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TREATMENT

Valproate Treatment of Acute Alcohol Hallucinosis: A Double-Blind, Placebo-Controlled Study

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Abstract — Aims: The aim of this study was to compare the efficacy and safety of valproate (Depakine-Chrono) versus placebo for the treatment of acute alcohol hallucinosis. **Methods:** 10 days' randomized, double-blind, parallel study was conducted; 40 patients with an ICD-10 diagnosis of acute alcohol hallucinosis were randomized to valproate (Depakine-Chrono) 3000 mg/day ($n = 20$) or placebo ($n = 20$). The primary efficacy measure was the Clinical Global Improvement (CGI) and the Positive and Negative Syndrome Scale (PANSS), subscale for hallucinosis. **Results:** Valproate-treated patients demonstrated a greater improvement than placebo-treated patients in CGI ($P < 0.001$) and PANSS subscale for verbal hallucinosis ($P < 0.001$). **Conclusion:** Valproate is effective in the treatment of acute hallucinosis and is generally well tolerated.

INTRODUCTION

According to the information of European regional office of WHO (2003) in Europe 41 million adults are abusing or dependent on alcohol. The incidence of alcoholic psychoses in some countries has increased in recent years, with alcoholic hallucinosis taking second place after delirium tremens.

Alcoholic hallucinosis presents with acoustic verbal hallucinations, delusions and mood disturbance arising in clear consciousness. The widely used treatment of acute alcoholic hallucinosis is neuroleptics (haloperidol, etc.), which caused numerous side effects and do not always produce improvement. Sometimes this illness passes to a chronic form and schizophrenia-like symptoms are observed. Patients who develop alcohol hallucinosis may be suicidal. Admission to psychiatric hospital is usually needed and the onset of alcohol hallucinosis is often an indication for neuroleptic treatment. Patients with alcohol hallucinosis experience the same side effects of neuroleptic treatment as those patients receiving standard neuroleptic for other psychiatric diseases (Soyka and Voelckler, 1988).

Various anticonvulsant medications may have efficacy in the treatment of certain anxiety states as well as withdrawal syndromes occurring after the discontinuation of sedative–hypnotic drugs and alcohol. A number of preclinical studies have demonstrated that valproate and other GABA agonists have anxiolytic properties (Simiand *et al*., 1984; Raevskii *et al*., 1985; Shephard, 1987; Becker and Anton, 1990; Corbett *et al*., 1991; Barros *et al*., 1992; Rodina *et al*., 1993; De Angelis, 1995; Dalvi and Rodgers, 2001; Lang and De Angelis, 2003).

Clinical studies suggest that valproate may have therapeutic effects in the treatment of bipolar depressive, anxiety (panic, social phobia and posttraumatic stress disorders) and psychotic disorders; alcohol withdrawal and dependence; tardive dyskinesia; agitation associated with dementia; and borderline personality disorders (Roy-Byrne *et al*., 1989; Ontiveros and Fontaine, 1992; Keck *et al*., 1992, 1993; Woodman and Noyes, 1994; Stein *et al*., 1995; Baetz and Bowen 1998; Clark *et al*., 1999; Davis *et al*., 2000; Hertzman 2000; Reoux *et al*., 2001; Longo *et al*., 2002; Brady, *et al*., 2002; Johnson *et al*., 2004; Book and Myrick, 2005). It is also possible that some patients in the heterogeneous generalized anxiety disorder category may respond to valproate and carbamazepine, particularly in light of the similarity between this type of anxiety and the symptoms of alcohol and sedative–hypnotic drug withdrawal (Aliyev and Aliyev, 2008). While benzodiazepines clearly have an important role in the treatment of anxiety and withdrawal states, the role of non-benzodiazepine anticonvulsants is a promising one that needs to be further delineated with careful, controlled studies (Roy-Byrne *et al*., 1989). The therapeutic effects of valproate in psychiatric conditions have been recognized by licensing bodies for bipolar disorder. However, this well-tolerated medication may be beneficial in the treatment of other mental illnesses. Davis *et al*. (2000) reviewed studies of valproate as treatment for psychiatric conditions, including bipolar, depressive, anxiety and psychotic disorders; alcohol withdrawal and dependence; tardive dyskinesia; agitation associated with dementia and borderline personality disorder. Valproate shows most promise in treating mood and anxiety disorders, with possible efficacy in the treatment of agitation and impulsive aggression and less convincing therapeutic response in treating psychosis and alcohol withdrawal or dependence. These authors conclude with a summary of its mechanism of action and therapeutic spectrum.

Although valproate has been studied in alcohol withdrawal and relapse prevention, there are no studies of its use in acute alcohol hallucinosis. Of possible relevance are data on a possible similarity of some clinical and pathophysiological mechanisms underlying verbal hallucinosis and convulsive syndromes (Bruens, 1971). Our preliminary study has shown that the subjects with acute alcohol hallucinosis had significantly lower values for inhibitory (GABA, glycine), while elevated values for excitatory (glutamate, asparate) neurotransmitters amino acids (Aliyev and Aliyev, 2004). On the basis of these results, the use of new anticonvulsants in the treatment of acute alcohol hallucinosis could then be proposed. The aim of the present study was to evaluate in a randomized, double-blind, placebo-controlled trial valproate in the form divalproex sodium (Depakine-Chrono, Sanofi-Aventis, France) in acute alcohol hallucinosis.

