Clomipramine Treatment of Panic Disorder: Pros and Cons

Laszlo A. Papp, M.D., Franklin R. Schneier, M.D., Abby J. Fyer, M.D., Michael R. Liebowitz, M.D., Jack M. Gorman, M.D., Jeremy D. Coplan, M.D., Raphael Campeas, M.D., Brian A. Fallon, M.D., and Donald F. Klein, M.D.

Background: Controlled trials suggest that clomipramine may be a highly effective antipanic drug. Lowering the starting dose may alleviate troublesome initial side effects and increase acceptability and compliance.

Method: Fifty-eight patients with DSM-III-R panic disorder with or without agoraphobia underwent 13 weeks of clomipramine treatment. Starting at 10 mg/day, the dose was gradually increased to a mean dose of 97 mg/day.

Results: While completers showed highly significant improvement, the benefits were severely limited by a high dropout rate due to adverse reactions occurring mostly during the first 2 weeks of treatment.

Conclusion: Given the alternatives, clomipramine should not be used as a first-line antipanic medication.

(J Clin Psychiatry 1997;58:423–425)

Received Feb. 11, 1997; accepted June 23, 1997. From the New York State Psychiatric Institute; the Department of Psychiatry, College of Physicians and Surgeons, Columbia University; the Freedom From Fear Clinic, Staten Island; and the Phobia, Anxiety and Stress Disorders Clinic at Hillside Hospital, New York, N.Y.

Supported in part by an educational grant from Ciba-Geigy Pharmaceuticals.

Reprint requests to: Laszlo A. Papp, M.D., New York State Psychiatric Institute, 722 West 168th Street, New York, NY 10032.

Growing evidence from controlled studies[1–5] and open trials[6–10] suggests efficacy of the predominantly serotonergic tricyclic antidepressant clomipramine for treatment of panic disorder and agoraphobia with panic attacks. Although treatment with standard antidepressant doses of clomipramine (150–250 mg/day) may be limited by sedation and other adverse effects, several controlled trials have reported effective panic blockade at clomipramine doses of 100 mg/day or less.[3,6,7]

High rates of early dropouts due to adverse effects seem to be the most important factor limiting the use of clomipramine. Fahy et al.,[3] using a 25-mg twice-a-day starting dose, reported a dropout rate of 30% in the first 3 weeks. Johnston et al.,[4] using a 25-mg/day starting dose in a study of agoraphobic women, reported a 58% dropout rate. Clomipramine dropout rates exceeded placebo dropout rates in both studies. It is unclear whether use of a lower starting dose would improve the acceptability of clomipramine.

The objective of the current study was to assess predictors of acceptability and efficacy of clomipramine in the treatment of panic disorder, when clomipramine is initiated at an even lower dosage (10 mg/day) than in previous studies.

METHOD

Subjects presented for outpatient treatment to two participating anxiety disorders clinics (Sites 1 and 2). Subjects had to be 18–65 years of age, speak fluent English (at Site 1), or English or Spanish (at Site 2), meet DSM-III-R criteria for panic disorder with or without agoraphobia by Structured Clinical Interview for DSM-III-R, Upjohn version,[11] and report at least one panic attack during each of the 4 weeks prior to study entry. They had to be without serious medical problems, current major depression or obsessive-compulsive disorder, alcohol or drug abuse in the past 6 months, and history of bipolar disorder or psychosis. Subjects were free of antidepressant, neuroleptic, or investigational medications for at least 1 month prior to study entry and were free of all other psychoactive medications for at least 2 weeks prior to study entry. All eligible subjects signed informed consent to participate.

To maximize patient acceptability of clomipramine, dosage was initiated at 10 mg at bedtime and raised slowly (to 20 mg/day after 4 days, then by 10 mg at 1- to 2-week intervals up to 80 mg after 8 weeks). After 9 weeks of treatment, nonresponders' daily dosage could be gradually raised as tolerated to a maximum of 250 mg. Dosage could be lowered or maintained for patients who had adverse effects. Patients were treated for up to 13 weeks. For a subset of 11 patients who tolerated the initial dosage well, the level was escalated more rapidly, resulting in daily dosage of 100–225 mg after 8 weeks.

