had regained consciousness. This tracing was normal and the background activity consisted of occipital dominant alpha rhythm. The blood glutethimide level had dropped to 0.38 mg/dl by this time. A third EEG tracing obtained 12 days later was again normal. BAERs were obtained a day after admission and were normal. Her hospital course was complicated by transient aspiration pneumonia. After recovery, she was transferred to a psychiatric hospital without any neurological deficit.

Although previously commented on by a few authors,\(^{7,9,11}\) alpha coma has not been widely recognised in drug intoxication uncomplicated by cerebral anoxia. One needs to keep in mind that drug-induced alpha coma has a distinctly different prognosis from that in patients with hypoxic encephalopathy of primary brainstem lesions; the patients with drug-induced alpha coma have an excellent prognosis. All nine cases of alpha coma caused by drugs, including the patient in this report, recovered without any neurological sequelae. Drug-induced alpha coma has resulted from an overdose of sedative drugs such as amitriptyline, barbiturates, glutethimide, nitrazepam, and chloromethiazole. Two patients had the further complication of respiratory depression and hypoxia of variable duration; even these made a full recovery.

The EEG findings of drug-induced alpha coma are different from those observed in patients with hypoxic encephalopathy of brainstem lesions. The alpha activity is widespread and is usually predominant over the anterior regions. Unlike the patients with hypoxic encephalopathy, patients with drug-induced alpha coma may show some reactivity of their EEG to intense painful stimulation; slower activity (usually low amplitude theta-delta) may be induced for a short period during and after stimulation. The presence of reactivity does not, however, distinguish alpha coma due to drug intoxication from that due to brainstem lesions because the latter may also be associated with some EEG reactivity.\(^{8}\)

Multimodality evoked responses in coma have proved helpful in determining the level of the damage to the brainstem.\(^{13,14}\) BAERs, in particular, are helpful in the assessment of a patient with alpha coma where the cause of coma remains undetermined and are grossly abnormal in alpha coma secondary to intrinsic brainstem lesion.\(^{13}\) Normal BAERs on the other hand, suggest integrity of the brainstem structures and favour either drug intoxication or hypoxic encephalopathy responsible for the comatose state. The mechanism of normal BAERs, despite the absence of brainstem reflexes in sedative drug intoxication is unclear, but one may postulate that the generator site of the responses is suppressed,\(^{16}\) but anatomically is intact and reactive to auditory stimulus.

The recognition of sedative drug intoxication as an important cause of alpha-pattern coma is crucial because the prognosis in such patients with intensive supportive therapy is excellent.

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RAHMAN POURMAND  
Department of Neurology RHC,  
1001 W 10th Street,  
Indiana University School of Medicine,  
Indianapolis, Indiana 46202  
OMKA R N MARKAND  
Department of Neurology,  
Riley Hospital,  
1100 West Michigan Street,  
Indiana University School of Medicine,  
Indianapolis, Indiana 46224, USA

References


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Development of tolerance to anticonvulsant effect of clobazam

Sir: In 1983 we reported the results of a short double blind placebo controlled crossover study on the 1, 5 benzodiazepine clobazam in the treatment of patients with severe epilepsy.\(^{1}\) The results of this study were very encouraging, and from our experience at the Chalfont Centre for Epilepsy, to which over 100 patients each year are referred for assessment, we are aware that clobazam is now being used more frequently in an attempt to control patients with otherwise intractable seizures. We would therefore like to report our further experience with this drug, particularly as the results of a long term study are rather disappointing.

Following our initial controlled study, 11 residents at the Chalfont Centre (aged 16–69 years) having at least four seizures per month were studied. All these patients had seizures that were intractable to other currently available antiepileptic drugs and all had either secondary generalised or partial epilepsy. Baseline seizure frequencies were monitored as previously reported and then clobazam 10–30 mg was added to each patient’s drug regime, which otherwise remained constant. Those subjects showing a 50% reduction in fit frequency were included into a long term study and seen at monthly intervals, at which time fasting blood samples were taken for measurement of antiepileptic drug levels, including clobazam and desmethylclobazam. Seizure frequency was monitored and the development of tolerance was noted if the seizure frequency returned to baseline.

References

Of the original 52 subjects, 26 (50%) responded by a 50% reduction in fit frequency. Thirteen (25%) failed to respond to clobazam 30 mg daily and a further 13 were withdrawn because of adverse effects. Of the 26 responders, 20 (77%) developed tolerance to the anti-epileptic effect at a median of 3-5 months (range 1-8 months), three (11.5%) showed no tolerance at 12 months and three (11.5%) dropped out (two due to adverse effects and one was lost to follow up).

