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Does viloxazine have epileptogenic properties?

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SUMMARY Six cases of convulsive seizures occurring during treatment with viloxazine notified to the Committee on Safety of Medicines (CSM) and two other cases from Japan were reviewed. A critical study of the patient's histories suggests a possible causal connection between drug and seizures in only two of these cases. The occurrence of convulsions is not in keeping with the results of animal experiments and of clinical trials in which epileptic patients were included, both of which suggest that viloxazine does not have epileptogenic properties and may have anticonvulsant actions. A worldwide review of clinical trials in which unwanted effects have been recorded suggests that viloxazine, even if possessing convulsive properties like other anti-depressants, is probably less epileptogenic than conventional tricyclics and is not contraindicated in epileptic patients requiring antidepressant medication.

Viloxazine is a bicyclic antidepressant with atypical pharmacological properties.[1–3] It is prescribed infrequently in Britain but used extensively in Western Europe, especially in France.

A case of convulsive seizures occurring during the course of treatment with this drug was reported in 1977.[4] It was noted that convulsions had previously been observed in two patients (one of them an epileptic) during the course of a clinical trial of viloxazine[5] while five subsequent cases have been reported to the Committee of Safety of Medicines in the United Kingdom.[6 7] Imperial Chemical Industries PLC who manufacture viloxazine have on record only two other cases of convulsions, both reported from Japan (Holland, 1983; personal communication). These occurrences suggest that viloxazine, like most other antidepressants, has epileptogenic properties.

Convulsions due to this drug are difficult to explain pharmacologically. Viloxazine was derived from a series of aryloxypropanolamine beta-adrenoceptor antagonists, many of which have non-specific membrane-stabilising properties in animals.[8] However, such properties may not be relevant in the case of viloxazine as it is its S-enantiomer that has the greater potency.[3] Viloxazine possesses potent anti-convulsant properties in animals, protecting against electrically-induced seizures in male albino mice and male rats, seizures induced by metrazole in female brown mice and male albino rats, audiogenic seizures using "Friedland" chimes and a three inch doorbell in genetically susceptible mice of both sexes, and photically induced seizures in adolescent Senegalese baboons of the species, *Papio papio*.[1 2 9] Detailed recordings of the electrocorticogram in the cat *encéphale isolé* preparation after acute intravenous or chronic oral administration of viloxazine failed to reveal any overt epileptogenic activity.[10 11] In rabbits showing spontaneous electroencephalographic epileptiform discharges viloxazine given intravenously caused the disappearance of paroxysmal features which become replaced by synchronous low frequency activity.[12] The recent work on viloxazine has shown that, in contrast to several other antidepressants, it has little effect on spike activity in perfused guinea pig hypocampal slices.[13] In contrast to these observations at low/therapeutic dose levels, abnormally high blood levels may be associated with a proconvulsant action.[9]

In clinical trials of viloxazine in which epileptic patients were included (table 1) the frequency of seizures did not appear to increase and in the study of Cocchi and Occhialini there was a decrease in the number of attacks.[19] Some authors stated that they could decrease the dose of anticonvulsants without an increase in fit frequency,[15 20] while others noted no change in the EEG[16 18 20] or an "improvement" in the EEG.[14 18 20] However, most observations were made on small numbers of cases and the methodology of studying fit frequency does not allow firm conclusions to be reached.

Because reported cases of convulsive seizures occurring with therapeutic doses of viloxazine are not in accordance with the pharmacological proper-

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Table 1 *Trials in which epileptic patients were included*

Investigators	*No. of epileptic patients*	*Daily dose range (mg)**	*Duration of trial*
Brion *et al*, 1975[14]	4	200–300	60–240 days
Gonzalez Campo, 1976[15]	3	100–150	4 weeks
Castro Morales, 1977[16]	9	150–300	6 months
Kress *et al*, 1978[17]	3	100–600	3 months
Fontan *et al*, 1979[18]	2	100–600	not specified
	(+ 6 'vasculaires' with EEG abnormalities)		
Cocchi & Occhialini, 1981[19]	6	25–200	2–20 months
Leyrie, 1981[20]	11	150–400	'more than 3 months'–18 months

*These are the doses and durations of treatment for *all* patients included in the trials. It was not possible to determine from the publications the doses and durations of treatment for the epileptic patients.

ties and results of animal experiments, EEG studies or observations made during clinical trials, we investigated the background of the cases reported to the Committee on Safety of Medicine with the help of a structured questionnaire[7] and have added information gleaned from the two cases reported from Japan. In one of the Committee on Safety of Medicine patients, an epileptic woman who died suddenly and unexpectedly during an epileptic attack, viloxazine could not have been the cause of her convulsions because it was discontinued 32 days before the attack. We therefore report the remaining five cases.

