Sodium Valproate and Clonazepam for Treatment-Resistant Panic Disorder

Alfonso Ontiveros[1], Rejean Fontaine[2]
[1] University Hospital, Monterrey, Mexico.
[2] Louis H. Lafontaine Hospital, University of Montreal, Montreal, Canada

Submitted: November 6, 1991
Revised: April 7, 1992

Sodium valproate (VA) and clonazepam (CLZ) were combined in the treatment of 4 patients with panic disorders (PD) who were resistant to several antipanic drug treatments. A significant improvement was found in the symptomatology of these patients, but relapses occurred when CLZ dosage was reduced. A potentiation of the GABAergic properties of VA and clonazepam is posulated. This combined treatment could be advantageous for some treatment-resistant PD patients but needs to be studied further.

Key Words: panic disorder, agoraphobia, clonazepam, sodium valproate

L'acide valproique et le clonazepam ont été combinés dans le traitement de 4 patients souffrant de trouble panique avec agoraphobie et qui étaient resistants à plusieurs agents antipanique. L'utilisation de cette combinaison a entrainé une réduction significative de la symptomatologie chez ces patients et nous avons documenté des rechutes lorsque le clonazepam à été réduit. Ainsi, la potentialisation entre des agents agonistes sur le système gabaergique semble être pertinente dans le traitement des cas réfractaires de trouble panique. Des études contrôlées sont nécessaires afin de préciser cette hypothèse.

Mots clés: trouble panique, agoraphobie, clonazepam, sodium valproate

INTRODUCTION

Major progress has been made in the pharmacological treatment of patients with panic disorders (PD) (Levin and Liebowitz 1987). However, 25% to 30% of PD patients treated with imipramine (Zitrin et al 1983) or other tricyclics (Noyes et al 1989), and nearly 25% of PD patients on alprazolam (Noyes et al 1988) or clonazepam (Tesar 1990) remain resistant to treatment. Moreover, a significant number of PD patients are unable to tolerate the drugs' side effects (Noyes et al 1989). Panic disorder is a chronic anxiety disorder with a high prevalence in the general population (3%) (Noyes et al 1990). Thus, in clinical studies it is not uncommon to find PD patients who remain resistant or cannot tolerate the standard antipanic drug treatments. Sodium valproate (VA) and benzodiazepines (BZD) have GABA-ergic properties (Gram and Bentsen 1985), and when combined, a potentiation of GABA-ergic effects can be

Address reprint requests to: Dr. Rejean Fontaine, Research Centre, Louis-H. Lafontaine Hospital, 7331 Hochelaga, Montreal, Quebec, Canada, HlN 3M5.

expected. We are reporting 4 PD patients who remained resistant to several antipanic drugs but were successfully treated with a combined therapy of VA and clonazepam (CLZ).

Case 1

Mr. R., a 30-year-old engineer, had been suffering from panic attacks and agoraphobia for 4 years. After being treated with 18 mg/day bromazepam for 2 months along with alprazolam (maximum of 8 mg/day for 6 months), he still had an average of 2 or more panic attacks per week. After BZD withdrawal, a normal EEG recording was obtained and he was given imipramine. He was unable to take more than 100 mg/day of imipramine due to drug overstimulation, more panic attacks and agoraphobic behavior. Imipramine was discontinued and CLZ was started. Clonazepam dosage was increased to 6 mg/day, but there was still no improvement even after 8 weeks of treatment. He had several panic attacks accompanied with the usual symptoms each month, causing him to be nearly housebound. When 25 mg of clomipramine was added, he again presented more panic attacks and overstimulation. Since he refused to take monoamine-oxidase inhibitors, we decided to combine CLZ with VA. VA dosage was increased slowly to 2000 mg/day (serum levels 639 μ mol/L). After 4 weeks of treatment he reported a great improvement of his panic attacks. He remained without panic attacks for a 4-month period; however, when CLZ was decreased to 1.5 mg/day he had a relapse. He regained his previously improved state when CLZ dosage was increased to 3 mg/day. Later, he complained of hair loss but preferred to continue VA treatment. A few months later, VA was decreased to 1500 mg per day without any relapse.

