all patients on their maintenance dose of isoniazid, an effect noted previously.4

We followed-up the patients helped by isoniazid for a period of eighteen months. One patient (case 1) maintained her improvement; she made several attempts to stop the drug but each time the tremor got worse and her hand function deteriorated; there has been no recurrence of weakness. Case 3, who had developed the drowsiness and extensor plantar responses, developed a less severe form of the same condition and asked for the drug to be discontinued even though his tremor then became much worse. Cases 2 and 5 both developed increasing weakness of the legs which was not affected by stopping the isoniazid. In case 2 the weakness was accompanied by severe spasticity.

Isoniazid definitely helped the action tremor in four of our patients. Its beneficial effect was rapidly lost when the drug was stopped and it is unlikely that this was a placebo effect or related to drowsiness since all the patients had been previously treated with other drugs including levodopa, diazepam, chlorpromazine, sodium valproate, with no subjective or objective benefit. Dose-related weakness of pyramidal type also occurred in all the patients who benefited and on follow-up two developed paraparesis not affected by stopping the drug. Weakness has not been mentioned as a side effect of isoniazid when it has been used in comparable doses to treat multiple sclerosis or Huntington’s disease.5 Possibly isoniazid produces weakness by unmasking a sub-clinical lesion of the pyramidal tract, a lesion which became clinical in two patients due to progression of their disease. We feel that isoniazid has a place in the management of action tremor in some multiple sclerosis patients. Its usefulness may be limited by side effects and it would seem prudent to discontinue the drug if weakness increases.

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References

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Drug-induced alpha coma

SIR: Alpha frequency rhythms in the electroencephalogram (EEG) in comatose patients was initially described in intrinsic brainstem lesions,1,2 and more recently in patients who suffered from cerebral hypoxia following cardiopulmonary arrest.2,3 A review of the literature on drug-induced alpha pattern coma disclosed nine cases.2,4 We report an additional case of drug-induced alpha coma, and discuss the clinical significance of this pattern, and the value of brainstem auditory evoked responses (BAERs) in this condition.

A 43-year-old female was brought to the emergency room on March 30, 1983, in a deep coma, after being found unresponsive by her husband. Apparently, her husband left the home for approximately an hour and on return, found her to be unconscious. Subsequent to her admission, an empty bottle of glutethimide was found which originally contained 25–30 pills. The patient had a long history of psychiatric illness and had made two attempts at suicide in the past. She had been treated with thiouridine, benzhexol, and hydroxyzine pamoate.

On admission, she had a blood pressure of 95/60 mmHg, a heart rate of 76/min, and a rectal temperature of 34°C. The patient received 2 l of oxygen per minute by nasal catheter and her arterial blood gases revealed pO2 of 83-4 mmHg, pCO2 of 54-5 mmHg and pH 7-26. Her blood pressure was maintained by intravenous fluid. She was given 0-8 mg of naloxone hydrochloride, 50 mg of diphenhydramine and 100 mg of thiamin intravenously. After intubation, she was placed on a respirator. Neurological examination revealed an unconscious patient with reaction only to noxious stimuli. There were no spontaneous movements of the extremities, but painful stimuli elicited decorticate posturing. Her pupils were in mid-position and reacted slightly to light. Oculocephalic, oculovestibular, ciliospinal and corneal reflexes were absent. She was flaccid in the lower extremities but the tone was increased slightly in the upper extremities. All muscle stretch reflexes were symmetric but hyporeactive. There were no pathological reflexes. There was no nuchal rigidity.

Multi-drug screening tests established intoxication with glutethimide. Urine was positive for glutethimide metabolite. Blood glutethimide level was 2-28 mg/dl (toxic level, 1-09–9-7 mg/dl). Chest radiographs, ECG and computed tomography of the head were normal. The patient was comatose for four days. EEG was initially performed 24 hours after admission. It showed diffuse 9-10 Hz rhythmic activity of 40–120 µV in amplitude, most prominent over fronto-central regions. The background activity showed only a slight reactivity to painful stimuli which evoked brief theta-delta activity. The second EEG tracing was obtained four days later when the patient

Table Clinical details and results of isoniazid treatment

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Duration of tremor (yr)</th>
<th>Acetylator status</th>
<th>Optimum daily dose (mg)</th>
<th>Functional ability</th>
<th>Bedside tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46</td>
<td>F</td>
<td>4</td>
<td>Slow</td>
<td>700</td>
<td>+</td>
<td>+ +</td>
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<tr>
<td>2</td>
<td>34</td>
<td>F</td>
<td>3</td>
<td>Rapid</td>
<td>900</td>
<td>+</td>
<td>+</td>
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<tr>
<td>3</td>
<td>26</td>
<td>M</td>
<td>6</td>
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<td>600</td>
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<td>+ +</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>M</td>
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<td>F</td>
<td>1</td>
<td>Slow</td>
<td>1200</td>
<td>+</td>
<td>+ +</td>
</tr>
</tbody>
</table>

-, no improvement; +, mild improvement; + +, marked improvement.

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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,\textsuperscript{7,9}\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 amytalnyline, barbiturates, glutethimide, nitrazepam, and chlorpromazine. 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.\textsuperscript{8}

Multimodality evoked responses in coma have proved helpful in determining the level of the damage to the brainstem.\textsuperscript{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.\textsuperscript{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,\textsuperscript{10} 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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