Case reports

Cases notified to Committee on Safety of Medicine

Patient 1 was a 50-year-old man who had three grand mal convulsions on the sixth day of treatment with viloxazine 100 mg tds. Chlordiazepoxide 30 mg and nitrazepam 5–10 mg a day had been discontinued three days before the attack and diazepam 15–30 mg a day was stopped four days earlier still.[4]

Patient 2, a woman aged 24 years, had a series of convulsions occurring over the course of eight days after a single 50 mg dose of viloxazine. She was known to have hepatic cirrhosis complicated by portal hypertension and hepatic encephalopathy with a blood ammonia "three times the normal upper limit" at the time of the convulsions.

Patient 3, a woman aged 23 years collapsed and had a "? grand mal convulsion" on the second day of treatment with viloxazine 50 mg tds. Treatment with maprotiline, which she had been receiving for an uncertain length of time, had been stopped three days before the attack.

Patient 4 was a 32-year-old woman who had two fits on consecutive days after taking viloxazine 50 mg tds for only three days. She dislocated her jaw as a result of the convulsions. She had suffered from epilepsy since childhood but was not receiving anticonvulsants. Lorazepam 6 mg a day was stopped seven days before the attack. The patient was started back on viloxazine together with diazepam 5 mg tds. No further fits occurred.

Patient 5 was a 30-year-old woman. All we were able to learn about her was that she had a convulsive seizure after taking only two 50 mg doses of viloxazine and that a subsequent dose was not followed by an attack.

Cases from Japan We were able to obtain less background information on the cases reported from Japan. One of them, a 72-year-old woman with a raised blood urea, had a "clonic convulsion" on the second day of treatment with 150 mg of viloxazine a day. Amitriptyline had been discontinued prior to starting treatment with viloxazine. The second patient, a woman aged 42 years with a past history of "EEG abnormalities and convulsions", had convulsive seizures following eight days' treatment with viloxazine 150 mg a day.

Incidence of seizures

The numbers of cases of convulsions occurring during treatment with different antidepressants reported to the Committee on Safety of Medicine give clues as to the relative epileptogenic properties of the antidepressants. They cannot, however, provide an accurate measure of the incidence of fits as at most only about 10–15% of drug reactions are notified to the Committee[21 22] and reporting varies with the clinician, the drug and the type of reaction. There are also difficulties in establishing a cause and effect relationship in many cases.[6 7]

In an attempt to assess the incidence of seizures during treatment with viloxazine the worldwide literature on all studies in which viloxazine was administered to humans has been reviewed. Attention was focused on the 120 studies carried out in non-epileptic populations in which unwanted effects were recorded. These were carried out in 31 countries and involved 7,635 patients (table 2). Only three patients had convulsions during these studies[4 5 23] and in two cases there were more likely causes of the fits than viloxazine. No information was obtainable on the third case but assuming a causal connection between viloxazine

Table 2 *Viloxazine studies in humans*

Countries	*No. of studies*	*No. of patients*
United Kingdom	18	2152
France	36	3414
West Germany	7	586
Other Western European Countries	14	342
Eastern European Countries	6	337
North America	9	149
Central & South America	18	377
Japan	7	185
Other countries	5	93
Total	120	7635

Bibliography available on request.

and the seizure the incidence of fits, at least early in treatment, would appear to be as low as one case in 7,635 patients, that is 0·01%.

Discussion

We were successful in obtaining background data on five of the six cases reported to the Committee on Safety of Medicine. We found that in one of these the patient had stopped taking viloxazine before the attack which led to her death and it is therefore extremely unlikely that the drug could have been a contributing factor.

