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Original Article

A CROSS-SECTIONAL STUDY ON SODIUM VALPROATE, CARBAMAZEPINE, AND LEVETIRACETAM INDUCING ENURESIS IN EPILEPTIC CHILDREN

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ABSTRACT

Objectives: Enuresis or bedwetting is considered to be an underreported ADR of antiepileptic drugs (AEDs). This study assesses the incidence and comparative rate of occurrence of enuresis in children with epilepsy who are on AEDs treatment such as sodium valproate (SV); carbamazepine and levetiracetam (LEV).

Methods: The study was conducted with a sample size of 32 patients. Both inpatients and outpatients between the age group >5–18 years of age previously diagnosed with epilepsy that is on monotherapy and polytherapy with SV or carbamazepine or LEV were included in the study. Patients with urinary complications or urogenital abnormalities past 3 months before admission were excluded from the study. Assessment of enuresis was done based on a questionnaire prepared from NICE guidelines and analyzed using SPSS software version 20.

Results: Of 44 patients who were included in the study, only 34 came for review. Analysis of the questionnaire showed the occurrence of enuresis in 12 patients. Drugs prescribed versus assessment questions showed potent significance with eight questions; hence the hypothesis that the prescribed drugs can cause enuresis can be taken into consideration. The rate of occurrence of enuresis was analyzed in all the drugs with their respective doses, but the significant values were found only for SV 200 mg.

Conclusion: This study shows the possibility of enuresis in LEV and SV treatment with a significant difference in SV. Furthermore, it showed a relation between the duration of treatment and the occurrence of enuresis.

Keywords: Enuresis, Antiepileptics, Adverse drug reaction, Children.

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INTRODUCTION

Epilepsy is characterized by continuous seizures, which are short episodes of involuntary movement that may involve a part of the body (partial) or the entire body (generalized) and are followed by loss of consciousness and control of bowel or bladder function. Epilepsy is uniformly distributed around the world. There are no racial, geographical, or social class boundaries. It occurs in both sexes, at all ages, mostly in childhood, adolescence, and increasingly in aging populations. It is considered one of the most common childhood brain disorders. Patients with epilepsy are now treated with pharmacotherapy, occasionally with neurosurgical techniques, as well as with psychological and social support. One of the underreported adverse effects of antiepileptic drugs (AEDs) is enuresis [1,2].

Enuresis is commonly known as bed-wetting. Anti epileptics cause confusion or changes in behavior as a side effect which is associated to be the cause of enuresis in those under treatment with AED's. Some of the three main symptoms of enuresis included are frequent bed-wetting, wetting in the clothes, and wetting at least twice a week continuously for 3 months [3]. Several mechanisms are known to have caused enuresis, out of which bladder capacity and nocturnal urine production are considered to be concurring in the highest degree [4,5].

Sodium valproate (SV) is effective and well-tolerated for the treatment of epilepsy and mood disorders in children. Several reported cases of SV-induced enuresis were noted in epileptic patients. No alternative medication has been suggested to manage this problem [6,7]. Carbamazepine which had been used previously to treat nocturnal enuresis [8] however, is said to cause enuresis by a recent study [9]. Levetiracetam (LEV), a novel AED has recently been approved as an add-on treatment for various seizure types in epilepsy populations including children is reported by FDA to cause enuresis. But very few studies are conducted based on it [10,11]. Thus, this study is proposed based on the assumption that enuresis may occur in children on treatment with SV, LEV, and carbamazepine thereby, creating awareness to physicians, other health care professionals, and the patient's caregiver about this underreported ADR. The major objectives of the study are to assess the incidence of urinary frequency and enuresis in children with epilepsy who are on AEDs treatment such as carbamazepine, SV, and LEV. Furthermore, to compare the rate of enuresis in patients on treatment with carbamazepine, SV, and LEV.

METHODOLOGY

The study was conducted in a tertiary care hospital in Coimbatore for 6 months with a sample size of 32 patients. The Ethical Committee of the hospital approved the study (Ref: EC/AP/711/06/2019). Both inpatients and outpatients between the age group >5–18 years of age were included also, patients previously diagnosed with epilepsy who are on monotherapy and polytherapy with SV or carbamazepine or LEV were enrolled. Patients having any current urinary complication or urogenital abnormalities past 3 months before admission were excluded from the study. The enrolled patients were grouped under six categories (Fig. 1).