Case 2

Ms. M., a 25-year-old undergraduate student, had been suffering from panic attacks and agoraphobia since her adolescence. She had been unsuccessfully treated with behavioral therapy and imipramine. During the 6-month period prior to her visit, she had suffered 5 panic attacks per week. The symptoms were so severe that she was unable to leave home alone. Her EEG recording was normal. No improvement was seen when treated with 4 mg/day alprazolam for 2 months, followed by 4 mg/day CLZ for 6 weeks. Further dosage increases were not permitted due to memory disturbances. Sodium valproate was then added to the CLZ treatment. VA dosage was gradually increased to 1250 mg/day (serum levels 600 μ mol/L). After 6 weeks of treatment, the severe panic attacks had subsided, with an improvement in her agoraphobic behavior as well. However, upon decreasing CLZ to 2 mg, the panic attacks reappeared within a week. Thus, we increased CLZ to 4 mg daily. She is still doing very well after one year on a combined treatment, experiencing an occasional minor panic attack from time to time. Her phobic avoidance has shown a marked improvement as well.

Case 3

Mr. G., a 35-year-old worker, had been suffering from panic attacks and agoraphobia for at least 5 years. He was no longer able to work and had been confined to his home for 3 years. Mr. G. had been previously treated with alprazolam 10 mg/day for over a year, and had been undergoing behavioral therapy for 8 months with no significant improvement. He continued to have an average of 3-5 panic attacks per week, and was markedly agoraphobic. His EEG and MRI ratings were normal. We prescribed CLZ and dosage was increased slowly to 4 mg/day. Since he reported only a modest improvement with some drowsiness during the day even after 4 weeks, imipramine was added to his treatment. After receiving 250 mg/day imipramine combined with CLZ for 3 months, he had several side effects along with one or two panic attacks per month, with no improvement in his avoidance behavior. Although imipramine was replaced with desipramine, there was no improvement in side effects or efficacy. Therefore, we discontinued the tricyclic treatment and offered him VA 1500 mg/day (serum levels 671 μ mol/L). His panic attacks were completely blocked. However, during the first 2 months of treatment, he experienced some adverse reactions such as heartburn and feeling bloated after meals. Later, when CLZ dosage was slowly decreased to 2 mg/day, he had a relapse. After 2 years on a combined treatment of CLZ 4 mg and VA 750 mg daily, he remains free of panic attacks.

Case 4

Mr. L. is a 27-year-old waiter. He had been unemployed for more than 3 years as a result of his panic attacks and agoraphobia. He had a history of alcohol abuse and had been hospitalized for BZD addiction (lorazepam and alprazolam). He had tried several drug treatments (imipramine, phenelzine, CLZ) with only a slight improvement in his condition. When he first visited us, he was having 3 panic attacks a day. A normal EEG recording was obtained after which we began treatment with VA 250 mg b.i.d. and CLZ 1.5 mg/day. The following month, VA dosage was adjusted to 2000 mg/day (serum levels 577 μ mol/L) and CLZ was increased to 6 mg/day. On this dosage he reported a marked improvement, having an average of 1-2 mild panic attacks per month. Three months later he was able to return to work as a waiter. Clonazepam dosage was slowly decreased during a 3-month period, but he remained on 2 mg/day since a greater decrease provoked a return of his panic attacks. He reported a slight hair loss as a side

effect. After more than 2 years on VA and CLZ treatment he is still doing very well.

DISCUSSION

All our PD patients were resistant to different kinds of standard antipanic-drug treatments. The concept of drug-resistance in panic disorder is not well established but is commonly used in daily practice. From a research viewpoint, drug-resistance can be defined as less than 50% improvement in frequency and severity of panic attacks after 6 weeks of adequate pharmacological treatment. These cases were all drug resistant, had a normal EEG recording, and an epileptic disorder was ruled out. An excellent response to a combined treatment of VA and CLZ was observed in all these patients. Since CLZ withdrawal provoked a recurrence of panic attacks, it could postulate that CLZ potentiation with VA is possible, at least during the most acute phase of illness.