Patients were seen by psychiatrists weekly for assessment and medication adjustment. Patients recorded panic attacks and anticipatory anxiety daily on a diary form, which was reviewed at each visit. Outcome was assessed with the clinician-rated Clinical Global Impressions scale[12] and the Panic and Phobic Disorders Scale (PPDS),[13] rated separately by clinician and patient. Patients also completed the SCL-90[14] at each visit, and clinicians rated the 24-item Hamilton Rating Scale for Depression (HAM-D)[15] at baseline and at Week 13. Adverse effects were elicited in an open-ended fashion, and severity was recorded as mild (no impairment or significant distress), moderate (some impairment or significant distress), or severe (severe impairment or danger). Spanish-speaking patients were assessed in Spanish by bilingual clinicians and given Spanish versions of the self-rating instruments.

Patients were considered "evaluable" if they completed at least 6 weeks of treatment. Patients who completed less than 6 weeks of treatment were considered "dropouts." Patients who were panic-free for at least the last 2 weeks of the trial were considered "responders." Responders who also received a score of 1 (not ill) or 2 (minimally ill) on the clinician PPDS Overall Severity Scale at the last week of the trial were considered "remitters."

For evaluable patients who completed less than 13 weeks of treatment, last observations were carried forward. Student t tests were used to compare mean scores on number of panic attacks in the past week, PPDS Severity scales, SCL-90 subscales, and HAM-D scores for Weeks 0 versus 13. Baseline scores of dropouts versus evaluables and remitters versus nonremitters were compared by two-tailed t tests, chi-square tests, and Fisher's exact tests, as appropriate. Mean values are accompanied by standard deviation.

RESULTS

Fifty-eight patients entered the study, including 11 (19%) with panic disorder without agoraphobia and 47 (81%) with panic disorder with agoraphobia. Thirty-nine patients (67%) were female. Site 1 entered 25 patients (43%), and Site 2 entered 33 patients (57%). At Site 2, 15 patients were primarily Spanish speaking; the remainder of study patients were English speaking. All 11 subjects without agoraphobia were at Site 2. Sites did not differ in sex distribution. Mean age was 38.7 ± 10.7 years (range, 20–65).

Thirty-two patients (55%) completed at least 6 weeks of protocol treatment and were considered evaluable. Fourteen patients (24%) were known to have dropped out owing to adverse effects: 10 during the first week, and 4 over the next 4 weeks. The main adverse effects responsible for dropout included increased fear, anxiety, panic, or agitation (N = 9); skin rash or urticaria (N = 3); and insomnia (N = 2). There were 12 other dropouts: 2 patients decided not to start medication, 2 were removed for administrative reasons, and 8 were lost to follow-up. Dropouts (N = 26) differed significantly from evaluable patients (N = 32) at baseline in having fewer total panic attacks in past week (5.7 ± 6.8 vs. 10.2 ± 9.0; $t = 2.1$, $df = 56$, $p < .05$); fewer situational panic attacks in past week (1.0 ± 1.4 vs. 3.0 ± 3.8; $t = 2.6$, $df = 56$, $p < .01$); greater severity of patient-rated spontaneous panic attacks on the PPDS (4.8 ± 1.1 vs. 4.2 ± 1.3; $t = 2.1$, $df = 53$, $p < .05$); and lower weight (149.9 ± 36.1 vs. 174.2 ± 40.3 lb; $t = 2.4$, $df = 56$, $p < .05$). Post hoc analysis revealed that, independent of gender, the dropout rate was significantly higher among patients who weighed less than 150 lb (68 kg) than among those who weighed more than 150 lb (68% vs. 31%; $\chi^2 = 7.82$, $p < .01$). There were no significant differences between dropouts and evaluable patients on other baseline characteristics. The dropout rate was greater at Site 2 than at Site 1 (58% vs. 28%; $\chi^2 = 5.0$, $p < .05$).