MATERIALS AND METHOD

Informed written consent to participate was provided by the patient, or a significant family member (based on Helsinki protocol). (This study was not commercially sponsored. The local ethics committee (Azerbaijan Psychiatric Association) approved this study.)

A structured interview was used to diagnose acute alcohol hallucinosis according to ICD-10 (WHO, 1994). Thus hallucinations occurred in the absence of withdrawal symptoms and the hallucinosis had developed against a background on the long-term heavy drinking. The 40 patients (all men) whom we studied were in-patients in the Narcological Clinic of the Ministry of Health, Azerbaijan Republic. The length of the washout from all medication was 2 weeks. Alcohol dependence in these men was characterized by constant drunkenness with raised tolerance. Patients were excluded if the hallucinosis was due to withdrawal symptoms; if they displayed an acute systemic medical disorder or a medical disorder requiring frequent changes in medication; a history of seizures, cerebrovascular disease, structural brain damage from trauma; focal neurologic signs on examination; used other drugs than alcohol, with the exception of nicotine; evidence of any progressive neurologic disorder; or if a first-degree relative had a history of definite neurological or psychiatric disease.

Treatment with study medication started within 24 h of admission to a hospital. No other medications were prescribed. Patients were randomized using a table of random numbers to receive either Depakine-Chrono (Sanofi-Aventis, France) or placebo, increasing over 3 days from 1000 mg to 3000 mg, in three divided doses. Although in some countries the maximum recommended dosage for adults is less, we followed the United States prescribing information on valproic acid, which permits a larger dose (e.g. Anonymous, 2008). The randomization list was held by the senior investigator outside the treatment team. The placebo also was increased in the same way. Drugs were dispensed in identical-appearing capsules. Medication continued for 10 days. The treatment received was concealed from staff and evaluators. No other psychotropic medication was prescribed during the study period.

The primary efficacy variable was the scores on the PANSS (Positive and Negative Syndrome Scale) (Kay *et al*., 1986) subscale for verbal hallucinosis, which ranges from 1 to 7, 7 being the most severe. Response was defined *a priori* as at least a 50% improvement from baseline to end point. Secondarily, we assessed the proportion of responders at endpoint rated as very much improved (score = 1) or much improved (score = 2) compared to baseline on the Clinical Global Impression (CGI) global improvement scale. Side effects were recorded by spontaneous reports. The responder analysis was conducted by using chi-square (χ^2) and ANOVA according to Glantz (1999).

RESULTS

The patients studied were characterized by auditory verbal hallucinosis, delusion and an affect of fear and alarm. One patient who took Depakine-Chrono left the study earlier than 10 days, without a record of why he decided to quit. The groups did not differ in age, duration of abusing by alcohol or average daily consumption of ethanol (Table 1). Scores on auditory hallucinosis prior to treatment commencing were similar in both groups (Table 2).

Depakine-Chrono was superior to placebo in the rating for verbal hallucinosis of the PANSS scale (Table 2). By study end 73.68% taking Depakine-Chrono (14 of 19) and 26.31% of patients taking placebo (5 of 20) were deemed unequivocal responders: they had CGI improvement scores indicating 'much' or 'very much' improved compared to pretreatment ($\chi^2 = 8.18$, df = 1, $P < 0.001$).

Depakine-Chrono was generally well tolerated. No patient discontinued the study early because of adverse effects of the drug.

DISCUSSION

Our findings suggest that the anticonvulsant divalproex sodium may be a safe and efficacious alternative to benzodiazepines for the treatment to alcohol withdrawal. It may be an advantageous alternative for outpatient detoxification, as it has no abuse potential, pharmacologic synergy with alcohol or substantial cognitive or psychomotor side effects (Longo *et al*., 2002).

An experimental and clinico-pharmacological study of sodium valproate, a GABA-ergic drug, was conducted to elucidate the role of γ-aminobutyric acid in the mechanisms responsible for affective disturbances, in particular for anxiety. A tranquilizing effect of the drug, comparable to the action of diazepam, was established in a conflict situation model in experimental animals. The authors showed a distinct tranquilizing action of valproate in patients suffering from anxiety. This action was not accompanied by signs of muscle relaxation, ataxia or the somnolence characteristic of tranquilizers of the benzodiazepine series. The presence of tranquilizing properties in sodium valproate corroborates the suggestion of a relationship between the GABA system and anxiety (Raevskii *et al*., 1985).

