

Intravenous Clomipramine for Obsessive-Compulsive Disorder Refractory to Oral Clomipramine

A Placebo-Controlled Study

Brian A. Fallon, MD; Michael R. Liebowitz, MD; Raphael Campeas, MD; Franklin R. Schneier, MD; Randall Marshall, MD; Sharon Davies, RN; Debbie Goetz, MS; Donald F. Klein, MD

Background: Uncontrolled reports suggest that intravenous clomipramine hydrochloride may be effective for patients with obsessive-compulsive disorder (OCD) who are nonresponsive to oral clomipramine.

Methods: Fifty-four patients with oral clomipramine-refractory OCD were randomized to receive 14 infusions of either placebo or clomipramine hydrochloride, starting at 25 mg/d and increasing to 250 mg/d. Ratings were conducted double-blind after infusion 14 among 54 patients, single-blind 1 week later among 39 patients, and nonblind 1 month later among 31 patients. Response was based on a Clinical Global Impressions rating of at least "much improved."

Results: Six (21%) of 29 patients randomized to receive intravenous (IV) clomipramine vs 0 of 25 patients given IV placebo were responders after 14 infusions ($df=1$, $P<.02$). Dimensional ratings after infusion 14 revealed significant ($P=.007$) improvement on the National Institute of Mental Health–Obsessive-Compulsive Scale and

the Clinical Global Impressions Scale ($P=.03$), but not the Yale-Brown Obsessive Compulsive Scale. One week later, all dimensional measures of OCD showed significant improvement. At 1 week post-IV, 9 (43%) of 21 patients initially randomized to IV clomipramine and treated subsequently with oral clomipramine were responders, whereas 0 of 18 patients initially randomized to receive IV placebo and treated subsequently with several days of open-label IV clomipramine responded ($df=1$, $P<.002$). Of the 31 patients assessed 1 month after IV infusion (treatment not controlled), 18 (58.1%) were responders. Intravenous clomipramine treatment was safe with no serious adverse consequences.

Conclusions: Intravenous clomipramine is more effective than IV placebo for patients with OCD with a history of inadequate response or intolerance to oral clomipramine. Further study of this promising treatment for refractory OCD is needed.

Arch Gen Psychiatry. 1998;55:918-924

ALTHOUGH controlled studies have demonstrated the superiority of serotonin reuptake inhibitors (SRIs) over placebo in reducing symptoms of obsessive-compulsive disorder (OCD), the response is often limited.¹⁻³ Uncontrolled clinical reports have suggested that clomipramine administered intravenously (IV) is effective for OCD⁴⁻⁶ and that it may act more rapidly and be more effective,⁷ even among patients who have not responded to oral clomipramine.⁸⁻¹⁰ Summarizing his experience with 30 patients with OCD treated with IV clomipramine in an open setting, Warneke¹⁰ noted that 14 consecutive weekday IV clomipramine infusions starting at 25 mg and building to 350 mg appeared to be safe, well tolerated, and effective for some oral clomipramine-refractory or oral clomipramine-intolerant patients. In addition, treatment with IV clomipramine appeared to increase patients' tolerance for the adverse

effects associated with subsequent oral clomipramine.

Sallee et al¹¹ successfully used 2 consecutive nightly infusions of clomipramine hydrochloride (75 and 200 mg, respectively) to treat 3 adolescents with depression and OCD. Subsequently Koran et al,¹² in a controlled study of IV vs oral pulse loading of clomipramine, reported that the IV route led to more rapid improvement in OCD. Improvement was noted in 2 of 4 patients who had been nonresponders to adequate previous trials of oral clomipramine. We reported on the open treatment of 5 patients with OCD who were refractory to oral clomipramine using 14 consecutive weekday infusions of IV clomipramine hydrochloride that reached a final dose of 250 mg; 3 patients were responders with a mean Yale-Brown Obsessive Compulsive Scale (Y-BOCS) improvement of 39%.^{13,14}

These promising results suggested that IV clomipramine may be an effective treatment for patients with OCD refrac-

From the Department of Psychiatry, Columbia University and the Division of Therapeutics of the New York State Psychiatric Institute, New York.