Of the 32 evaluable patients, 18 (56%) were women, and 27 (84%) had agoraphobia. After 13 weeks of treatment, 21 patients (66%) had responded, and 14 (44%) had remitted. Response rates did not differ significantly between sites for either definition of response. By intent-to-treat analysis including all dropouts as nonresponders, response rate was 36% and remission rate was 24%.

On the clinician CGI Change scale at Week 13, 19 evaluable patients (59%) were rated markedly improved; 8 (25%) moderately improved; and 5 (16%) minimally improved, unimproved, or minimally worse. Clinician and patient Change ratings on each PPDS item showed improvement in phobic avoidance and anticipatory anxiety occurring later than improvement in spontaneous panic attacks. Patient PPDS Change scores were generally in close agreement with clinician ratings. There was also significant improvement on each subscale of the SCL-90 at Week 13. Most of the reduction in panic attacks occurred during the first 9 weeks.

Mean daily dosage at Week 9 was 80.6 ± 49.3 mg, and at Week 13 was 96.9 ± 60.4 mg. Distribution of dosages at Week 13 was as follows: < 50 mg (N = 5), 50–99 mg (N = 13), 100–149 mg (N = 7), 150–199 mg (N = 5), 200 mg (N = 1), and 250 mg (N = 1). There was no significant difference between mean dose at Week 13 for remitters (100.0 ± 63.7 mg) and nonremitters (94.3 ± 59.6 mg).

Baseline predictors were examined only for the remitter/nonremitter outcome definition, because it offered the most power to detect significant differences. Compared with nonremitters (N = 18), remitters (N = 14) reported less functional impairment (4.2 ± 0.7 vs. 5.3 ± 1.2; $t = 3.1$, $p < .01$) and less anticipatory anxiety (4.1 ± 1.0 vs. 5.5 ± 1.0; $t = 3.9$, $p < .005$) on the patient PPDS, and less somatization on the SCL-90 (12.1 ± 9.1 vs. 24.2 ± 10.9; $t = 3.4$, $p < .005$).

At each time point examined (Weeks 1, 6, and 13), about half of all patients remaining in the study reported adverse effects of moderate or severe intensity. Insomnia and hyperstimulation/jitteriness were the most common adverse effects early in treatment, and they remained among the most common at Week 13. Moderate or severe constipation, fatigue, and sweating, when present, tended to emerge after the first week of treatment.

DISCUSSION

Clomipramine was highly effective for panic disorder in those patients who could tolerate it. At the end of the trial, 84% (27/32) of the completers were rated markedly or moderately improved. There was, however, a 45% dropout rate with a peak during the first 2 weeks. At least 24% of all patients were known to have dropped out due to adverse effects, and for another 17% who dropped out, adverse effects may have been a factor. Patients weighing less than 150 lb were significantly more likely to drop out, perhaps because the higher per-weight dose was more poorly tolerated. No other consistent predictor of dropout was found. Among those patients who tolerated clomipramine and completed the study, 44% continued to experience at least one moderate or severe adverse effect at Week 13. This study is limited by lack of a placebo control group and lack of direct comparison with another antipanic drug.

The high dropout rate is similar to that reported by others.[3,4] In this study, some form of increased nervousness or agitation was responsible for 79% of the dropouts despite a low 10-mg starting dose. Studies with lower dropout rates permitted adjunctive use of benzodiazepines.[5,6] Use of benzodiazepines might be necessary when initiating treatment with clomipramine, even at lower dosages. The smallest dosage commercially available in the United States, however, is 25 mg.