Evidence supporting the role of a dysfunctional GABA system has resulted from clinical experience with the benzodiazepines, as well as subsequent determination of the mechanism of action, genetic engineering and neuroimaging studies of the GABA receptor. The major part of the results suggests a relative deficiency in GABA neurotransmission, which can be augmented by agents acting for different components of the GABA system. Agents such as the benzodiazepines, neuroactive steroids and barbiturates function as direct GABA agonists. Valproate, gabapentin, pregabalin and vigabatrin increase brain GABA levels or neurotransmission at least in part by targeting the metabolic pathways of GABA. Tiagabine selectively increases synaptic GABA availability by blocking the reuptake of GABA via transporter inhibition. Evidence exists, to a greater or lesser extent, that all these agents possess anxiolytic properties, as would be expected by their mechanisms of action (Nemeroff, 2003). Valproic acid is a branched chain fatty acid that was originally developed for the treatment of epilepsy. In addition to its anticonvulsant activity, valproic acid has demonstrated anxiolytic, mood-stabilizing, antimigraine and antinociceptive effects (i.e. reducing sensitivity to painful stimuli) and has been evaluated in the management of various other disorders, particularly psychiatric conditions. These activities appear to be mediated, at least in part, by the effects of valproic acid on GABA-mediated neurotransmission. Valproic acid

Table 1. Social-demographic and clinical characteristics of study patients

	Placebo ($n = 20$)	Depakine-Chrono ($n = 20$)
Age (mean ± SD years)	41.0 ± 9.3	42.0 ± 9.0
Education to university level	3	2
Marital status		
Single	2	2
Married	17	16
Dissolved	1	2
In employment	3	2
Duration of alcohol abuse (mean ± SD years)	10.0 ± 6.0	11.0 ± 6.5
Average daily amount of ethanol (g ethanol)	200–300	200—300

Note: Differences between groups are not significant.

Table 2. Mean scores on the verbal hallucinosis subscale of PANSS during treatment

	Treatment group		
	Depakine-Chrono	Placebo	*P*
Intention to treat ($n = 40$)	$n = 20$	$n = 20$	
Mean scores on the verbal hallucinosis subscale of PANSS at start of the study (day 0)	6.0 ± 0.5	5.9 ± 0.6	NS
Completers $n = 39$	$N = 19$	$N = 20$	
Mean scores on the verbal hallucinosis subscale of PANSS at start of the study (day 0)	6.0 ± 2.3	5.9 ± 0.6	NS
Mean scores on the verbal hallucinosis subscale of PANSS at day 10	2.0 ± 0.9	5.0 ± 1.4	0.001

Note: NS = not significant.

increases CNS concentrations of GABA, possibly by increasing its synthesis and/or inhibiting cell firing induced by *N*-methyl-D-aspartate, and by exerting a direct neuronal membrane depressant effect via modulation of sodium and potassium conductance. Valproic acid is generally well tolerated, does not induce hepatic drug metabolism and has a low propensity for interactions with psychotropic agents. However, as has been observed with several other antiepileptic drugs, it is teratogenic and can cause elevated hepatic enzyme levels and rare fatal hepatotoxicity. Weight gain and alopecia are relatively common (Balfour and Bryson, 1994).

A general hypothesis of ethanol potentiation of GABA neurotransmission has been proposed. Ethanol stimulated GABA-receptor-mediated uptake of 36 Cl^- into isolated brain vesicles at pharmacologically relevant concentrations, and this effect was blocked by GABA antagonists (Suzdak *et al*., 1985). When alcohol intake ceased, the stimulating effects of ethanol on the GABA-ergic system were lost. This loss of ethanol's effects occurred also in other tissues containing GABA and glycine, for example the liver, kidney adrenal glands, pituitary gland, skin, spleen, thyroid, pancreas, ovaries and enteric neurons (Zachmann *et al*., 1966). The brain seems to be the primary source of GABA found in plasma, as 99% of the total body GABA content is found in the brain and manipulations of brain GABA are strongly correlated with subsequent changes in plasma GABA (Apud *et al*., 1981). Similar changes could take place in the GABA-ergic system.

Thus, it is possible that an impaired balance between excitatory and inhibitory transmission may contribute to some symptoms of acute alcohol hallucinosis. Depakine may therefore provide the treatment necessary to re-establish the brain's balance between its excitatory and inhibitory pathways.

Among the questions left unanswered by our study, and indeed by all pharmacological studies of acute alcohol hallucinosis in general, is the duration of treatment. Although we know that obtaining the treatment effects requires 10 days, we do not know how long an optimal therapeutic trial should last nor, importantly, how long responders should continue the treatment. It is for this group of patients (acute alcohol hallucinosis) that the advent of a drug with established safety, efficacy and lack of abuse potential is essential.

The results of the recent study may be duplicated in patients which suffering other psychiatric disorders with symptoms of verbal hallucinosis.

LIMITATIONS OF OUR STUDY

Three limitations should be noted. (1) The time of treatment was very short (10 days). (2) We had a small study group and we recommend that these results be replicated in a larger group so that the effect sizes can be estimated more precisely. (3) The possibility of applying these data in women should be explored. Notwithstanding these limitations, this study suggests that Depakine-Chrono is efficacious and well tolerated in the treatment of acute alcohol hallucinosis.

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