April 2014 and April 2015. The patient population was generated from the epilepsy patients who were receiving VPA monotherapy. Control group population was generated from nonepileptic patients who visited our clinic for headache. Age range of the patients and the control group was determined to be 5–15 years. **Results:** The patients group consisted of 189 (53.7%) boys and 163 (46.3%) girls and mean age of the patients was 9.1 ± 3.02 (5–15) years. The control group consisted of 92 (51.1%) girls and 88 (48.9%) boys and mean age of the patients was 8.75 ± 3.23 (5–15) years. We found the incidence of VPA-induced NE to be 5.7%. In the control group, incidence of NE was found to be 10.7%. **Conclusion:** This study is one of the largest series about VPA-induced NE. NE is a side effect of VPA that is generally overlooked by clinicians and slightly less well-known too. The literature on VPA-induced NE is very inadequate, and its etiology is not clear. In our study, we did not detect renal dysfunction in the patients with VPA-induced NE; therefore, we may speculate that the NE was caused by the increased sleep depth with VPA treatment. We believe that larger prospective studies including polysomnography may be helpful to shed light on the cause of VPA-induced NE.

Keywords: *Enuresis, epilepsy, side effect, sodium valproate, valproic acid*

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Introduction

Valproic acid (VPA) is an effective broad-spectrum antiepileptic drug for the pharmacological treatment of epilepsy. It is used for the treatment of absence, myoclonic, partial, tonic, and tonic–clonic seizures, and for the epileptic syndromes of childhood, such as West syndrome and Lennox-Gastaut syndrome. VPA is also used for the treatment of Sydenham's chorea, migraines, and mood disorders.[1,2] However, VPA has various multisystemic side effects, with major side effects being hepatic impairment, pancreatitis, hair loss, acne, thrombocytopenia, tremor, ataxia, and weight gain.[3]

Nocturnal enuresis (NE) is defined as follows: "an involuntary voiding of urine during sleep, with a severity of at least twice a week, in children aged 5 years or older, in the absence of congenital or acquired defects of the nervous system."[4] NE is the most common voiding problem in the pediatric population, with a peak prevalence of approximately 15–20% in 5-year-old children, which decreases with age.[5,6] NE is one of the side effects of VPA treatment, and it is generally underdiagnosed or overlooked by clinicians; therefore, it has been rarely reported. The reported incidence of

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Address for correspondence: Dr. K Ozan, Department of Pediatric Neurology, Eskisehir Osmangazi University Hospital, Meselik – Eskisehir, Turkey.
E-mail: ozankocak79@gmail.com

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VPA-induced NE is 2.2–24%.[7-9] The pathophysiology of VPA-induced NE is still largely unknown; however, it has been speculated that the NE is secondary to the central effect of the VPA on the thirst center, resulting in polydipsia. It may also be related to an increase in deep sleep after VPA treatment.[9-11]

In this study, we aimed to evaluate the presence of NE as a side effect in children receiving VPA treatment as a monotherapy in order to detect the incidence of VPA-induced NE.

Materials and Methods

This retrospective cohort study was performed at the Department of Pediatric Neurology, Eskisehir Osmangazi University Hospital, in Eskisehir, Turkey, between April 2014 and April 2015. The aim of the present study was to establish the incidence of VPA-induced NE in epilepsy patients receiving VPA monotherapy.

This study was approved by the Institutional Ethics Committee of our hospital. Written informed consent was obtained from the parents and older children. This research was conducted according to the Declaration of Helsinki.

The patients' clinical, demographic, and laboratory data were obtained by retrospectively evaluating the hospital files. The following tests and imaging studies are routinely performed in our clinic in epilepsy patients receiving VPA treatment and developing VPA-induced NE: urine and blood amino acids, blood urea nitrogen (BUN), serum creatinine (Cr), alanine aminotransferase (ALT), aspartate aminotransferase (AST), urinary pH (before and after VPA therapy commencement and at enuresis onset), serum levels and therapeutic doses of VPA (after VPA therapy commencement and at enuresis onset), urinary tract ultrasonography (with full and empty bladder), and cerebral imaging results. The laboratory test and imaging data were obtained using standard formats.