PATIENTS AND METHODS

ENTRY CRITERIA

Patients aged 18 to 55 years whose obsessions and compulsions were poorly responsive to oral clomipramine were eligible. The diagnosis of OCD determined by *DSM-III-R*¹⁵ was made by the intake psychiatrist and confirmed by the Y-BOCS¹⁴ Symptom Checklist, a Y-BOCS score of greater than 16, and discussion with the patient's psychiatrist. A patient was considered to be "poorly responsive" or "oral clomipramine refractory" if adequate treatment with oral clomipramine had led to (1) no improvement or only a partial improvement or (2) an inability to tolerate oral clomipramine's side effects, prohibiting an adequate oral clomipramine trial. An "adequate" trial of oral clomipramine was defined as 8 weeks in duration with at least 2 weeks at a dosage of 200 mg/d or more.^{2,16} Patients were recruited by mailings to psychopharmacologists and by notices in the *Obsessive Compulsive Foundation Newsletter*.

Patients retrospectively assessed their prior response to oral clomipramine based on the percentage of reduction in symptoms. Treatment history was then categorized into one of the following: (1) inadequate prior trial due to intolerable oral clomipramine-related side effects; (2) no response ever to oral clomipramine (ie, <20% response); (3) no response to a recent oral clomipramine trial, but a partial response (20%-59%) to an earlier clomipramine trial; (4) partial response (20%-59%) to the most recent oral clomipramine trial; and (5) good response to a recent oral clomipramine trial ($\geq 60\%$) but clinically troublesome OCD remained.

Prior to randomization, patients were off therapy with all centrally active medications for 2 weeks (or 4 weeks if taking fluoxetine hydrochloride). Exclusion criteria included unstable medical disease, evidence of cardiac conduction abnormalities, or a history of seizures. Psychiatric exclusion criteria included comorbid substance abuse, Tourette's disorder, mania, psychosis, or comorbid depression in which depression was severe and preceded the onset of the OCD. Patients with major depression judged secondary to the OCD were entered into the study.

Subjects provided informed written consent. The protocol was approved by the institutional review board of the New York State Psychiatric Institute.

TREATMENT AND RATINGS

Patients were treated on 14 consecutive weekdays either on an outpatient or on an inpatient basis. For most patients, the duration of the acute-phase treatment spanned 18 days (including 2 weekends with no medication). Patients received 14 infusions of 500 mL of 0.9% isotonic sodium chloride solution that contained either placebo or clomipramine under double-blind conditions. The infusions lasted 1 hour. Blood pressure and pulse were recorded every 15 minutes. Cardiac rhythm was monitored by telemetry. The clomipramine dosage schedule was 25 mg \times 2 days, 50 mg \times 1 day, 75 mg \times 1 day, 100 mg \times 1 day, 125 mg \times 1 day, 150 mg \times 1 day, 175 mg \times 1 day, 200 mg \times 1 day, and 250 mg daily for 5 days. Assignment to IV clomipramine or placebo was based on computer-generated random numbers. Syringes filled with either clomipramine or isotonic sodium chloride solution, prepared by a research technician, were given in a blinded fashion to the research physician (B.A.F., R.C., F.R.S., or R.M.).

Independent evaluations by a rater blind to side effects and randomization were conducted at baseline, after infusion 7, and after infusion 14 using the Y-BOCS, the National Institute of Mental Health Obsessive-Compulsive (NIMH-OC) Scale, the Hamilton Depression scale, and the Clinical Global Impressions (CGI) severity and change scales.¹⁷⁻¹⁹ Ratings after infusion 14 were done 24 hours later to allow any postinfusion sedation to wane before the independent evaluator's rating. Patients were considered "CGI responders" if they received a rating of "much improved" or "very much improved." Very much improved indicated virtually complete resolution of obsessive-compulsive symptoms, whereas much improved referred to clinically meaningful improvement such that the patient would want to continue on the same medication. Side effects were monitored using the physician-administered Systemic Assessment for Treatment Emergent Events (SAFTEE) checklist.²⁰ Clomipramine and desmethylclomipramine blood levels were obtained

Continued on next page

tory to oral clomipramine. Alternatively, improvement may have been the result of patient and investigator bias associated with the placebo effect of a dramatic, invasive treatment. Given the paucity of treatment alternatives for patients with refractory OCD and the possibility that IV clomipramine might provide an alternative to neurosurgical intervention, we designed the following placebo-controlled trial.

RESULTS

ACUTE PHASE

Description of Study Sample

The mean (\pm SD) age of the 54 patients was 32.4 \pm 9 years. There were 33 women and 21 men. The average age of

onset was 17.5 \pm 8 years. The mean duration of illness was 14.9 \pm 10 years. No significant differences were found between the 2 treatment groups on the following parameters: age, age of onset, duration of illness, sex distribution, historical oral clomipramine response status (no response [categories 2 + 3]) vs partial or good response [categories 4 + 5]), and baseline scores on the Y-BOCS, the NIMH-OC Scale, and the Hamilton Depression scale.