Although some patients experienced adverse effects such as VA gastric symptoms or hair loss, they preferred to continue treatment nonetheless. In 2 cases, VA was gradually decreased and subsequently stopped without any relapse, whereas in 2 others, a dosage reduction of 500 mg (case 2 and 3) had triggered a relapse. In addition, the potentiation effect of VA occurred gradually over a 3-to 4-week period.

Studies indicate that VA increases GABA transmission via different mechanisms of action (Lloyd and Morselli 1987), and decreases GABA destruction by inhibiting GABA-transaminase and aldehydeshydrogenase enzymes (Fowler et al 1975). Also, VA exerts an effect on GABA synthesis by stimulating the glutamate acid decarboxylase enzyme (Loscher and Frey 1977). It has also been postulated that VA increases selectively the post-synaptic GABA response (Macdonald and Bergey 1979). However, VA does not seem to act at the BZD link site in the GABA receptor complex (Ticku and Davis 1981). Therefore, it should be postulated that when CLZ and VA are combined in treatment, a potentiation of their GABA-ergic properties via different mechanisms of action occurs. An increase in the GABA-transmission could account for the antipanic response observed in our PD patients. Furthermore, studies have reported VA antipanic properties (Primeau and Fontaine 1988; Primeau et al 1990). The addition of VA to CLZ treatment seems to be advantageous for some treatment-resistant PD patients and deserves to be studied further.

REFERENCES

Fowler LJ, Beckford J, John RR (1975) The analysis of the kinetics of the inhibition of rabbit brain aminobutyrate aminotransferase by sodium n-dipropylacetate and some other simple carboxylic acids. *Biochem Pharmacol* **24**:1267-1270.

Gram K, Bentsen KD (1985) Valproate: an update review. *Acta Neurol Scand* **72**:129-139.

Levin AP, Liebowitz MR (1987) Drug treatment of phobias. Efficacy and optimum use. *Drugs* **34**:504-514.

Lloyd KG, Morselli PL (1987) Psychopharmacology of GABAergic drugs. In: *The Third Generation of Progress.* New York: Raven Press, pp 183-195.

Loscher W, Frey HH (1977) Effect of convulsant and anticonvulsant agents on level and metabolism of gamma-aminobutyric acid in mouse brain. Naunyn Schmiedebergs *Arch Pharmacol* **296**:263-265.

Macdonald RL, Bergey GK (1979) Valproic acid augments GABA-mediated postsynaptic inhibition in cultured mammalian neurons. *Brain Res* **170**:558-562.

Noyes R, DuPont RL, Pecknold JC, Riskin A, Reuben RT, Swenson RP, Ballenger JC, Burrows JD (1988) Alprazolam in panic disorder and agoraphobia: results from a multicenter trial. 11. Patient acceptance, side effects, and safety. *Arch Gen Psychiatry* **45**:423-428.

Noyes R, Garvey MJ, Cook BL, Samuelson L (1989) Problems with tricyclic antidepressant use in patients with panic disorder or agoraphobia: result of a naturalistic follow-up study. *J Clin Psychiatry* **50**:163-169.

Noyes R, Reich J, Christiansen J, Suelzer M, Psohl B, Coryell WA (1990) Outcome of panic disorder. Relationship to diagnostic subtypes and comorbidity. *Arch Gen Psychiatry* **47**:809-818.

Primeau F, Fontaine R (1988) GABAergic agents and panic disorder. *Biol Psychiatry* **24**:941-960.

Primeau F, Fontaine R, Beauclaire L (1990) Valproic acid and panic disorder. *Can J Psychiatry* **35**:248-250.

Tesar GE (1990) High-Potency benzodiazepines for short-term management of panic disorder: The U.S. experience. *J Clin Psychiatry* **51**:5.

Ticku MK, Davis WC (1981) Effect of valproic acid on 3H-diazepam and 3H-dihydropicrotoxin binding sites at the benzodiazepine-GABA receptor-ionophore complex. *Brain Res* **223**:218-222.

Zitrin CM, Klein DF, Woerner MG, Ross DC (1983) Treatment of phobias: 1. Comparison of imipramine hydrochloride and placebo. *Arch Gen Psychiatry* **40**:125-138.