In this study, a patient was diagnosed with NE according to the following definition, which is based on the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, fourth edition:[4] "an involuntary voiding of urine during sleep, with a severity of at least twice a week, in children aged 5 years or older, in the absence of congenital or acquired defects of the nervous system." The patient population was generated retrospectively, according to the inclusion criteria, from those patients receiving VPA monotherapy for the treatment of epilepsy. We identified two major criteria for the diagnosis of VPA-induced NE: no previous history of NE and the enuresis should end after stopping the VPA therapy, without recurring during 6 months of follow-up. The other inclusion criteria were: age between 5 and 15 years old, normal liver and renal function test results with VPA, absence of any metabolic disease and any personal or familial history of urinary system disease, without seizures after VPA treatment, normal cerebral imaging, without intellectual disability, and the absence of any drug use with VPA.

The control group population was generated from nonepileptic patients at the Pediatric Neurology Clinic who presented with headaches. We used G*Power 3.0.10 program for calculating the sample size.[12] When we took the lowest prevalence as 10% and marginal sampling error as 2.9%, at 95% confidence interval, the least number of children needed to represent is 131. The age range for the control group was 5–15 years old. None of the control subjects had histories acquired or chronic urinary system diseases. All of the control subjects had normal neurological examinations.

All of the continuous variables were evaluated using the Shapiro–Wilk test for normality before the use of the independent samples *t*-test. The categorical variables were analyzed using Yates's Chi-squared test. The Pearson's correlation coefficient (r) was used to investigate the relationships between all of the continuous variables. Significance was attributed at $P < 0.05$. The statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0.

Results

Between April 2014 and April 2015, a total of 756 epilepsy patients (age range 5–15 years old) were admitted to our clinic. However, 404 patients were eliminated because of combined therapy with other antiepileptic drugs, abnormal cerebral imaging, poor seizure control, urinary system anomalies, or intellectual disability. Eventually, 352 epileptic patients were accepted for the study. The patient group consisted of 189 (53.7%) boys and 163 (46.3%) girls, and the mean age of the patients was 9.1 ± 3.02 (5–15) years old. The VPA doses given to the patients were a minimum of 20 mg/kg/day and a maximum of 26 mg/kg/day, with an average of 23.2 ± 4.1 mg/kg/day. The blood VPA levels were a minimum of 24 μg/ml and a maximum of 99 μg/ml, with an average of 71.1 ± 16.9 μg/ml. The patient group consists of generalized onset epilepsy (generalized onset tonic–clonic: 224 patients, generalized onset tonic; 52 patients, generalized onset myoclonic; 32 patients, generalized onset absence; 44 patients).

VPA-induced NE was detected in 20 (5.7%) patients (12 males and 8 females), and their mean age was 8.55 ± 2.5 years old. The enuresis began

Table 1: Clinical and laboratory features of patients with VPA-induced NE

Patient (year)	Age	Sex	Type of epilepsy	Therapeutic dose of VPA (mg/kg)	Serum level of VPA (mg/ml)	Time of occurrence of enuresis after VPA (day)
1	5	F	Generalized onset tonic-clonic	25.00	55.00	4.00
2	5	M	Generalized onset tonic-clonic	25.00	55.00	5.00
3	6	M	Generalized onset tonic-clonic	23.00	64.00	10.00
4	6	M	Generalized onset tonic-clonic	38.00	45.00	22.00
5	6	M	Generalized onset tonic-clonic	37.00	67.00	19.00
6	7	F	Generalized onset tonic-clonic	25.00	56.00	24.00
7	7	F	Generalized onset tonic-clonic	22.00	77.00	11.00
8	7	M	Generalized onset tonic-clonic	23.00	74.00	14.00
9	7	M	Generalized onset tonic-clonic	30.00	91.00	15.00
10	8	M	Generalized onset tonic-clonic	32.00	82.00	13.00
11	9	M	Generalized onset tonic-clonic	28.00	77.00	22.00
12	9	M	Generalized onset tonic-clonic	30.00	97.00	9.00
13	9	F	Generalized onset absence	34.00	82.00	17.00
14	10	M	Generalized onset tonic	21.00	73.00	18.00
15	11	M	Generalized onset myoclonic	32.00	89.00	8.00
16	11	M	Generalized onset tonic-clonic	35.00	97.00	34.00
17	11	F	Generalized onset myoclonic	35.00	98.00	14.00
18	12	F	Generalized onset tonic-clonic	34.00	86.00	34.00
18	12	F	Generalized onset tonic	32.00	78.00	16.00
20	13	M	Generalized onset absence	35.00	87.00	32.00