The baseline Y-BOCS for the sample was 27.9 \pm 5 and the baseline NIMH-OC score was 11.2 \pm 2. Approximately two thirds of our sample were receiving federal Social Security disability payments. In addition to failing to benefit sufficiently from or to tolerate treatment with oral clomipramine, 53 (98%) of the 54 patients had also not responded adequately to at least 1 selective SRI and 21 (38.9%) of the 54 had failed to respond to 2 SRIs. Forty-nine (90.7%) of the 54 patients had received an ad-

prior to each infusion. Drug code was broken after infusion 14 to allow patients who had been randomized to IV placebo to receive IV clomipramine openly.

FOLLOW-UP TREATMENT AND RATINGS

For the last 39 patients, we added the Y-BOCS and CGI assessments at 1 week and 1 month after infusion 14. Follow-up assessments were no longer double-blind ratings as the patient's randomization was broken after the 14th infusion. The 1-week rating after IV infusion was conducted single-blind: the independent rater but not the patient remained blind to the treatment randomization; the patient was instructed not to reveal details about the treatment or side effects. Patients who had received IV clomipramine were encouraged to start oral clomipramine therapy after the last infusion, even if they had not shown any improvement after infusion 14. Our rationale was that the full response might occur 1 or more weeks after the infusions and that maintenance with oral clomipramine appeared to be necessary from our pilot study.¹³ The dosage of oral clomipramine hydrochloride was 150 mg orally every night \times 2 days, 200 mg orally every night \times 2 days, and 250 mg orally every night thereafter. After the 14th infusion, patients who had received IV placebo were entered into the open-label study of IV clomipramine using the same dosing schedule as in the double-blind phase. Therefore, following the double-blind IV infusions, all patients were taking clomipramine, but some were receiving it orally and some IV.

At the nonblind 1-month postinfusion rating, in addition to the Y-BOCS and the CGI change ratings, we asked the patients 2 questions: (1) Has your improvement been sustained over the last month? and (2) Is your current degree of improvement meaningfully more than you had obtained on oral clomipramine in the past? If the patient answered yes to these 2 questions and if their 1-month Y-BOCS score showed a 25% or greater improvement over the baseline score, then the patients were categorized as "overall IV clomipramine responders." To maximize the number of patients assessed in these nonblinded ratings, the 1-month data after IV infusion were analyzed using the results on all patients, ie, those who received IV clomipramine during the double-blind phase and those who

received IV clomipramine in open treatment after the blind was broken. Because patients were encouraged but not obligated to continue taking oral clomipramine during the second to fourth weeks after IV infusion and because most patients had returned to their private psychiatrists, not all patients rated at the 1-month follow-up ratings were necessarily still receiving oral clomipramine.

SIDE EFFECTS

The SAFTEE side-effects checklist was administered to each patient at baseline, infusion 7, and infusion 14. A side effect was considered "emergent and meaningful" if at infusion 14 it was rated as either "moderate" or "severe" and if there was a 2-point increase over the baseline rating.

CLOMIPRAMINE AND DESMETHYLCLOMIPRAMINE BLOOD LEVELS

Clomipramine and desmethylclomipramine levels were drawn 23 hours after the last dose. The assessment of clomipramine and desmethylclomipramine levels was quantitative using gas-liquid chromatography (Hewlett-Packard, Sunnyvale, Calif) fitted with a nitrogen detector. The actual extraction method is a minor modification of the method of Cooper et al,²¹ developed for imipramine and desmethylclomipramine hydrochloride. The fraction of the metabolite recovered is 95% for clomipramine (range, 92%-97%) and 89% for desmethylclomipramine (range, 85%-93%). For clomipramine and desmethylclomipramine, respectively, the coefficients of variation were 3.9% and 4.7% for intraday and 5.1% and 6.0% for interday assessments.