Currently, for the treatment in place of carbamazepine, oxcarbamazepine (OX) is given due to its lesser side effects. OX is the keto analogue of carbamazepine. It was developed to mimic the efficacy of carbamazepine while minimizing the side effects of the original drug [12,13]. Hence, the drug was changed from carbamazepine to OX. Informed consent was obtained from the patients included in the study. Details on demographics, medication prescribed, the dose of the drugs, and duration were noted. Assessment of the enuresis was done by the

questionnaire formulated as per NICE guidelines during the review visit. Those patients who failed to come for a second review were reminded over the telephone regarding their review and follow-up. The collected data was finally analyzed using SPSS software version 20.0.

RESULTS

This study included a total of 44 patients but only 34 patients came for review at the requested period. Among the 34, 55.9% (19) belonged to the age group 5–≤9, 38.2% (13) to 10–≤14, and 5.9% (2) in the 15–≤19 age group. The study consisted of a majority of males with 61.8% (21) and a minor female population of 38.2% (13) (Table 1). The duration of treatment showed a major difference ranging from 3 months to 2 years. With a majority of 39.1% (14) in 1–3 months and a minority of 5.8% (2) in 7–9 months.

Assessment of the questionnaire

- Q1) Is the child occasionally or regularly wet at night?
  In this 35.3% (12) responded as yes and 64.7% (22) as no. This showed enuresis positive cases in 12 members. Furthermore, the cases were all of the monotherapy

- Q2) Does the child wake after wetting?
  Deeper sleep and increased slow brain-wave activity are potential reasons for NE. In question Q2 only 14.7% (5) did not wake up after wetting and the remaining 23.5% (7) did get up. This initiated a possibility that increased sleep depth may be a reason to cause enuresis.

- Q3) Is the wetting: Primary/Secondary
  The wetting was found to be secondary 35.3% (12) of the total population which included the 12 positive cases.

- Q4) Does the child get up to void during the night?

About 38.2% of the patient did not get up to void which makeup 13 persons out of 34 cases. Out of the 12 positive enuresis cases, 7 (20.6%) cases were shown to get up once a night for urination whereas five did not get up to urinate.

- Q5) Volume of wetting
  Seven out of 34 wets just the nightwear as per assessment that constitutes 20.6% of the population and five of them seems to have voided with a patch the size of a dinner plate that makes up 14.7% of the total population. This showed the significance of wetting in persons induced with enuresis due to the drug.

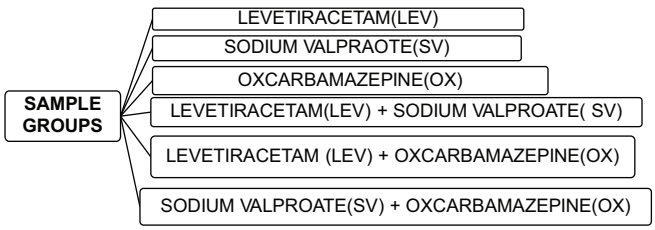

Fig. 1: Grouping of patients understudy

Table 1: Demographic distribution of the study population

Demographics	No. of patients	Percentage
Age		
5–≤9	19	55.9
10–≤14	13	38.2
15–≤18	2	5.9
Total	34	100.0
Gender		
Male	21	61.8
Female	13	38.2
Total	34	100.0

- Q6) Time of wetting:
  The persons affected are shown to have voided later in the night which included 35.3% (12) of the positive cases.

- Q7) Size of the morning void:
  The size of the morning void was found to be larger in 11 cases (32.3%), 7 of which were positive of enuresis. It could be taken as an increased bladder activity due to the intake of the drug.

- Q8) Color of the morning void:
  About 64.7% (22) had dilute urine during morning void and 35.3 (12) of them had concentrated. Those reported to have enuresis seem to have diluted urine may be due to a high intake of water and increased bladder activity. However, the cases varied and did not show a correct assessment of intake of fluids time

- Q9) When was the last time the child drank water/any other fluids?

Analysis showed 16 of them drank fluids after breakfast of which five had drunk a few minutes before assessment similar in the case after lunch including three persons. However, this question was not relevant in assessing the thirst as a whole.

- Q10) What time does the child go to sleep?
  The assessment showed a maximum of 14 persons each in 8–9 pm and 9–10 pm but was not a substantial question to assess the depth of sleep.

- Q11) Does the child void before going to bed?
  About 79.4% of the people voided before going to bed with 20.6% not getting up to void as analyzed by Q11. The positive cases are shown to have voided before going to bed and still bed wetted later at night, hence it's an indication of increased urine production in those cases.

