Use of Clonazepam in Mania

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ABSTRACT. A combination clonazepam and psychotropic drugs was used to treat 21 manic patients. The symptoms of two patients who received a high daily dose of clonazepam (8-12 mg) dramatically improved. However, the symptoms of the other 19 patients who received a low daily dose of clonazepam (0.5-3 mg) did not improve. High daily doses of clonazepam have a rapid onset of action and show severe side effects. Therefore, we advocate clonazepam should at this time be considered only as a treatment alternative in patients nonresponsive to conventional therapy and should be used in a high daily dose in combination with other psychotropic drugs.

Key words: clonazepam — mania — antimanic effect

Many different psychiatric psychotherapeutic agents have been employed successfully in the treatment of acute mania, including lithium and antipsychotic drugs. Lithium is the first choice for mania. Conventional therapy for manic episodes includes the use of an antipsychotic drug combined with lithium. The antipsychotic drug is used for initial control of the manic episode because lithium has a slow onset of action with two to three weeks needed for full effectiveness. The dose of the antipsychotic drug needed may be high and most patients can be controlled with this approach. However high doses of antipsychotic drug cause many side effects including parkinsonism, tardive dyskinesia and akathisia. Clonazepam, a potent benzodiazepine used primarily as an anticonvulsant[1], has been reported as safe and rapidly effective in the control of manic agitation in combination with other agents.[2-5] The intent of this paper is to discuss when clonazepam should be used for the treatment of mania.

METHODS AND RESULTS

We reviewed retrospectively the records of 96 patients who had received clonazepam for psychiatric (nonseizure) indication in 1996. Of these 96 patients, 21 (12 females and 9 males) received clonazepam for mania. The mean age was 49.8 years (range, 21 to 72 years). Five of the 21 suffered from severe mania and the remainder had hypomania. Diagnosis is used by DSM-III-R criteria.[6]

In all cases, physicians added clonazepam to the conventional regimen of drugs (lithium, carbamazepine, antipsychotic drugs). Nineteen patients received

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a low daily dose of clonazepam, the average low daily dose of clonazepam being 1.58 mg (range, 0.5 mg to 3 mg). Two severe manic patients received a high daily dose of clonazepam (8 mg and 12 mg). The group with low daily dose of clonazepam showed no reduction in manic symptomatology within four weeks. In two patients with high dose treatment all manic symptoms were dramatically reduced within a few days.

The 19 patients with low dose treatment showed no side effects. The two patients with high dose treatment experienced severe drowsiness. Clonazepam was decreased and severe drowsiness was immediately decreased.

Case: Ms. A, a 25-year-old married woman, had a history of manic episodes at 18 years old. When she was 23 years old, she suffered from systemic lupus erythematosus. She was brought to our hospital by her family subsequent to an episode of wild behavior. Her symptoms included an expansive and irritable mood, decreased sleep and appetite, motor overactivity, abusive language, and an act of violence. She was admitted and initially received lithium 600 mg/day and levomepromazine 125 mg/day, which were ineffective in controlling her symptoms during the first three weeks. Clonazepam 12 mg/day was added to the lithium and levomepromazine. Within four days we noted a dramatic improvement in her symptoms. Because of a side effect, severe drowsiness, the clonazepam and levomepromazine were immediately decreased, clonazepam to 1.5 mg/day and levomepromazine to 25 mg/day within six days. She did not have a relapse in over five weeks and was subsequently discharged.

DISCUSSION

Clonazepam is a 5-(2-chlorophenyl)-1, 3-dihydro-7-nitro-2H-1, 4-benzodiazepine-2-one with a half-life of 18 to 50 hours and a maximum blood level occurring within one to two hours after a single oral dose. The drug is mainly excreted through urinary route. It has been prescribed for seizure disorders in the United States since 1976 and in Japan since 1981.

Chouinard *et al* first reported the antimanic effect of clonazepam in a double-blind crossover study.[2] They found a combination of clonazepam (mean daily dose, 10.4 mg) and haloperidol to have a rapid onset of action and to be highly sedating. Other investigators have also reported that a high daily dose of clonazepam with lithium, carbamazepine and antipsychotic drugs reduced manic symptoms.[2–7]

The results of this study also show that the combination of a high dose of clonazepam and psychotropic drugs is effective for acute mania but such a dose results in severe drowsiness.

Bradwejn *et al* reported on the antimanic effect of clonazepam in a double-blind study.[8] Treatment with clonazepam alone did not reduce manic symptoms. Clonazepam therefore is the therapeutic adjunct to acute mania.

However, the mechanism of its antimanic action has not yet been clearly explained. With a high affinity for central benzodiazepine receptors, clonazepam is a facilitator of the γ-aminobutyric acid system[9], and also increases central synthesis of serotonin[10] dopamine[11] and noradrenaline[11], a combination of effects that may offer antimanic action.

The use of clonazepam for mania raises a few concerns. In acute mania, high doses that cause several side effects including drowsiness, ataxia, behavior change and cyclic coma[1)] are needed. Dorevitch reported that an 8 mg daily dose of clonazepam induced mania.[12)]

We suggest that clonazepam should at this time be considered only as an alternative treatment in patients nonresponsive to conventional therapy and should be used in a high daily dose in combination with other psychotropic drugs.

REFERENCES

1) Browne TR : Clonazepam. N Engl J Med **299** : 812-816, 1978
2) Chouinard G, Young SN, Annable L : Antimanic effect of clonazepam. Biol Psychiatry **18** : 451-466, 1983
3) Freinhar JP, Alvarez WA : Clonazepam : A novel therapeutic adjunct. Int J Psychiatry Med **15** : 321-328, 1985-86
4) Edwards R, Stephenson U, Flewett T : Clonazepam in acute mania. Aust NZ J Psychiatry **25** : 238-242, 1991
5) Gouliaev G, Licht RW, Vestergaard P, Merider L, Lund H, Bjerre L : Treatment of manic episodes. Acta Psychiatr Scand **93** : 119-124, 1994
6) American Psychiatric Association : Diagnostic and Statistical Manual of Mental Disorders 3rd, revised. Washington, DC, American Psychiatric Association. 1897, pp111, p228
7) Santos AB, Morton WA : More on clonazepam in manic agitation. J Clin Psychopharmacol **7** : 439-440, 1987
8) Bradwejn J, Shriqui C, Koszycki D, Meterissan G : Double-blind comparison of the effects of clonazepam and lorazepam in acute mania. J Clin Psychopharmacol **10** : 403 -408, 1990
9) Jenner P, Chadwick D, Reynolds EH, Marsden CD : Clonazepam-induced changes in 5 -HT metabolism in animal and man. J Pharm Pharmacol **27** (Suppl 2) : 1-28, 1975
10) Jenner P, Chadwick D, Reynolds EH, Marsden CD : Altered 5-HT metabolism with clonazepam, diazepam and diphenylhydantoin. J Pharm Pharmacol **27** : 707-710, 1975
11) Fennessy MR, Lee JR : The effect of benzodiazepines on brain amines of the mouse. Arch Int Pharmacodyn Ther **197** : 37-44, 1972
12) Dorevitch A : Mania associated with clonazepam. DICP **25** : 938-939, 1991