Maprotiline-Induced Seizures

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MAPROTILINE (Ludiomil) is a tetracyclic antidepressant used in this country since 1981. Since its introduction there have been eight case reports in the American literature of seizures occurring in patients receiving therapeutic doses of maprotiline and at least 20 such reports in the British and South African literature.[1-16] We report five additional cases of apparent maprotiline-induced seizures seen over a six-month period in northern Virginia.

CASE REPORT

A 27-year-old woman was seen in May 1982 because she had been feeling sad, had a poor appetite, and was having difficulty sleeping. The diagnosis of major depressive episode was made, and treatment was started with maprotiline, 50 mg/day, which was gradually increased to 150 mg/day over a week. Other medications at the time included danazol (Danocrine) and ibuprofen (Motrin) for endometriosis. She had a history of allergic rhinitis and asthma, but no history of seizures.

One week after starting maprotiline, the patient had a seizure while driving. Paramedical personnel took her to the emergency department, where she was found to be postictal, with amnesia for the event, and with a headache. Maprotiline was suspected as the cause of the seizure and was discontinued. Subsequent work-up, including blood chemistry studies, electroencephalograms, visual evoked response, brain stem auditory evoked response, and computerized tomographic scan of the brain, showed no abnormality. She was treated with carbamazepine (Tegretol), which was tapered over the next year, and has had no further seizures.

Comment. We have observed four other cases of maprotiline-induced seizures. Each patient had a single seizure from three to 14 days after starting maprotiline therapy for clinical depression. There were no other identifiable predisposing factors, and no patient had recurrent seizures after discontinuing maprotiline. Because of the experience with the first patient, the other four patients were not treated with anticonvulsants, and merely had follow-up clinically, without maprotiline. All were seen by one neurologist (P.G.B.) after the seizure. Pertinent data for our five patients and from the eight other case reports in the American literature are summarized in the Table.

DISCUSSION

Maprotiline has been reported to be as effective as standard tricyclic antidepressants such as imipramine and amitriptyline. It has received support as a faster acting antidepressant with fewer anticholinergic and cardiovascular side effects than its tricyclic counterparts.[12] Tricyclic-induced seizures are rare, though documented.[13] It is well known that toxic doses of maprotiline and other antidepressants are frequently associated with seizures, but the seizure-inducing potential of maprotiline in therapeutic doses is thought to be minimal. A small percentage of patients taking tricyclic antidepressants in therapeutic doses have grand mal seizures. Being a newer antidepressant, maprotiline is less well known to cause seizures. This tetracyclic antidepressant is derived from the earlier tricyclic structures and is one of the dibenzo-bicyclo-octadienes; it possesses an ethylene bridge across the central ring, and thus is designated a tetracyclic compound. Maprotiline inhibits uptake of catecholamines at the neural membrane and also antagonizes the action of serotonin and acetylcholine. The exact mechanism of seizure production is poorly understood. It produces convulsions in overdosage,[17] which are best treated with diazepam. The anticholinergic and antimuscarinic side effects of the cyclic antidepressants lower the seizure threshold and induce seizure activity.[18] The new interest in this antidepressant medication is the result of reported cases in which maprotiline caused seizures when the medication was taken in therapeutic dosage.

We have reported five cases of what appeared to be maprotiline-induced seizures in patients taking therapeutic doses of the drug. As noted previously by others it appears that seizure potential is greater with doses above 150 mg/day. All

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TABLE. Data on Patients With Maprotiline-Induced Seizures

Reference	*Sex*	*Age*	*Dose of Maprotiline (mg/day)*	*Time From Start of Maprotiline to Seizures (days)*	*Maprotiline Level (ng/ml) (Therapeutic Range 180-300)*	*EEG Results (Length of Time After Seizures)*
Ramirez[1]	M	29	50-75	20		Normal. (Not mentioned)
Bick[2]	F	54	175	20	Not available	Med. volt. diffuse epileptic discharge. (Not mentioned)
Price and Mukherjee[3]	F	38	150	18	NA	Mild R temporal and bilateral slow wave activity (1 day); mild R temporal and bilateral slow wave activity. (13 days)
Kim[4]	F	46	50-150	35	NA	Normal. (1 day)
Holliday et al[5]	M	32	100-175	3	NA	Generalized type II dysrhythmia. (Not mentioned)
Hoffman and Wachsmuth[10]	M	20	200	9	NA	Diffuse symmetrical beta activity. (Not mentioned)
	F	39	200	41	NA	Normal. (Immediate and follow-up)
Schwartz and Swaminathan[11]	M	63	25-75	8	NA	Periodic lateralized epileptiform discharge. (Not mentioned)
Bernad and Levine	F	27	50-150	7	NA	Normal. (17 days)
	M	35	50-125	3	57	Normal. (3 days)
	F	30	50-200	4	336	Diffuse high voltage slow activity and spike wave activity. (1 day)
	F	21	50-200	14	NA	Normal. (2 days)
	F	60	50-200	7	NA	Normal. (2 days)

five of our patients and six of the eight other cases involved doses above 150 mg/day.[5]

Our five cases of maprotiline-induced seizures contrast with not a single seizure associated with any other antidepressant medication during the same period. These five cases, seen over a six-month period in a single neurology practice, would seem to be a disproportionately large number of cases of maprotiline-induced seizures. Of course, factors as yet unknown may be contributing in susceptible individuals. For example, some researchers have postulated that fluid retention from oral contraceptives may increase the seizure susceptibility in some female patients.[15]

Maprotiline is an effective antidepressant, but many cases of seizures associated with the drug have been reported during its relatively short period of use. Therefore, until further studies are available to clarify the issue, physicians should be alert to this potential side effect of maprotiline. In particular, emergency physicians, psychiatrists, and neurologists should be vigilant for possible maprotiline-related seizure activity. A registry should be established to report adverse effects such as seizures, which could be reviewed and published in timely fashion.

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