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Case Report

Caution in usage of clobazam in elderly patients

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ABSTRACT

Introduction: Clobazam, one of the newer benzodiazepines, is now used extensively as first add on therapy in focal epilepsy.
Materials and Methods: A 67-year-old diabetic and hypertensive gentleman with a history of frontal contusion one year ago, presented with clustering of seizures. He was started on clobazam 20 mg, and levetiracetam 1000 mg/day. Recurrence of seizures prompted a dose escalation of clobazam to 40 mg/day. The patient developed hepatic encephalopathy and his decompensation was probably precipitated by the use of high dose of clobazam. Clobazam was thus gradually tapered off along with hepatic precoma regimen, and other supportive measures leading to an uneventful recovery.
Results and Conclusion: Caution must be taken while administering clobazam to elderly and debilitated patients or those with organic brain syndrome as they are more prone to the central nervous system (CNS) depressant activity of benzodiazepines. Since clobazam requires dealkylation and hydroxylation prior to conjugation, it should be used with caution in patients with hepatic involvement.

1. Introduction

Clobazam, one of the newer benzodiazepines, is now used extensively in both generalized as well as focal epilepsy. It has been regarded as a safe antiseizure medication (ASM) for young children as well as the elderly.[1] This article focuses on an inadvertent side effect of clobazam suggesting cautious use of the drug in elderly, particularly in those with decompensated liver disease.

2. Materials and Methods

2.1. Case

A 67-year-old diabetic and hypertensive gentleman with a history of frontal contusion one year back, initially presented with three episodes of tonic posturing over 24 hours, associated with loss of consciousness and urinary incontinence. He was started on clobazam 20 mg and levetiracetam 1000 mg per day. One month later, there was recurrence of similar episodes even while on medication. This prompted a dose escalation of clobazam to 40 mg per day.

Ten days after increase in medications, he became irritable, confused, and disoriented. He was shown to a psychiatrist and put on anti psychotics. However, his condition worsened to such a level that he remained drowsy most of the time and had two episodes of documented hypoglycemia. He developed aspiration pneumonia which led to further worsening of sensorium.

On admission he was drowsy, febrile, and disoriented with bilateral chest crepitations on auscultation and no focal neurological deficits. His arterial blood gas (ABG) analysis showed hypoxemia. He was intubated and started

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on antibiotics.

His investigations revealed altered liver functions (SGOT=220, SGPT=206) with a prolonged prothrombin time (PT INR=1.9↑) and elevated arterial ammonia. His scalp EEG showed typical triphasic waves often seen in hepatic encephalopathy (Figure 1). The patient was diagnosed to have developed hepatic encephalopathy and his decompensation was probably precipitated by drugs mainly clobazam at a high dose of 40 mg per day. Clobazam was thus gradually tapered off and antipsychotics were withdrawn. He was treated with hepatic precoma regimen, antibiotics, and other supportive measures. He gradually made an uneventful recovery over three weeks and was discharged. His hepatic decompensation was thought to have precipitated seizures, which was aggravated by increasing clobazam which pushed him further into the abyss. No other additional ASMs were required.

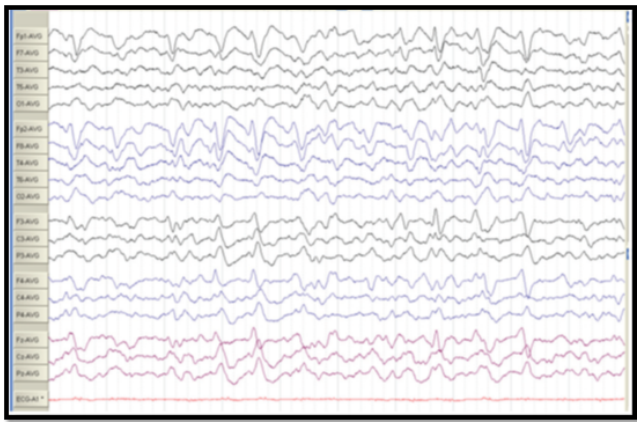

Fig. 1: Scalp electroencephalograph in common average montage revealstriphasic waves with antero-posterior lag and a diffusely slow background activity of ~ 4 Hz on either hemisphere

