Meprobamate Withdrawal After Forty Years of Drug Treatment

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ABSTRACT

The case describes an 80-year-old woman found unconscious by her husband who then witnessed her having 6 generalized seizures, each lasting 30 seconds over the next few hours. She had no previous history of epilepsy, but had fallen several times because of poor mobility from osteoarthritis. Amitriptyline overdosage was suspected, but unlikely. In the light of the further drug history, clinical course, and EEG changes, the diagnosis of meprobamate withdrawal was made.

INTRODUCTION

An 80-year-old right-handed woman was found unconscious by her husband who then witnessed her having 6 generalized seizures, each lasting 30 seconds over the next few hours. She had no previous history of epilepsy, but had fallen several times because of poor mobility from osteoarthritis.

Her medication, brought with her, was recorded as amitriptyline 50 mg taken once a day at night. On examination, the patient was afebrile, Glasgow Coma Score was 3/15, and blood pressure was 118/52. The pupils were dilated but reactive to light and there was no papilledema, tone was generally increased, and reflexes were symmetrically brisk; both plantar responses were extensor.

There was blood and protein in the urine but no ketones; blood glucose concentration was 13 mmol/L. She had severe metabolic acidosis: pH 6.9, p_aCO_2 5 kPa, p_aO_2 28 kPa and bicarbonate 7.2 mmol/L. A CT brain scan showed cerebral atrophy but no focal lesion. The electrocardiogram showed sinus tachycardia.

Treatment was started with cefuroxime for a presumed urinary tract infection, flucloxacillin for phlebitis of the left arm, and diazepam. The patient improved initially, but deteriorated when the diazepam dose was reduced, showing increasing poverty of speech, drowsiness interrupted by short bouts of agitation, startle myoclonus, and generalized hypertonia. A repeat CT brain scan showed no new changes, but an electroencephalogram showed evidence of focal and generalized seizure activity, consistent with drug withdrawal (Figure 1). Examination of the cerebrospinal fluid was normal.

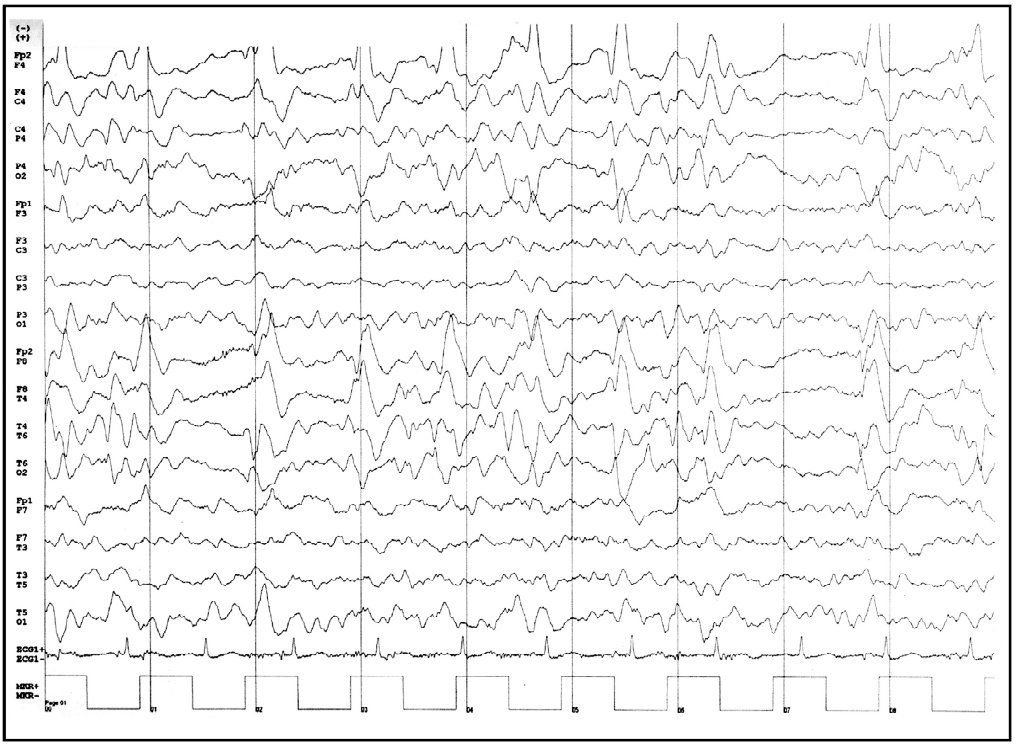

Figure. Patient's electroencephalogram during her rapid mental and physical decline. The tracing shows generalized slow and focal seizure activities localized to the right prefrontal region, in the absence of clinical localizing signs or structural abnormalities on brain imaging.

Two days after admission, the patient's daughter disclosed that her mother had been taking meprobamate 400 mg tablets for her "nerves". She had been prescribed 200 tablets a month by her general practitioner since the 1960s. She had recently reduced her intake to two tablets three times daily and 24 hours before admission had run out of tablets.

During the course of the following week, the patient began to improve on treatment with phenytoin, carbamazepine, and clonazepam, as well as ciprofloxacin and ceftazidime for proven *Pseudomonas* septicemia.

DISCUSSION

Amitriptyline overdosage was suspected, but unlikely. In the light of the further drug history, clinical course, and EEG changes, the diagnosis of meprobamate withdrawal was made. Meprobamate, a carbamate derivative, synthesized in 1950 and used as an anxiolytic and muscle relaxant, is hardly ever encountered in clinical practice today. Physical dependence, an abstinence syndrome and abuse are well described. [1-5]

In dogs, abruptly withholding meprobamate after several months' therapy led to withdrawal symptoms 12 to 16 hours following the final dose, with major convulsions after 20 to 26 hours, hyperpyrexia and high mortality.[1]

Marked anxiety, tremulousness, hyperreflexia and then generalized seizures followed the abrupt withdrawal of meprobamate in a patient who was taking 50 tablets daily. Meprobamate was reintroduced, then slowly withdrawn, with no further symptoms.[2]

In volunteers, meprobamate treatment for 40 days prior to abrupt withdrawal provoked insomnia, vomiting, tremor, muscle twitching and overt anxiety and in some subjects convulsions 36 to 48 hours after withdrawal.[3]

Acute psychotic reactions and hallucinations resembling delirium tremens have also been described.[4]

Withdrawal from drugs no longer widely used can still cause serious clinical problems. The meprobamate withdrawal syndrome (with or without major seizures) is similar to barbiturate-alcohol withdrawal from drugs, including alcohol, chloral, paraldehyde, glutethimide and ethchlorvynol, that act at GABA-receptors. In this case, the findings are consistent with withdrawal syndromes from benzodiazepine or other sedatives, including meprobamate (Figure).[5]

This case emphasizes the relevance of accurate information about previous medication and encourages gradual rather than abrupt withdrawal of drugs like meprobamate. It is a reminder that medications not only have the potential to cause adverse effects when started or used for a period of time but also withdrawal symptoms when stopped.

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