



Day Time Urinary Incontinence due to Valproate in a Patient with Idiopathic Generalized Tonic Clonic Seizures

Azharuddin Mohammed Malik, Amir Usmani¹

From the Department of Medicine and Psychiatry¹, JN Medical College, Aligarh, India.

Abstract:

Uncontrolled painless day time micturition is a serious social problem. Till date, there has been no report in literature of day time uncontrolled micturition in adult patient subsequent to therapy with valproic acid. A young adult male patient with idiopathic generalized tonic clonic seizures was started on valproate but continued to have breakthrough convulsions despite administration of valproate 300 mg twice a day. The dose of valproate was increased to 900 mg per day which controlled seizures but he developed uncontrolled painless passage of urine even during daytime while remaining conscious and alert. Detailed physical examination and investigations did not reveal any abnormality. Keeping in mind, the rare association of valproate with nocturnal enuresis, dose of valproate was decreased to 600 mg leading to abolition of day time enuresis. Unfortunately, convulsive movements returned. The dose of valproate was increased gradually over a period of two weeks to 900 mg per day. Once again, urinary incontinence recurred. Gradual switching over from valproate to carbamazepine controlled his seizures and stopped day time enuresis. In conclusion, this case report highlights the need to keep valproic acid in mind during differential diagnosis of uncontrolled painless day time micturition if this drug is being used in therapy.

Key words: Valproic acid, Carbamazepine, Nocturnal Enuresis, Urinary Incontinence, Seizures.

Introduction

Urinary incontinence is a significant medical as well as a social problem. Urinary incontinence has been very infrequently associated with antiepileptic drug use and that too has been mainly reported with the use of carbamazepine and phenytoin [1]. There has been no reported case of day time urinary incontinence due to valproic acid; though nocturnal enuresis has been reported with its use [2,3]. We are reporting a case of valproic acid induced day time urinary incontinence.

Case Report

A male patient in his mid-twenties, presented to the out patients clinic with complaints of headache off and on, for last one and half years. The headache was localized in occipital region, severe, throbbing in nature and

Corresponding Author: Azharuddin Mohammed Malik

E-mail: malikazharuddin@gmail.com

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persisting for few hours in morning as he woke up. There was no history of nausea, vomiting, photophobia or phonophobia associated with headache. The pain used to be relieved after taking analgesics. On occasions, he also noticed bitten tongue in the morning upon waking up. In view of patient not recalling history of abnormal movement during sleep, he was advised to follow up next day with a reliable informant.

Subsequent interaction with his mother revealed, she had noticed episodes of abnormal movement during his sleep. This was characterized by twisting of bilateral upper and lower limbs with extension of neck, rolling up of eyeballs and fine frothing from mouth. It was followed by jerky movements of all the limbs. These episodes persisted for about 4-5 minutes. The patient did not have any memory of these episodes. His main concern was headache in the morning.

There was no history of head trauma or any other CNS insult in the past. There was no family history of neurological or psychiatric disorder up to second degree relatives of the patient. Physical and systemic examination including neurological examination revealed no abnormality. The patient was advised MRI brain, electroencephalography (EEG), along with routine investigations. None of these investigations revealed any abnormality except EEG which showed "generalized epileptiform discharges".

The patient was diagnosed as a case of idiopathic generalized tonic clonic seizures and was advised valproate 300 mg twice a day. On next follow up, after two weeks, the patient complained of persistent abnormal movements suggestive of breakthrough seizure episodes. The dose of valproate was increased to 900 mg per day in two divided doses which controlled his seizures.

On next follow up after the increase in the dose of valproate, patient did not complain of any abnormal movements but he developed urinary incontinence in the form of painless passage of urine in daytime while the patient was conscious and alert. The bladder sensations were intact. There was no history of urgency, frequency or any history suggestive of stress incontinence. His investigations including routine and microscopic examination of the urine, urine culture and abdominopelvic ultrasound (pre-void with additional post-void residual volume estimation) did not reveal any abnormality. In addition, the patient was advised urodynamic studies.

The dose of valproate was reduced to 600 mg day in two divided doses. On next follow up there was no history of urinary incontinence. Unfortunately, convulsive movements returned. It was decided to increase the dose of valproate gradually over a period of two weeks to 900 mg day. The patient again developed urinary incontinence with this increased dose of valproate. The patient was then switched from valproate to carbamazepine by gradually tapering valproate and gradually increasing the dose of carbamazepine to 900 mg a day in two divided doses. The patient is well maintained since then with no history of headache or seizure. Unfortunately, the patient ignored the advice of undergoing urodynamic studies since his urinary incontinence had resolved.

Discussion

The probability of patient's urinary incontinence being an adverse drug reaction to valproate was judged based on adverse drug probability scale by Noranjo *et al* [4]. As per this scale, our patient scored a total of 7 points [patient's adverse event appeared after the administration of valproate (2 points), the symptom

improved when it was decreased/discontinued (1 point), no other contributory factor for the symptom (2 points), and adverse event reappeared when the drug was re-administered (2 points)], which is suggestive of a probable adverse drug reaction.

Pathophysiology of urinary incontinence due to antiepileptic drugs is incompletely understood. Urinary continence requires a complex interplay of parasympathetic and skeletal innervation. The afferent limb of the voiding reflex is formed by the sensory nerve fibers of the pelvic nerves, which also carry the parasympathetic fibers to the bladder that constitute the efferent limb of the voiding reflex. The reflex is integrated in the sacral portion of the spinal cord. This reflex arc is modulated by the activity of facilitatory and inhibitory centers in the brainstem as well other higher centers. Stimulation of the cholinergic receptors of the parasympathetic nerve fibers leads to contraction of the detrusor muscle and relaxation of the urinary sphincter to facilitate emptying of the urinary bladder. Valproic acid has been shown to increase cholinergic sensitivity although the exact molecular mechanism is not clear [5]. Heightened cholinergic response might lead to urinary incontinence as happened in our patient as well as the nocturnal enuresis reported by other authors.

Conclusion

On the basis of this case report, we can conclude that the patient's day time urinary incontinence was dose dependent association with valproic acid. We obtained a demonstrable cause and effect relationship between occurrences of urinary incontinence with increasing dose of valproate. This case report would be a useful tool to clinicians in providing therapeutic targets of valproic acid while dealing with patients complaining of urinary incontinence.

Consent: Written informed consent has been obtained from the patient prior to submission of this manuscript.

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