STATISTICAL ANALYSIS

Both χ^2 and Student *t* tests and analyses of covariance (ANCOVA) were used. None of the ANCOVA findings indicated nonhomogeneous variances. A Mann-Whitney *U* test was used to evaluate the frequency of side effects in each treatment group. Our hypothesis is 1-tailed (ie, drug is more effective than placebo) but, to be conservative, we used a 2-tailed test with $P < .05$ to indicate significance.

equate prior oral clomipramine trial and 5 (9.3%) of 54 had been unable to tolerate taking an adequate oral clomipramine trial (although all 5 had a prior poor response to a 12-week trial of at least 1 SRI). Of the sample, 30 (55.6%) of 54 patients reported having either failed to tolerate or to respond adequately to behavior therapy. Because we did not explore this treatment in detail, we cannot be certain that these patients had received adequate behavior therapy.²²

Dropouts

Fifty-four patients entered the study and 51 patients completed the 14 infusions. Three patients (5.6% of the sample) dropped out of the double-blind phase. One reported, after starting the infusions, that he had previously had a manic episode while taking oral clomipra-

mine; this was one of our exclusion criteria, so he was dropped from the study. A second dropout had erroneously received a higher dose of IV clomipramine than indicated in the protocol; she suffered no sequelae. The third patient dropped out for unspecified reasons.

Double-blind Categorical Analysis

Our measure of response was the categorical CGI change score. After infusion 7, no patients showed improvement in OCD. After infusion 14, IV clomipramine was significantly more effective than IV placebo using both an "intent to treat" analysis and a "completer" analysis. Of the 54 randomized patients who started infusions (intent to treat), the percentage of CGI responders after infusion 14 was 20.7% (6/29) for the IV clomipramine patients vs 0% for the 25 IV placebo patients ($\chi^2_1 = 5.8, P < .02$).

Table 1. Double-blind Treatment: Oral Clomipramine-Refractory Patients Who Completed 14 Infusions*

Scale†	Clomipramine Hydrochloride (n = 28)		Placebo (n = 23)		F‡	df	P
	Day 1	Infusion 14	Day 1	Infusion 14			
Y-BOCS, total	28.6 ± 5	25.2 ± 7	27.0 ± 5	26.1 ± 5	2.1	1	.15
NIMH-OC	11.5 ± 2	10.4 ± 2	10.8 ± 1	10.8 ± 1	7.9	1	.007
CGI, severity	5.9 ± 1	5.3 ± 1	5.7 ± 1	5.7 ± 5	4.9	1	.03
HAM-D	13.9 ± 6	12.0 ± 6	14.3 ± 5	12.7 ± 7	0.02	1	.90

*Values are expressed as mean ± SD unless otherwise indicated.

†Y-BOCS indicates Yale-Brown Obsessive Compulsive Scale; NIMH-OC, National Institute of Mental Health Obsessive-Compulsive Scale; CGI, Clinical Global Impressions Scale; and HAM-D, Hamilton Depression scale.

‡Between-group analysis of covariance comparing infusion 14 rating, adjusted for baseline scores.

Table 2. Follow-up of Intravenous Infusion Completers 1 Week Later*

Scale†	Clomipramine Hydrochloride (n = 21)		Placebo (n = 18)		F‡	df	P
	Day 1	1-wk Follow-up	Day 1	1-wk Follow-up			
Y-BOCS, total	28.5 ± 5	22.8 ± 6	27.1 ± 5	25.2 ± 5	5.2	1	.03
NIMH-OC	11.5 ± 2	9.5 ± 2	10.8 ± 1	10.7 ± 1	11.1	1	.002
CGI, severity	5.8 ± 1	5.2 ± 1	5.7 ± 1	5.7 ± 5	9.4	1	.004
HAM-D	13.9 ± 6	10.8 ± 5	14.3 ± 5	10.7 ± 5	0.2	1	.65

*Values are expressed as mean ± SD unless otherwise indicated.

†See footnotes to Table 1 for expansion of scale names.

‡Between-group analysis of variance, adjusted for day 1 preinfusion scores.

Similar findings resulted when considering only the 51 patients who completed 14 infusions (“completers”): 21.4% (6/28) given IV clomipramine were CGI responders vs 0% of the 23 patients receiving IV placebo ($\chi^2_1 = 5.6$, $P = .03$). Six of 28 patients receiving IV clomipramine had at least a 25% improvement in the Y-BOCS vs none of the 23 patients receiving IV placebo. One IV clomipramine responder who sustained improvement in the 1-month follow-up period showed a particularly rapid and dramatic change, with the Y-BOCS score dropping from 34 at baseline to 10 after infusion 14.

Double-blind Dimensional Analysis

Unlike the categorical analysis of the Y-BOCS, the dimensional analysis did not show significant improvement; the mean improvement over baseline was $11\% \pm 24\%$ for clomipramine vs $3\% \pm 9\%$ for placebo (**Table 1**).