Withdrawal from benzodiazepines was thought to be the most likely cause of the convulsions in patients 1 and 4. Benzodiazepine withdrawal was considered as a possible explanation in the first of these[4] but at the time the case was reported convulsive seizures due to withdrawal from therapeutic doses of benzodiazepines were regarded as extremely rare.[24] Withdrawal from benzodiazepines as a cause of convulsions has since become more widely recognised and in our opinion it is a cause that is frequently overlooked. Depressive illnesses are often accompanied by symptoms of anxiety or present as anxiety states and benzodiazepines are prescribed for their treatment. When it becomes apparent that the patient is suffering from a depressive illness the benzodiazepines are discontinued and antidepressants substituted. Benzodiazepine-withdrawal symptoms occur and the antidepressants are erroneously incriminated.

The most likely cause of the convulsion in patient 2 was hepatic encephalopathy although if viloxazine has epileptogenic properties it is possible that abnormally high plasma levels due to hepatic failure could have caused or contributed to the convulsion. In the case of patient 3, maprotiline 25 mg tds had been stopped three days before the convulsion. It is not known how long the patient had been receiving this drug but with a mean plasma half-life that ranges from 27 to 108 hours[25,26] it is highly probable that maprotiline was still present in the circulation. More cases of convulsions occurring during treatment with this drug have been reported to the Committee on Safety of Medicine than with any other antidepressant marketed in the United Kingdom. It is therefore just as likely that maprotiline caused the attack as viloxazine.

Insufficient information was obtained on patient 5, but in so far as the seizure occurred after the first two doses of viloxazine this drug must be considered as a possible (though not probable) cause of the attack.

We also had insufficient information on the Japanese cases. Uraemia must be considered as a more likely cause of the attack than viloxazine in the first (elderly) patient while amitriptyline may also be implicated. The second patient had a history of convulsions preceding the use of viloxazine which at worst could be regarded as a contributory (rather than causative) factor.

Rating the relationship between viloxazine and convulsions on a five-point scale ranging from "almost certainly" due to the drug to "almost certainly not" due to the drug[27] we believe that in only two out of the seven cases referred to could viloxazine be regarded as a "possible" cause of the convulsions. As already stated we had insufficient background information on one of these and in the other maprotiline could be an equally likely cause.

It is noteworthy that in all but one of the seven cases cited the patient was a woman. This probably reflects the higher prevalence of depression in women[28] and the fact that antidepressants are prescribed more often for them than for men.[29,30]

The discussion has focused on viloxazine as a possible cause of convulsions when given in therapeutic doses. It cannot be concluded that this

Table 3 *Incidence of seizures*

Investigators	*Antidepressant*	*Daily dose*	*No. of patients**	*No. of patients who had seizures*	*Incidence of seizures*
Peck *et al*, 1983	imipramine	≤ 200	2986	3	0·10
		> 200	958	6	0·63
		50–600†	1390	6	0·43
		Total	5334	15	0·28
	amitripyline	< 200	1037	0	0·00
		≥ 200	1811	1	0·06
		Total	2848	1	0·04
Edwards and Glen-Bott, 1984 (this study)	viloxazine	150–800 (most 150–300)	7635	1	0·13

*excluding those with epilepsy
†dose at which seizure occurred not known

drug does not cause convulsions when taken in overdose. Four cases of convulsions were reported out of a series of 64 cases of self-poisoning by overdose although other drugs were taken with viloxazine and these could equally well have been responsible.[31] Whether or not the other drugs taken had epileptogenic properties, a more likely explanation for the convulsions is cerebral anoxia due to respiratory depression.

It is difficult to assess accurately the incidence of convulsive seizures occurring during treatment with antidepressants but the best available estimates in those taking imipramine and amitriptyline are shown in table 3 while Jick *et al*[32] reported an incidence of 0·1% for a wider range of tricyclics. Our study suggests that the incidence of attacks occurring during treatment with viloxazine is 0·01%. This is a quarter of the estimate of Peck *et al*[33] for amitriptyline and a twenty-eighth of that of imipramine; it is a tenth of the estimate of Jick *et al* for a wider range of tricyclics. If these figures are a true representation of the relative incidence they indicate that viloxazine is not contraindicated in epileptic patients who require antidepressant medication. However, if it is prescribed one should be alert to the possibility that it could precipitate phenytoin intoxication.[34]

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