Chi-square test assessment

- Assessment of the relation between two variables showed no significance in age versus drugs given (0.373) and gender versus drugs given (0.47). The significance of age versus assessment and gender versus assessment questions also showed they are independent of each other with values all >0.05
- The assessment of age and gender versus the questionnaire also showed not much significance. However, the analysis of duration versus assessment showed significance in Q1, Q2, Q3, Q4, Q5, Q6, and Q11 which indicated a relationship between the duration of treatment and the occurrence of enuresis.
- The analysis of drugs prescribed vs. assessment questions showed potent significance in Q1, Q2, Q3, Q4, Q5, Q6, Q8, and Q11 with that the hypothesis that the prescribed drugs can cause enuresis can be taken into consideration (Table 2). Furthermore, it showed the occurrence of enuresis in two drugs that is LEV and SV.

Analysis of variance (ANOVA) assessment

- All the questions were formulated from the NICE guidelines up to 19 years of age, used to analyze the occurrence of enuresis in children.

Table 2: Duration versus assessment question Chi-square analysis)

S. No.	Questions	p-value
1.	Is the child occasionally or regularly wet at night?	0.00
2.	Does the child wake after wetting?	0.202
3.	Is the wetting primary/secondary	0.00
4.	Does the child get up to void during the night?	0.00
5.	The volume of wetting:	0.01
6.	Time of wetting:	0.00
7.	Size of morning void:	0.33
8.	Color of morning void:	0.05
9.	When was the last time the child drank water/any other fluids?	0.45
10.	What time does the child go to sleep?	0.19
11.	Does the child void before going to bed?	0.01

To check the rate of enuresis occurrence in different drug groups, each drug with their prescribed doses were analyzed by one-way ANOVA. However, the significant result was only found in the case of SV 200 mg (Table 3)

- The dose SV 200 mg was prescribed for all the seven cases presented with enuresis at the requested time also the patients were all under the treatment for 6 months–2 years.

DISCUSSION

This study provides an insight into the rare ADR of AEDs used frequently in children. Due to the irrelevance of bedwetting as a habit outgrown with age it is overlooked in most cases and at times is underreported due to embarrassment. Suman and Gosavi [14] in children visiting pediatric OP at tertiary care teaching hospital with complaints of epilepsy and who were prescribed with AED`s were evaluated for ADR In that ADRs such as nocturnal enuresis and increased frequency of micturition were observed in 4.4% of patients, especially in VPA therapy. The study also revealed nocturnal enuresis and increased frequency of micturition as a less reported ADR. Many of the studies show more prevalence in males than in females. *Linehan* and Kerr [15] showed males are reported more with seizures frequently than females (6.5% vs. 1.7%; p<0.001). Polytherapy was only seen in two cases 2.9% each, one constituting a combination of LEV- SV and another SV-OX. OX-LEV combination was not prescribed during the study course. During the past 20 years, the use of monotherapy remains the mainstay of treatment among pediatric seizures. Raj *et al*., [16] study showed 70–90% of newly diagnosed common forms of epilepsy can be controlled using a single agent.

Assessment of the questionnaire showed the occurrence of enuresis in monotherapy patients also an increased sleep depth pattern. Esposito *et al*., (2013) [17] evaluated the presence of sleep disturbances in a population of children affected by nocturnal enuresis, it showed that sleep could be strongly altered, thus affirming the hypothesis that nocturnal enuresis tends to alter the sleep architecture of affected children, or it could itself be the consequence of an abnormal sleep structure. However, since the present study did not include any sleep depth measurement such as polysomnography in the study we couldn't say for sure it is a possible cause.

The occurrence of enuresis was observed to be secondary. Ramakrishnan and Krishnan [18] proposed the following details of secondary enuresis in their review study. Secondary nocturnal enuresis (SNE) accounts for about one-quarter of children with bedwetting. By age 10 years, up to 8% of children are estimated to develop SNE. The reported etiologies are sleep problems, bladder problems, medical conditions, psychological stress, and hormone problems.

Out of the 12, positive enuresis cases in this study were shown to get up once a night for urination, whereas five did not get up to urinate. Zrubavel *et al*., [19] conducted a study including 32 children who were referred with enuresis in a hospital study. The study concludes that children with NE slept significantly worse than did the control subjects and were reported to get up at least once at night to urinate. According to their study, this sleep fragmentation leads to an increased arousal threshold, which, in turn, leads to failure to respond to full-bladder signals and additional bedwetting.