FOLLOW-UP PHASE

Single-blind 1-Week Post-IV Ratings

At 1 week after IV infusion, the percentage of CGI responders was 43% (9/21) of the patients who had received IV clomipramine vs none (0/18) of the patients who had received IV placebo (43% vs 0%, $\chi^2_1 = 10.0$, $P = .002$). Using the Y-BOCS improvement of at least 25% as a measure of response, 4 of 21 patients who had received IV clomipramine were responders vs 0 of 18 patients who had

received IV placebo. The sample size is smaller for the 1-week follow-up single-blind ratings than for the day 14 double-blind ratings because these follow-up assessments were added after the study had already begun. On the dimensional measures of change at the 1-week follow-up (**Table 2**), significantly greater improvement was noted across all measures of OCD among patients given IV clomipramine. The mean percentage Y-BOCS improvement over baseline was $17\% \pm 19\%$ for the IV clomipramine group vs $3\% \pm 12\%$ for the placebo group.

Nonblind 1-Month Ratings After IV Infusion

At 1 month after IV infusion, 18 (58.1%) of 31 patients were categorized as “CGI responders,” each of whom also had a Y-BOCS improvement of at least 25%. The mean percentage Y-BOCS improvement over baseline for the 31 patients was $26\% \pm 24\%$. The sample of 31 includes patients who received IV clomipramine in the double-blind phase and in open treatment. Of the 18 CGI responders, 17 met the more rigorous and hypothesis-relevant criteria for “overall IV clomipramine responder.” In other words, more than half (17/31 [55%]) also reported that their improvement was meaningfully greater than when they had taken oral clomipramine previously. Among these 17 patients, the range of Y-BOCS improvement over baseline was 26% to 72%, with a median improvement of 50%. Among the patients who reported no prior or no recent response to oral clomipramine, 9 (56.3%) of 16 were rated overall IV clomipramine responders 1-month after IV infusion (**Table 3**).

Table 3. Prior Oral Clomipramine Treatment Response and Its Relationship to Intravenous Clomipramine Response: Overall Ratings 1 Month After Intravenous Infusion*

Response	Baseline, No. Who Entered	Infusion 14, No. Who Completed	No. (%) of 1-mo Overall† Intravenous Clomipramine Hydrochloride Responders
Inadequate prior oral clomipramine trial	5	3	2/3 (67)
Adequate prior trial			
No response ever to oral clomipramine	27	27	7/14 (50)
No response to recent therapy with clomipramine, but had a partial prior response	5	5	2/2 (100)
Partial (20%-59%)‡ response to most recent oral clomipramine trial	14	14	4/10 (40)
Good (≥60%)‡ response to most recent oral clomipramine trial but still had obsessive-compulsive disorder	3	2	2/2 (100)
Total	54	51	17/31(55)

*Includes all patients: double-blind and open.

†Only 31 of the 51 patients who completed 14 infusions received 1-month ratings. The rating "overall intravenous clomipramine hydrochloride responder" excluded 2 Clinical Global Impression responders who felt that, although their obsessive-compulsive disorder was improved at 1 month, they were not better than when taking oral clomipramine in the past.

‡These percentages are based on the patients' recollections of how much the oral clomipramine improved the obsessive-compulsive disorder.

Table 4. "Emergent and Meaningful" Side Effects Reported at Infusion 14

Side Effect	Clomipramine Hydrochloride, No. (%) (n = 28)	Placebo, No. (%) (n = 23)
Sedation	8 (28.6)	3 (13.0)
Dry mouth	7 (25.0)	5 (21.7)
Constipation	6 (21.4)	2 (8.7)
Dizziness or faintness	3 (10.7)	0 (0)
Sexual dysfunction	3 (10.7)	0 (0)
Muscle twitching	3 (10.7)	1 (4.3)
Abnormal muscle tone/movements	3 (10.7)	0 (0)
Decreased libido	2 (7.1)	0 (0)

Safety and Side Effects

There were no noteworthy cardiac conduction abnormalities or adverse consequences associated with IV clomipramine. Of the 5 patients who had been unable to tolerate oral clomipramine in the past, 2 developed similarly troublesome side effects (urinary retention and jitteriness), while the other 3 completed the 14 clomipramine infusions and subsequently tolerated oral clomipramine.

