LETTER TO THE EDITOR

THE IRREVERSIBLE \( \gamma \)-AMINOBUTYRATE TRANSAMINASE INHIBITOR VIGABATRIN IN THE TREATMENT OF THE ALCOHOL WITHDRAWAL SYNDROME

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(Received 4 September 1995; accepted 30 October 1995)

The pathophysiology of alcohol withdrawal is complex and still not fully understood in spite of intensive research. The variety of different theories accounts for the fact that at least 150 different drugs and drug combinations have been reported to be useful in the treatment of the alcohol withdrawal syndrome (AWS; Walinder and Svenson, 1989). Benzodiazepines are the most commonly used substance class in this context, with proven efficacy (Liskow and Goodwin, 1987) but also with serious abuse and dependence potential (Busto, 1986). The use of barbiturates, chloral hydrate or clormethiazole should be avoided, because of their toxicity and also high dependence risk. Other substances like tiapride, piracetam, nimodipine, bromocriptine, clonidine and \( \beta \)-adrenoceptor-blocking agents also showed good results in clinical trials, but their actions cannot cover the complexity of symptoms in AWS (Rommelspacher et al., 1991). In the early 1970s, research began to focus on anticonvulsant agents, such as carbamazepine or valproic acid. Carbamazepine especially proved to be a successful treatment strategy (Brune and Busch, 1971). Our group (Stuppaec et al., 1991) conducted a double blind trial of carbamazepine vs oxazepam in AWS and showed equal efficacy of both substances. But, after a period of use of carbamazepine in AWS, we have also observed several cases of carbamazepine abuse (Stuppaec et al., 1993).

The search for an effective and safe treatment of AWS therefore continues. \( \gamma \)-Aminobutyrate (GABA)ergic mechanisms have been thought to be responsible for both the withdrawal syndrome and chronic alcohol abuse (Coffmen and Petty, 1985). The pathophysiology of withdrawal seizures is also closely linked to GABA\(_A\) receptor-operated chloride channels (Allan and Harris, 1987). The new anticonvulsant compound vigabatrin is an irreversible blocker of GABA transaminase. Treatment of mice with vigabatrin leads to an increase of presynaptic GABA levels (Jung et al., 1977). Maximal plasma levels are reached 2 h after oral administration. Plasma half life is 5–8 h, but the duration of its action depends not on plasma half life, but on the rate of resynthesis of GABA transaminase (Schechter, 1989). Animal studies have shown that 4 days after the last administration of vigabatrin, GABA levels were twice as high as before treatment (Schechter and Grove, 1980). Vigabatrin showed no effects on sleep, cognitive function, heart rate or blood pressure in healthy volunteers (Saletu et al., 1986). The most frequent side-effect in patients suffering from treatment-resistant epilepsy was fatigue; the overall side-effect profile appears favourable (Grant and Heel, 1991). We should now like to present a summary of the results of the first open trial with vigabatrin in the treatment of AWS.

The 25 inpatients (22 males and three females) studied were all alcohol-dependent and showed an AWS fulfilling DSM-III-R criteria (American Psychiatric Association, 1987). Four of the patients had a history of alcohol withdrawal delirium and nine had experienced withdrawal seizures in the past. Polydrug abusers were excluded from the trial. On the day of admission

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and during the trial, breathalyser tests were performed regularly. Vigabatrin was given 1 g b.i.d. during 3 consecutive days. The first dose was usually given in the evening of day 1. A B-multivitamin preparation was given orally during the whole 7-day study period. Oxazepam was allowed as concomitant medication. Frequency and dose of oxazepam were recorded daily. The following ratings were obtained on days 1, 2, 3, 5 and 7: the modified and translated (German) version of the Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-A) (Stuppaeck et al., 1994) and the Clinical Global Impression Scale (CGI) (National Institute of Mental Health, 1976).

Blood chemistry, white and red blood counts and an EEG were assessed on days 1 and 7.

The mean age of the patients (±SD) was 41.1 ± 9.6 years, the mean body weight amounted to 74.1 ± 12.1 kg. The mean age at the first alcohol consumption was 17.9 ± 3.2 years, mean age at first appearance of AWS was 29.0 ± 8.4. The patients had consumed an average amount of 316 ± 191 g of alcohol per day during the weeks before admission. All 25 patients stayed in the trial during the first 3 days, 18 patients could be evaluated on day 5, and 14 patients remained in the trial throughout the whole study period. Patients were not followed beyond day 3 if their withdrawal syndrome had subsided or if they had shown a marked amelioration that allowed them to be discharged from acute inpatient units and referred to a long-term treatment centre.

