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CASE REPORT

A unique effect of clonazepam on frontal lobe seizure control

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In a 16-year-old female, clonazepam (CZP) changed randomly occurring intractable tonic seizures of frontal lobe origin to a few sleep seizures when used as an adjunctive therapy. The significance of this change in the seizure pattern is discussed with an explanation of possible pathophysiologic mechanism.

Key words: clonazepam; sleep; tonic seizures; frontal lobe epilepsy.

INTRODUCTION

Clonazepam (CZP) (a 1.4 benzodiazapine) is effective in myoclonic and generalized absence seizures, but less so in generalized tonic–clonic seizures[1,2]. It may exacerbate generalized tonic–clonic seizures and may be disadvantageous in patients with juvenile myoclonic epilepsy[3,4]. Hence, CZP is rarely used as a primary antiepileptic drug, though it still has a role as an adjunctive therapy.

We describe a case of intractable frontal lobe tonic seizures in which CZP was successful in changing the randomly occurring rhythm of the tonic seizures to a sleep pattern, though CZP was previously reported to exacerbate tonic seizures[5]. Our purpose of reporting this case is to document such a unique finding and secondly to discuss its significance.

CASE REPORT

A 16-year-old Saudi girl was referred to King Khalid National Guard Hospital (KKNGH) Epilepsy Clinic on May 1994 for evaluation of intractable epilepsy. The patient was a product of normal pregnancy and delivery. Her parents were unrelated and had no family history of epilepsy. As a baby, she was well until the age of 6 months when she was hospitalized with a febrile illness that lasted for 2 weeks. She then developed brief attacks of tonic seizures which occurred randomly. She was prescribed an unspecified anticonvulsant medication, which resulted in complete control of the fits. After 6 months of treatment, the mother discontinued the medication and 4 months later the child started to have 3–4 seizures when asleep and similar numbers while awake. At age 4, the seizure frequency increased to 10 during both awake and sleep periods. She was given phenytoin 100 mg daily and carbamazepine was added subsequently at a dose of 200 mg TID to no avail. At age 11, valproic acid was added at a dose of 200 mg TID and did not influence the seizure frequency. When seen in KKNGH Epilepsy Clinic, she was on carbamazepine 400 mg TID and vigabatrin 500 mg TID but continued to have frequent seizures. She was admitted for documentation of the seizures regarding their nature and frequency during awake and sleep periods; and also to observe her sleep quality and quantity. During the hospital stay the seizures were witnessed as follows: the patient developed tonic deviation of neck and tonic extension of her limbs with upper limbs more affected than the lower with complete loss of conscious-

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ness. The seizures lasted for 20–60 seconds and were followed by post-ictal confusion lasting 4–5 minutes and at times were associated with a brief automatism. When asleep, the seizures woke her up and it took her 10–15 minutes to resume sleep again. She had 20–40 seizures while asleep and 5–10 during the awake state. In the absence of video-EEG polysmnography, several EEGs were performed which documented that most seizures were detected during drowsiness. The EEGs showed frequent discharges of spike, sharp and sometimes slow wave complexes seen predominantly in the right frontal regions, occasionally bilateral and rarely generalized. Two previous MRI scans were normal and a third MRI scan while in hospital showed a discrete lesion of high intensity signal on T2-weighted images of the right anterior aspect of the opercula adjacent to the Sylvian region. This discrete lesion disappeared on a subsequent MRI and hence we speculated that it was a transient, seizure-related abnormality. The patient was diagnosed as having supplementary motor seizures. During hospitalization, acetazolamide and pyridoxine were tried in desperation with no effect. Lamotrigine was introduced at a dose of 50 mg BID and increased to 100 mg BID to no avail. Clonazepam was then introduced at a dose of 0.5 mg BID and on reaching a dose of 1 mg BID, complete control of the seizures during the awake period and reduction of sleep seizures to 3–4 a day was achieved. The patient was discharged home on clonazepam, vigabatrin, valproic acid and carbamazepine. She was referred to an Epilepsy Center for further management where vigabatrin and clonazepam were discontinued and primidone was introduced at a dose of 250 mg BID. The patient reported back to us because of the recurrence and worsening of both awake and sleep seizures, as a result of which she fell down and sustained trauma to the skull. She was admitted to the intensive care unit (ICU) for seizure monitoring and clonazepam was re-introduced at a dose of 1 mg BID with complete control of the awake seizures and a significant reduction of the sleep seizures to 3–4 a day which was similar to the CZP effect when it was initially introduced. The carbamazepine and the primidone were discontinued and she was discharged to be followed in the clinic. In the past 3 months, the patient, on clonazepam and valaproic acid, has had no seizures during the awake period with only 3–4 seizures during sleep according to the seizure calendar recorded by the parents. She was able for the first time as a teenager to leave her house and socialize with friends.

DISCUSSION

Frontal lobe seizures may occur primarily or predominantly during sleep[6–8]. The inter-ictal epileptiform discharges are more prevalent during non-rapid eye movement (NREM) sleep than during rapid eye movement (REM) sleep[6–8]. In our patient, the frontal lobe seizures occurred randomly during the wake–sleep cycle and were resistant to different types of anticonvulsants used singly or in combination. It is only through the addition of CZP that the awake seizures were completely stopped and the sleep ones were reduced significantly. This improvement may possibly be a result of improving the sleep pattern of the patient. Prior to CZP introduction, the patient's sleep was fragmented by repeated arousal and there was reduction of sleep efficacy as documented by ICU nurses on the two occasion during hospitalization. The sleep deprivation effect of the seizures may have a role in provoking the seizure occurrence during awake and sleep states.

We cannot dismiss the possibility that the long duration of action of clonazepam might have a direct effect on reduction of both sleep and awake discharges as clonazepam's half-life is 20–80 hours[9]. This may be difficult to reconcile with the fact that benzodiazepines are known to reduce NREM sleep onset latency, elevate the time spent in light REM during which time epileptogenic discharges are proved to be increased[8, 10]. The response of our patient and the excellent control of the rolandic discharges in children with rolandic epilepsy of centrotemporal spike supports the notion that clonazepam can affect sleep and seizures jointly or independently[10, 11]. The major disadvantage of clonazepam is tolerance in long-term usage. This problem can be helped by using clonazepam on an alternate day regimen as clonazepam is slowly eliminated[9]. Recently, flumazenil may possibly reverse tolerance without provoking withdrawal seizures as shown in a preliminary report, but the problems of tolerance have not yet been fully resolved[12].

In conclusion, we think that there is still a role for clonazepam as an adjunctive therapy particularly in sleep seizures and we recommend its trial in resistant cases of sleep epilepsy syndromes.

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