Using a χ^2 analysis, there was no significant difference in the proportion of patients who reported emergent and meaningful side effects when the clomipramine group and the placebo groups were compared on each of the most common side effects at infusion 14 (Table 4). However, using a Mann-Whitney *U* test to contrast the 2 groups, adding all emergent and meaningful side effects for each person, the IV clomipramine-treated group had significantly more side effects than the placebo-treated group ($U = 228.5$, $P = .02$).

Clomipramine and Desmethylclomipramine Blood Levels and Relationship to Response

Pooling together patients in the open-label and double-blind clomipramine study, we assessed correlations

between serum levels just prior to the last infusion and response at 2 assessment points: at the end of 14 infusions and at 1 week after IV infusion. No significant correlations were found (Table 5).

COMMENT

This controlled study demonstrated the significant superiority of IV clomipramine over placebo at the end of 14 infusions categorically on 2 major outcome measures (CGI and Y-BOCS) and dimensionally on 2 scales (NIMH-OC and CGI-severity), indicating that IV clomipramine is an effective treatment for some patients with OCD who have a history of an inadequate response or intolerance to oral clomipramine. In our oral clomipramine-refractory sample, the degree of reduction in OCD symptoms (5-6 points on the Y-BOCS) by the end of the fourth week of this study (1 week after IV infusion) is the same or better than that obtained after 10 to 12 weeks in many pharmacologic trials of SRIs and is comparable with the results obtained in the multicenter oral Clomipramine Collaborative Study at the end of 4 weeks among serotonin reuptake inhibitor-naïve patients with OCD.¹⁻³ Many patients in the latter trials would not be considered treatment refractory. Examining these IV clomipramine data from a categorical perspective, at the double-blind rating conducted after the 14 infusions, 6 (21%) of the 9 patients receiving IV clomipramine were responders using the criteria of either a CGI rating of at least much improved or a Y-BOCS improvement over baseline of at least 25%. Although lower than the 40% to 60% responder rate seen in OCD pharmacologic trials after 10 to 12 weeks of treatment,² a responder rate of 21% after 3 weeks of IV clomipramine treatment is clinically meaningful because our sample consisted of pharmacologically refractory patients. The absence of any IV placebo responders reflects the severity of the illness in this sample. Because no serious adverse consequences occurred, we conclude that IV clomipramine is not only an effective treatment but also a safe one.

Table 5. Serum Desmethylclomipramine and Clomipramine Levels and Their Ratio Among Patients With Obsessive-Compulsive Disorder Treated With Intravenous Clomipramine*

Serum Levels at End of Intravenous Phase, ng/mL	End of Intravenous Phase		df	P	1 Week After Intravenous Clomipramine Hydrochloride		df	P
	Responders (n = 9)	Nonresponders (n = 36)			Responders (n = 12)	Nonresponders (n = 23)		
Desmethylclomipramine	137.6 ± 51.0	196.8 ± 96.1	43	.08	175.9 ± 107.2	198.3 ± 85.2	33	.50
Clomipramine	134.7 ± 54.0	154.6 ± 75.9	43	.46	140.0 ± 52.3	154.3 ± 72.7	33	.55
Desmethylclomipramine/clomipramine	1.13 ± 0.49	1.52 ± 0.97	43	.25	1.25 ± 0.56	1.47 ± 0.79	33	.39

*Values are expressed as mean ± SD.

Does improvement increase with time? For the IV clomipramine-treated patients, the mean improvement in Y-BOCS scores over baseline was 11% at the end of the infusions, 17% 1 week later, and 26% at the 1-month evaluation. In addition, the percentage of CGI responders to IV clomipramine increased with time: 21% (6/28) in the double-blind rating after infusion 14, 43% (9/21) in the single-blind rating 1 week later, and 58% (18/31) in the open CGI rating 1 month after IV infusion. A similar but less dramatic pattern occurs if one uses a 25% improvement in the Y-BOCS as the response criterion: 21% after infusion 14, 19% 1 week later, and 58% 1 month after IV infusion. Although there was a dimensional improvement in the Y-BOCS scores for the group receiving IV clomipramine between the 14th infusion and the 1-week follow-up rating, the discrepancy at 1 week after IV infusion between the CGI responder rate of 43% and the categorical Y-BOCS responder rate of 19% suggests that there may have been a patient bias toward overstating global improvement on the CGI when the initial treatment randomization was known. Although in general both categorical and dimensional ratings improved further during the 1-month period after IV infusion, we cannot yet conclude that this improvement was due to the IV clomipramine because the follow-up ratings were not done double-blind to treatment randomization and the follow-up treatment was not controlled.