Table 3: Assessment of rate of occurrence of enuresis in different drug groups – one way ANOVA test

Drug	Question no.	p-value
SV200	Q1	0.000
SV200	Q2	0.000
SV200	Q3	0.000
SV200	Q4	0.002
SV200	Q5	0.000
SV200	Q6	0.000
SV200	Q7	0.022
SV200	Q8	0.001
SV200	Q9	0.046
SV200	Q10	0.843
SV200	Q11	0.009

A significant increase in urine volume was also observed during this study. Nevéus [20] conducted a study to measure the volume of urine in enuresis using anamnestic data and voiding charts, including measurement of nocturnal urine production. The study concludes that the amount of urine voided in bed in enuretic children is found to be highly correlated to nocturnal urine production but only rarely large enough to represent the voiding of a full bladder.

Thiedk [21] says that though in most studies, sleep electroencephalograms have demonstrated no differences or only nonspecific changes in children with and without nocturnal enuresis. But when surveyed, parents consistently maintain that their children with nocturnal enuresis are "deep sleepers," and they seem to wet later in the night compared with their offspring who are non-bed-wetter. The same was observed in the positive cases of the study subjects.

Chi-square assessment showed a significant relationship between the drugs given and enuresis of which SV was predominant. Reza *et al*., (2018) [6] which evaluated the effect of sodium evaporate monotherapy on the enuresis and urinary frequency in children with epilepsy and compared it with carbamazepine showed there was no statistically significant difference found between demographic parameters such as age and gender. But a significant value was obtained with the disease duration (0.09%). Hence, it could be concluded that a longer duration of treatment can induce the chance of occurrence of enuresis. Apart from that, it could be a secondary cause induced due to the effect of drugs in the renal tubules and sleep pattern resulting in increased thirst and deep sleep [22-25].

Gosavi *et al*., [7] concluded that enuresis was an underreported ADR of SV. Although the exact cause of this ADR was not established, it can be attributed to increased thirst and/or increased depth of sleep.

Egger *et al*., (1981) [26] emphasized enuresis as a possible side effect of SV treatment. Herranz *et al.* [27] also evaluated the adverse event profile of valproate in children with epilepsy mentioned that 5 out of 88 children (6%) developed nocturnal enuresis.

Recent studies have shown that there might be a relation between consumption of SV and urinary complications such as enuresis, polyuria, and urine incontinency. According to the pieces of literature, these side effects are more likely to occur in patients who require dosage increase [28,29].

Despite these reports, there is a lack of solid shreds of evidence on the association of urinary complications with SV. The limitation of this study is that this study did not include the measurement of sleep depth and the measurement of the volume of morning void. Also, the assessment questionnaire to measure the thirst factor was insufficient. Hence, we could not strongly emphasize enuresis as a known side effect of this drug, but it showed the possibility of occurrence in LEV and SV which could be taken as the base for further future research involving a larger subject and longer duration of the study.

CONCLUSION

Enuresis is a rare side effect of AEDs. It is considered to be a condition that is outgrown with age. The underreporting of this ADR is yet another factor that makes it an unnoticeable side effect, owing to the embarrassment of the situation. Since antiepileptics are drugs that could not be stopped or which sometimes need to be taken for a long duration till epilepsy relapses the occurrence of enuresis in these situations can be troublesome on both the lives of the child and the parent. This study shows the possibility of enuresis occurrence in LEV and SV treatment with a significant difference in SV. No occurrence was

noted in the case of OX. Since there is no scoring pattern this extend of enuresis could not be established however, the statistical analysis showed a relation between the prescribed drugs and the association of enuresis occurrence in SV treatment. A significant result was obtained for SV dose 200mg that constituted seven cases out of the 12 positive cases. Various hypotheses have been proposed towards the etiologies of drug-induced enuresis primly thirst and sleep disturbance was noted. However, this study did not focus on any special mechanism to measure sleep depth or thirst. Hence further studies enumerating the association of sleeping patterns and increased thirst with SV treatment are needed to create a solid awareness of this adverse drug reaction.

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CONFLICT OF INTEREST

The author(s) declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

AUTHORS CONTRIBUTIONS

Ms. Arya Sathyan is the main researcher and corresponding author of the study. Ms. Reshma Scaria, M pharm is the co-author responsible for helping out with data collection, analysis, and article preparation.

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