The baseline data concerning blood chemistry and haematology showed elevated liver enzymes (ASAT and GGT). During the study, no relevant changes in blood chemistry and haematology were noted, except a slight decrease in liver enzymes. Also systolic and diastolic blood pressure, pulse and respiratory rate decreased during the trial. The breathalyser tests at admission gave a mean alcohol concentration of 130 mg/dl (range 0-340), whereas during the trial, all tests were negative. Scores of the CIWA-A (German version) decreased from a mean (±SD) of 26.3 ± 4.9 at baseline to 20.6 ± 5.3 on day 2, 14.4 ± 3.2 on day 3, 14.2 ± 3.3 on day 5 and 13.8 ± 2.1 on day 7. CGI levels decreased from 5.7 ± 1.1 on day 1 to 5.2 ± 1.0 on day 2, 4.2 ± 0.8 on day 3, 4.1 ± 1.0 on day 5 and finally to 4.0 ± 0.9 on day 7 (last observation carried forward in the ratings from days 5 and 7). This amelioration was statistically significant (P < 0.001; Wilcoxon matched-pairs signed-rank test).

Eight patients showed slightly abnormal EEG patterns, three of them had suffered from a withdrawal seizure immediately before admission. There was no difference in their mean total CIWA-A scores from the group without withdrawal seizures. A 56-year-old female patient with a body weight of 100.5 kg suffered from a tonic-clonic seizure during the control EEG monitoring on day 3. Oxazepam (50 mg) was given concomitantly on day 1, 200 mg on day 2, and 150 mg/day from day 3 to day 7. She had not been in the group of patients who had had withdrawal seizures prior to the trial, but her EEG at the beginning of the trials had shown a slightly abnormal pattern with a reduced basal rhythm on the left side. Fifteen patients received a total dose of 25 to 1000 mg oxazepam (median 75 mg) during the study. Nine of these patients received more than 75 mg oxazepam during the whole trial, two patients had 150 mg concomitantly, three patients received 300, 350 or 400 mg, and one patient was treated with a total of 1000 mg of oxazepam. Seven patients received oxazepam only on the first day of the trial, four needed a second dose on day 2, and only four were treated with oxazepam concomitantly during the whole trial period. Ten patients were treated with vigabatrin alone. At the beginning of the study the mean CIWA-A scores in the group treated with vigabatrin monotherapy (n = 10) were 28.6 ± 4.2; the patients receiving adjunct oxazepam (n = 15) showed a mean score of 24.7 ± 4.9. No side-effects were registered in any patient.

To our knowledge this is the first trial using the irreversible GABA transaminase inhibitor vigabatrin in AWS. The dose used was based on experience in epilepsy management (Tartara et al., 1986). Symptoms of AWS were influenced positively in all patients. The severity of their illness is illustrated by the liver enzyme values, the daily alcohol consumption and the duration of illness. Withdrawal of vigabatrin after 3 days of treatment did not lead to a worsening of symptoms. Three days were considered as a sufficient treatment period, because the duration of action of vigabatrin persists beyond that due to ongoing blockade of GABA transaminase. Possibly less oxazepam would have been necessary if the dose of vigabatrin had been increased to 3 g/day, the
highest effective dose used in clinical trials in patients suffering from epilepsy (Dam, 1991). On the other hand, patients who had a need for concomitant benzodiazepines and patients with vigabatrin monotherapy had not differed in CIWA-A mean total scores at the beginning of the study. Oxazepam was prescribed only as hypnotic in all patients, except the one who had a seizure during the trial. The very low dose of oxazepam used rules out the possibility that withdrawal symptoms were influenced primarily by the benzodiazepine.

One patient suffered from a seizure that occurred on day 3 after a total of 4 g of vigabatrin. The seizure could possibly have been avoided with a higher dose of vigabatrin. An advantage of vigabatrin over most substances used in the treatment of AWS is that it can be withdrawn abruptly after 3 days. A short duration of drug treatment appears to be a very important strategy in the treatment of AWS.

In conclusion, vigabatrin showed encouraging results in the study presented here and could become an effective alternative in the treatment of AWS. Double-blind studies comparing vigabatrin to well-established substances are needed to confirm our findings.

REFERENCES