M=Male; F=Female

Table 2: Laboratory and demographic features of children with and without enuresis

	Age (year)	Sex F/M	BUN (mg/dl)	Cr (mg/dl)	ALT (U/L)	AST (U/L)	Therapeutic dose of VPA (mg/kg)	Serum level of VPA (mg/ml)
Children with enuresis	8.5±2.5	8/12	13.6±3.8	0.7±0.1	20.0±14.4	20.8±11.3	24.8±5.3	76.5±3.4
Children without enuresis	9.1±3.0	155/177	11.8±4.7	0.9±0.9	22.8±11.1	22.4±10.9	29.9±6.30	70.8±16.9
P	>0.12	>0.4	>0.08	>0.71	>0.87	>0.89	>0.23	>0.29

between the 4th and 34th day (mean 17.05 ± 1.97 days) of VPA treatment. The therapeutic dose of VPA was 24.8 ± 1.2 mg/kg, and the mean blood drug level was 76.50 ± 3.45 mg/ml [Table 1]. None of these children experienced diurnal enuresis. We did not find a relationship between the development of enuresis and the age, sex, urine and blood amino acids, BUN, serum Cr, ALT, AST, urinary pH, serum VPA levels, and therapeutic VPA dose ($P > 0.05$).

All the patients' urine and blood amino acids, liver and kidney function tests, urine tests, and urinary tract ultrasonography examinations were normal. The enuresis improved in all of the patients after they stopped the VPA (mean 13.7 ± 1.41 days), and it was not detected during the 6 months of follow-up.

No statistically significant differences were found between the epilepsy patients with and without VPA-induced NE with respect to the age, sex, urine and blood amino acids, BUN, serum Cr, ALT, AST, urinary pH, serum VPA levels, and therapeutic VPA dose ($P > 0.05$) [Table 2].

The control group consisted of 92 (51.1%) girls and 88 (48.9%) boys, with a mean age of 8.75 ± 3.23 (5–15) years old. The patient and control groups were similar with regard to their average age and sex ($P > 0.05$). The NE incidence in the control group was 10.7% (20/180). All of the patients' urine and blood amino acids, BUN, serum Cr, ALT, AST, urinary pH, and urinary tract ultrasonography examinations were normal. No statistically significant differences were found between the patient group and the control group with respect to the age, sex, BUN, serum Cr, ALT, AST, and urinary pH ($P > 0.05$).

Discussion

The current study was conducted to identify the patients' demographic features, risk factors, and VPA-induced NE frequency. Our study included 352 patients and 180 control subjects. We found that this is the largest study

about VPA-induced NE, and the first study to include a control group.

The etiology of enuresis is currently unclear, and it is believed to be multifactorial. NE is more common in children living in unfavorable social conditions, and who are under psychosocial stress. Central nervous system maturation delays, sleep disorders, an under-capacitated bladder, urinary tract malformations, insufficient nocturnal antidiuretic hormone secretions, and psychogenic factors constitute the etiological factors of enuresis.[6,13] In Turkey, the prevalence of enuresis ranges from 12.4 to 25.5%.[14,15]

VPA has various well-established side effects, from vomiting to fulminant hepatitis, which can be fatal. The gastrointestinal side effects include anorexia, pancreatitis, nausea, and vomiting, while the central nervous system side effects include hyperammonemic encephalopathy, sedation, ataxia, and tremors, which are all dose-related side effects. Chronic VPA therapy can cause a rash, alopecia, appetite stimulation, and weight gain. Moreover, VPA also has teratogenic effects, such as neural tube defects.[1,3] Renal dysfunction associated with VPA is extremely rare, but it can present as a tubulopathy, such as Fanconi syndrome or tubulointerstitial nephritis, proximal and distal tubular dysfunction, or subclinical renal tubular abnormalities.[16,17]

VPA-induced NE has been reported very infrequently.[8-11,18-21] Egger and Brett[10] published a large study about VPA-induced enuresis. Their study was concerned with excessive weight gain in 100 patients taking VPA, and they reported that seven of those patients developed VPA-induced NE. In another two studies focused on the adverse effects of VPA, the reported frequencies of VPA-induced NE were 6% (5/88)[19] and 2% (1/48).[20]