The respective antiepileptic drug levels (mean ± SD, µmol/l) for the 1–2 month period prior to and at the development of tolerance were: phenytoin 48.7 ± 8.2 and 46.3 ± 9.2; carbamazepine 27.5 ± 3.2 and 26.9 ± 2.9; phenobarbital 93.3 ± 28.0 and 88.3 ± 13.0; sodium valproate 492.0 ± 106.9 and 495 ± 119.6; clobazam 0.3 ± 0.3 and 0.27 ± 0.3 and desmethylclobazam 61.6 ± 35.2 and 62.1 ± 32.7.

The development of tolerance is a major limiting factor in the use of benzodiazepines in the chronic treatment of epilepsy. Gastaut1 reported a 50% incidence of tolerance in patients treated with clobazam and Martin2 reported a median time to tolerance of 6.5 months. Our study confirms this finding, but we are unable to explain the development of tolerance by changes in the levels of concomitant anti-epileptic drugs, clobazam or desmethylclobazam, which did not vary significantly. Clobazam had to be withdrawn in 29% of the 52 patients because of adverse effects (mainly sleepiness, unsteadiness and irritability). This is a higher incidence than previously reported but the different populations studied may explain the discrepancy. On discontinuation of clobazam withdrawal fits were a problem in some patients, but they occurred less frequently than in our previous study and status epilepticus was not encountered. The rate of reduction was not more than 10 mg every seven days.

Although the development of tolerance is a major drawback to the use of clobazam, we would still advocate its use, with caution, in otherwise intractable cases. A significant number of our patients had a useful reduction in their seizures, albeit for a limited period. One long term resident, moreover, has been able to leave the Centre because of the complete cessation of tonic clonic seizures. There should be adequate follow up to ensure that the drug is discontinued carefully it it becomes ineffective, in order to avoid the hazards of unnecessary polypharmacy. We feel that patients should be advised, before treatment is started, of the possible development of tolerance, otherwise false hopes may be raised. We have, however, been able to manage tolerance successfully in a few patients, by discontinuing clobazam completely for a month and then reintroducing it at the same dose.

JW ALLEN
S JAWAD
J OXLEY
M TRIMBLE

Chalfont Centre for Epilepsy,
Chalfont St. Peter, Bucks. SL9 0RJ, UK

References

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Juvenile muscular atrophy of distal upper extremities

SIR—In 1959, Hirayama et al.1 reported 12 young patients from Japan with unilateral hand and forearm wasting which was termed “juvenile muscular atrophy of unilateral upper extremity.” Since then, at least another 100 patients have been described.2–13 The other main features were: predominant male involvement, insidious onset, stationary stage after a progressive course, absence of sensory and pyramidal tract involvement, normal CSF and radiological findings, neuropathic changes in the EMG and muscle biopsy. Though patients from Western Europe4–11 and Australia10 has been described, the majority of the cases in fact came from Japan4–9,13 and India12 suggesting an ethnic predisposition to the development of the disease. Malaysia is a multi-racial country, the ethnic composition in the peninsula is made up of 50% Malay, 37% Chinese and 11% Indian. The University Hospital, Kuala Lumpur, Malaysia is one of the two centres in the country providing neurological service and its patients come from all over the peninsula. I would like to report here 19 similar patients seen in this centre since 1967.

Fourteen of the patients were male and five were female. The age of first onset ranged from 11 to 34 years with an average of 20.7 years. The average age at presentation was 22.9 years. The racial composition was eight Malays, seven Chinese and four Indians. The patients came from diverse background with no contact with known toxins. Five were factory workers, four were students, two were clerks and two were housewives. One each was in the various occupations as follows: staff nurse, farmer, soldier and teacher. None has a family history of similar illness. There was no evidence of clustering with 10 of the patients from the state of Selangor, three from Penang, two from Johor and four from the other states.

The onset of the illness was usually insidious, with muscle wasting and weakness developing over several months and then becoming static. Fourteen patients had one hand affected only; with 10 involving the right hand and four the left hand. Five patients had both hands involvement which was asymmetrical over both sides. In four patients, the right hand was predominantly involved and in one patient, the left hand was more severely affected. All except two patients were right handed. Among the two left handers, one had unilateral involvement of left hand only. The other patient has both hands asymptomatically involved with the right side more severely affected.

The illness always started as wasting and weakness of small muscles of one hand. The involvement was not always global. In three patients, the thenar muscles were relatively spared. Tremor of fingers was an early symptom in some and was seen on out-stretched in 12 subjects. The forearm was affected in all the patients, but always less severe than the small muscles of the hand. In eleven patients, the flexor muscles was selectively or predominantly involved. The upper arm muscle was mildly affected in five patients. The weakness and wasting here did not follow any obvious segmental distribution. The opposite hand, when involved, followed the same pattern. Muscle fasciculation was seen in six patients and clawing of the fingers was seen in three patients. Most patients showed mild hyporeflexia of the biceps and supinator jerks over the same side. Sensory examination was normal and the plantar response was flexor in all the patients. We were impressed with the good functional ability in majority of our subjects.

Letters

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