Our reported 1-month response rate after IV infusion may be higher than the actual result because 8 patients were unavailable for follow-up assessments. If we make the conservative assumption that all of these 8 patients were in fact nonresponders, then the adjusted IV clomipramine response would be 18 (46.2%) of 39 ("conservative estimate"). Therefore, we expect that the actual 1-month response rate after IV infusion falls between 46% and 58%.

We know that IV clomipramine is more effective than IV placebo, but we cannot yet be certain that IV clomipramine is more effective than oral clomipramine because the 2 treatments were not directly compared. Although 7 (55%) of 31 accessible patients at 1 month after IV infusion reported that clomipramine administered IV was more effective than their prior experience with oral clomipramine, the reliability of their reports is limited by the effect of recall bias and by their nonblinded status. It is possible (although we believe unlikely, given their treatment history) that a direct controlled comparison of IV clomipramine to

oral clomipramine would not have shown treatment differences.

The hypothesized mechanism for the preferential efficacy of IV clomipramine over oral clomipramine focuses on the greater bioavailability of the more serotonergic parent compound clomipramine vs the more noradrenergic metabolite desmethylclomipramine, as a result of bypassing the first-pass hepatoenteric metabolism through the IV route. Prior studies have noted a significantly lower plasma level of desmethylclomipramine/clomipramine when clomipramine is given by the IV route rather than orally.²³ Comparing our serum results from 45 patients obtained 23 hours after the last IV dose to serum results Mavissakalian et al²⁴ obtained 12 hours after the last oral dose (mean end dose of 239 mg), significant differences were noted in the nanogram per milliliter level (±SD) of desmethylclomipramine (185.0 ± 91.6 vs 379.0 ± 260.6, *df* = 76, *P* < .001) and the ratio of desmethylclomipramine/clomipramine (1.44 ± 0.91 vs 2.57 ± 1.19, *df* = 76, *P* < .001) but not in the level of clomipramine (150.6 ± 71.9 vs 169.9 ± 102.1, *df* = 76, *P* = .20). Although these results indicate that the IV route results in a lower desmethylclomipramine serum level and a lower desmethylclomipramine/clomipramine ratio than the oral route, a direct comparison of our results with the published literature is compromised by the difference in time (23 vs 12 hours) between serum level assessments. Although higher levels of serum clomipramine may be obtained IV than orally, we were not able to demonstrate that in this study. Our study also was not able to demonstrate any statistically significant relationship between clinical response and levels of clomipramine, desmethylclomipramine, or their ratio.

The strengths of this study rest on the placebo-controlled double-blind design and the inclusion of patients who were severely ill and refractory to not only oral clomipramine but many other pharmacotherapies and psychotherapies. The limitations of this study are that the patients receiving IV clomipramine experienced more side effects than the patients receiving IV placebo and so the blind may have been harder to maintain, that the significant dimensional improvement in Y-BOCS scores was not seen until the single-blind assessment 1 week after the IV infusion, and that the follow-up phase was not part of the initial study, resulting in single-blind and non-blind ratings, follow-up treatment that was not uniform among all patients, and a duration of follow-up that extended only 4 weeks after IV infusion.

Liquid clomipramine for IV administration is not Food and Drug Administration approved for use in the United States, although it is available in many European countries and Canada. While this study demonstrated that gradual dosing of IV clomipramine can be administered safely among medically healthy patients with OCD, clinicians are reminded that the safety of IV clomipramine has not been demonstrated among patients with histories of medical or neurologic problems, such as cardiac conduction delay, head trauma, or seizures. Should additional studies support the efficacy of IV clomipramine treatments, then a pharmaceutical company could petition the Food and Drug Administration for approval. In conclusion, intravenous clomipramine is a beneficial alternative treatment for patients with OCD who by history have had either no response or an inadequate response to oral clomipramine. Further study with a longer and controlled follow-up is needed to assess the stability of the response to IV clomipramine and its efficacy compared with a rapidly escalating course of oral clomipramine and other treatment regimens.

Accepted for publication July 1, 1998.

This study was supported by the Orphan Products Division of the Food and Drug Administration. Medication was supplied by Ciba-Geigy Corp, Summit, NJ.

Presented as a New Research Abstract at the 1994 American Psychiatric Association meeting, Philadelphia, Pa.

Reprints: Brian Fallon, MD, New York State Psychiatric Institute, 1051 Riverside Dr, New York, NY 10032 (e-mail: BAFallon@aol.com).