In recent years, there have been only two studies that focused primarily on VPA-induced NA, and those studies reported VPA-induced NE frequencies of 2.2%[7] and 24%.[9] In our study, the incidence of VPA-induced NE was 5.7%. Yamak *et al*.[9] conducted a prospective study including 72 epilepsy patients being treated with VPA monotherapy, and they found that the mean time to an enuresis occurrence after initiating valproate was 19.8 days. The other findings of their study were as follows: the enuresis spontaneously recovered in a mean of 210 days, and they did not find any evidence that the maintenance valproate dose, weight change, or duration of treatment with valproate could predict the enuresis occurrence. Kanemura *et al*.[7] conducted a prospective study including 226 epilepsy patients; however, their study also included patients receiving VPA combination therapy with other antiepileptic drugs. They found that the time to enuresis occurrence after initiating the valproate was at a mean of 19 days. They did not find any correlations between the enuresis occurrence and the daily dose or serum level of the VPA. Our study included 352 epilepsy patients undergoing VPA monotherapy treatment, and it is the largest study about VPA-induced enuresis, according to the literature. Our study also had a control group. We found that the incidence of VPA-induced NE was 5.7%, and it was 10.7% in the control group. None of the patients had diurnal enuresis. The mean time to enuresis occurrence after initiating the valproate was 17.05 days, and we did not find any relationships between the development of enuresis and the therapeutic VPA dose or serum VPA level. All of the patients' urine amino acids, urine tests, VPA serum levels, urinary tract ultrasonography examinations, and cerebral MRIs were normal, and there were no other adverse VPA effects. After stopping the VPA, all of the epileptic patients were administered appropriate antiepileptic drugs, and the patients were followed for a minimum of 6 months without detecting enuresis.

The pathogenesis of VPA-induced NE has not yet been fully explained, although several mechanisms have been emphasized. Several clinical studies have reported that VPA can affect the renal tubules, and it may cause the increased excretion of the tubular enzymes (e.g., *N*-acetyl-beta glycosaminidase, beta-2 microglobulin, and beta-galactosidase).[7,22-24] Among the previous studies about renal tubular dysfunction with VPA, only Kanemura *et al*.[7] reported NE; however, most of the patients in that study were receiving VPA combination therapy. Enuresis may occur secondary to polydipsia resulting from the stimulation of the thirst center.[10,11,19] Another proposed mechanism is that VPA increases the cholinergic activity due to the contraction of the detrusor muscle, and urinary sphincter relaxation stimulates micturition, resulting in enuresis.[25] We expected that these possible mechanisms would also cause daytime enuresis in conjunction with NE; however, we could not find any studies in the literature that reported diurnal enuresis with VPA treatment. VPA can cause sleep disorders, an increased deep sleep period,[26-28] and increased slow-wave sleep activity.[27] Deeper sleep[6,29] and increased slow brain-wave activity[29,30] are potential reasons for NE. In our study, we did not detect tubular dysfunction, and we were not able to perform polysomnography in our hospital. Moreover, Yamak *et al*.[9] found that only the age (≤8 years old) could significantly predict the occurrence of enuresis. We did not find a relationship between the development of enuresis and the age, however, most of the patients were under 10 years old (13 of 20 patients).

Conclusion

NE is one of the VPA side effects that is slightly less well-known and generally overlooked by clinicians. The literature on VPA-induced NE is very inadequate, and its etiology is not clear. We found that our study is the largest study investigating VPA-induced NE. Our study did have some limitations, including the retrospectively obtained patient data and inability to perform polysomnographies. We showed that VPA-induced NE is not higher than the NE rate in the general population. Moreover, it is not associated with the therapeutic dose or serum level of the VPA. In addition, our study showed that the enuresis occurred mainly during the first 30 days after the initiation of VPA treatment, and it was totally reversible. In our study, we did not detect renal dysfunction in the patients with VPA-induced NE; therefore, we may speculate that the NE was caused by the increased sleep depth with VPA treatment. We believe that larger prospective studies including polysomnography may be helpful to shed light on the cause of VPA-induced NE.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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