3. Discussion

Clobazam is a 1,5-benzodiazepine, structurally different than traditional 1,4-benzodiazepines like diazepam. The 1,5-benzodiazepines are less lipophilic and acidic than the 1,4-benzodiazepines, changing their distribution characteristics resulting in less sedation and a slower development of tolerance.[2] Clobazam binds between the alpha and gamma subunits of gamma-aminobutyric acid (GABA) receptor, potentiating GABA-mediated inhibition of neurotransmission, resulting in a decrease in the firing rate of critical neurons in many regions of the brain.

Out of 19 published studies of clobazam use in patients with epilepsy, the overall incidence of side effects was 33%. Of this, drowsiness, dizziness and fatigue were most frequently reported. Canadian experience provides a similar overall incidence (32%) with drowsiness reported in 17.3% of patients, and 12% of patients terminating treatment due to side effects, mainly tolerance.[3] The most common clobazam adverse events reported in the elderly (> 60 years) in the order of prevalence include somnolence, drug interaction, confusional state, asthenia, cheilitis, conjunctivitis, face oedema, purpura, rash maculo-papular and anaemia.

Clobazam forms a number of metabolites in the body with N-desmethylclobazam being the most important. The half-life of N-desmethylclobazam is longer (mean 42 hours; range 36 to 46 hours) than that of clobazam (mean 18 hours; range 10 to 30 hours) and the half-life increases with the patient's age. The incidence of side effects is lower in patients under 16 years of age (23.7%) than in adults (43.1%), whereas treatment discontinuation incidences are similar across age groups, 10.6% and 13.8%, respectively. N-desmethyl clobazam reaches higher serum levels, especially with long term administration of clobazam. The drug is about 85% protein-bound, and hepatic disease alters both the metabolism of the drug and its protein binding thus affecting plasma clobazam levels and doubling its half-life compared to healthy volunteers.[4]

Symptoms of tiredness may sometimes appear, especially at the beginning of treatment with clobazam and when higher doses are used. Also, in rare instances, paradoxical reactions, for example, restlessness and irritability may occur. After prolonged use of benzodiazepines, impairment of consciousness combined with respiratory disorders has been reported in very rare cases, particularly in elderly patients.[5]

Caution must be taken while administering clobazam to elderly and debilitated patients or those with organic brain syndrome as they are more prone to the CNS depressant activity of benzodiazepines. Since clobazam requires dealkylation and hydroxylation prior to conjugation, precautions should be taken if clobazam is used in patients with hepatic involvement.[6]

It is common to see elderly people on various other medications for other medical conditions like diabetes mellitus, hypertension and coronary artery disease. While selecting an antiepileptic, the one with the least drug interaction must be chosen.[7] Lamotrigine, levetiracetam and lacosamide are newer AEDs with least drug interaction. One must be very cautious while using oxcarbazepine in elderly as they are more prone to hyponatremia, especially if they are on diuretics.

4. Conclusion

This patient who was a chronic alcoholic and had a hepatic decompensation leading to encephalopathy precipitated by increasing clobazam, all of which could have been averted if the drug was used judiciously. His hepatic decompensation was thought to have precipitated seizures, as no other additional ASMs were required. Levetiracetam is the safest in liver disease states. Those contraindicated

include valproate, lorazepam, clobazam and midazolam. Rest may be used but with extreme caution. Clobazam is classically described as a safe drug while it needs to be used with caution in elderly patients, especially in those with a history of alcohol dependence, hepatic disease, or organic brain syndrome as illustrated in this case.

5. Source of Funding

None.

6. Conflict of Interest

None.

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