For those patients who remained in the study, the response rate was high: 66% were panic-free for 2 weeks at Week 13. The large majority of the responders did well at less than 100 mg/day, a finding consistent with prior studies reporting efficacy for low doses of clomipramine in panic disorder.[3,7] Clomipramine differs in this respect from imipramine, which is most effective at daily doses of 200 mg/day or greater.[16] This difference may be due to clomipramine's greater affinity for the 5-HT system compared with other tricyclic antidepressants.

The place of clomipramine within the armamentarium of medications for panic disorder remains somewhat unclear. Modigh et al.[5] have suggested that clomipramine appears superior to imipramine in the treatment of panic disorder, but use of clomipramine for panic disorder has received less attention in the United States than in Europe. Treatment selection between clomipramine, imipramine, and other less serotonergic tricyclic antidepressants, high-potency benzodiazepines, and more recently, serotonin selective reuptake inhibitors (SSRIs) for panic disorder involves a complex equation of short- and long-term efficacy, tolerability, safety, and cost. Future research should examine whether even lower starting doses or temporary adjunctive medication such as benzodiazepines might reduce the problem of early stimulation effects and increase the tolerability of clomipramine. In the absence of this information, and in view of the relative ease of administration of other medications of comparable efficacy, clomipramine should not be recommended as a first-line drug for the pharmacologic management of patients with panic disorder.

Drug names: clomipramine (Anafranil), diazepam (Valium and others), imipramine (Tofranil and others).

REFERENCES

1. Allsopp LF, Cooper GL, Poole PH. Clomipramine and diazepam in the treatment of agoraphobia and simple phobia in general practice. Curr Med Res Opin 1984;9:64–70
2. Cassano GB, Petracca A, Perugi G, et al. Clomipramine for panic disorder, I: the first 10 weeks of a long-term comparison with imipramine. J Affect Disord 1988;14:123–127
3. Fahy TJ, O'Rourke D, Brophy J, et al. The Galway study of panic disorder, I: clomipramine and lofepramine in DSM-III-R panic disorder: a placebo controlled trial. J Affect Disord 1992;25:63–76
4. Johnston DG, Troyer IE, Whitsett SF. Clomipramine treatment of agoraphobic women. Arch Gen Psychiatry 1988;45:453–459
5. Modigh K, Westberg P, Eriksson E. Superiority of clomipramine over imipramine in the treatment of panic disorder: a placebo-controlled trial. J Clin Psychopharmacol 1992;12:251–261
6. Gloger S, Grunhaus L, Birmacher B, et al. Treatment of spontaneous panic attacks with clomipramine. Am J Psychiatry 1981;138:1215–1217
7. Gloger S, Grunhaus L, Gladic D, et al. Panic attacks and agoraphobia: low dose clomipramine treatment. J Clin Psychopharmacol 1989;9:28–32
8. Grunhaus L, Gloger S, Birmacher B. Clomipramine treatment for panic attacks in patients with mitral valve prolapse. J Clin Psychiatry 1984;45: 25–27
9. Judd FK, Burrows GD, Marriott PF, et al. A short-term open trial of clomipramine in the treatment of panic disorder with agoraphobia. Human Psychopharmacology 1991;6:53–60
10. Pecknold JC, McClure DJ, Appeltauer L, et al. Does tryptophan potentiate clomipramine in the treatment of agoraphobic and social phobic patients? Br J Psychiatry 1982;140:484–490
11. Spitzer R, Williams JBW. Structured Clinical Interview for DSM-III, Upjohn Version, Revised. New York, NY: Biometric Research, New York State Psychiatric Institute; 1986
12. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
13. Zitrin CM, Klein DF, Woerner MG, et al. Treatment of phobias, I: comparison of imipramine and placebo. Arch Gen Psychiatry 1983;40: 125–138
14. Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale: preliminary report. Psychopharmacol Bull 1973;9:13–28
15. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56
16. Mavissakalian MR, Perel JM. Imipramine dose-response relationship in panic disorder with agoraphobia. Arch Gen Psychiatry 1989;46:127–131