REFERENCES

1. Clomipramine Collaborative Study Group. Clomipramine in the treatment of patients with obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1991;48:730-738.
2. Greist JH, Jefferson JW, Koback KA, Katzelnick DJ, Serlin RC. Efficacy and tolerability of serotonin transport inhibitors in obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1995;52:53-60.
3. Koran LM, McElroy SL, Davidson JRT, Rasmussen SA, Hollander E, Jenike MA. Fluvoxamine vs. clomipramine for obsessive-compulsive disorder: a double-blind comparison. *J Clin Psychopharmacol*. 1996;16:121-129.
4. Capstick N. Chlorimipramine in obsessional states: a pilot study. *Psychosomatics*. 1971;12:332-335.
5. Rack PH. Clomipramine (Anafranil) in the treatment of obsessional states with special reference to the Leyton Obsessional Inventory. *J Int Med Res*. 1973;1:397-402.
6. Walter CS. Clinical impressions on treatment of obsessional states with intravenous clomipramine (Anafranil). *J Int Med Res*. 1973;1:413-416.
7. Koran LK, Faravelli C, Pallanti S. Intravenous clomipramine for OCD [letter]. *J Clin Psychopharmacol*. 1994;14:216-218.
8. Warneke LB. The use of intravenous chlorimipramine in the treatment of obsessive compulsive disorder. *Can J Psychiatry*. 1984;29:135-141.
9. Warneke LB. Intravenous chlorimipramine in the treatment of obsessional disorder in adolescence: case report. *J Clin Psychiatry*. 1985;46:100-103.
10. Warneke LB. Intravenous chlorimipramine therapy in obsessive-compulsive disorder. *Can J Psychiatry*. 1989;34:853-859.
11. Sallee FR, Pollock BG, Perel JM, Ryan ND, Stiller RL. Intravenous pulse loading of clomipramine in adolescents with depression. *Psychopharmacol Bull*. 1989;25:114-118.
12. Koran LM, Sallee FR, Pallanti S. Rapid benefit of intravenous pulse loading of clomipramine in obsessive-compulsive disorder. *Am J Psychiatry*. 1997;154:396-401.
13. Fallon BA, Campeas R, Schneier FR, Hollander E, Feerick J, Hatterer J, Goetz D, Davies S, Liebowitz MR. An open trial of IV clomipramine in 5 treatment refractory patients with OCD. *J Neuropsychiatry Clin Neurosci*. 1992;4:70-75.
14. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger CG, Charney DS. The Yale-Brown Obsessive Compulsive Scale. *Arch Gen Psychiatry*. 1989;46:1006-1011.
15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994:10-72.
16. March JS, Frances A, Carpenter D, Kahn D. The Expert Consensus Guideline Series: treatment of OCD. *J Clin Psychiatry*. 1997;58(suppl 4):27.
17. Murphy DL, Pickar D, Alterman IS. Methods for the quantitative assessment of depressive and manic behavior. In: Burdock EI, Sudilovsky A, Gershon S, eds. *The Behavior of Psychiatric Patients*. New York, NY: Marcel Dekker Inc; 1982:355-392.
18. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62.
19. National Institute of Mental Health. Special feature: rating scales and assessment instruments for use in pediatric psychopharmacology research. *Psychopharmacol Bull*. 1985;21:839-844.
20. Rabkin J, Markowitz J, Ocepek-Welickson K, Wager S. General vs systematic inquiry about emergent clinical events with SAFTEE: implications for clinical research. *J Clin Psychopharmacol*. 1992;12:3-10.
21. Cooper TB, Allen D, Simpson GM. A sensitive GLC method for the determination of imipramine and desmethylimipramine using a nitrogen detector. *Psychopharmacol Commun*. 1975;1:445-454.
22. Goisman RM, Rogers MP, Steketee GS, Warshaw MG, Duneo P, Keller MB. Utilization of behavioral methods in a multicenter anxiety disorders study. *J Clin Psychiatry*. 1993;54:213-218.
23. Thakur AK, Remillard AJ, Meldrum LH, Gorecki DK. Intravenous clomipramine and OCD. *Can J Psychiatry*. 1991;36:521-523.
24. Mavissakalian M, Jones B, Olson S, Perel JM. The relationship of plasma clomipramine and N-desmethylclomipramine to response in obsessive compulsive disorder. *Psychopharmacol Bull*. 1990;26:119-122.