Citalopram Intravenous Infusion in Resistant Obsessive-Compulsive Disorder: An Open Trial

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Background: Treatment with intravenous clomipramine is rapidly effective in some obsessive-compulsive disorder (OCD) patients unresponsive to orally administered serotonin reuptake inhibitors (SRIs). The selective serotonin reuptake inhibitor citalopram is effective for OCD when administered orally. We investigated whether intravenous citalopram would rapidly benefit OCD patients unresponsive to orally administered SRIs.

Method: Thirty-nine adult outpatients participated in a 3-week open-label trial of intravenous citalopram. Eligible patients had moderate-to-severe DSM-IV OCD of ≥ 1 year's duration, a baseline Yale-Brown Obsessive Compulsive Scale (YBOCS) score ≥ 25, and no other active Axis I diagnosis and had failed at least 2 adequate oral SRI trials, excluding citalopram. Intravenous citalopram was administered daily for 21 days, followed by oral citalopram until treatment day 84. Intravenous citalopram was started at 20 mg/day and was increased to 40 to 80 mg/day as tolerated.

Results: Intravenous citalopram was well tolerated even at higher doses (dropout rate = 2.6%). At day 21, 23 (59%) of the 39 patients had YBOCS score decreases of ≥ 25%, of whom 4 had decreases of ≥ 35%. Twenty-seven patients with YBOCS score decreases of ≥ 20% were allowed to continue on treatment with oral citalopram, and by day 84, all had substantial further improvement. All 27 patients also showed significant improvement in several dimensions of quality of life.

Conclusion: Intravenous citalopram was safe and rapidly effective in a group of treatment-resistant OCD patients. The early onset of response suggests a means of accelerating OCD symptom relief and predicting response to oral citalopram treatment. Double-blind, double-dummy, placebo-controlled trials of intravenous versus oral citalopram in patients with treatment-resistant OCD are indicated.

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Many patients with obsessive-compulsive disorder (OCD) have an unsatisfactory response to the standard anti-OCD medications, the serotonin reuptake inhibitors (SRIs), when these are administered orally. The proportion of poorly responsive patients ranges from 20%[1] to 40%.[2–5]

In addition, the response of OCD symptoms to orally administered SRIs is slow. After 4 weeks of clomipramine treatment, mean scores on the Yale-Brown Obsessive Compulsive Scale (YBOCS) have fallen only about 20%.[6,7] A clinically substantial response (a YBOCS decrease of ≥ 35% or a global rating of "much" or "very much" improved) usually takes at least 6 weeks to develop.[6–8] Quantifying "usually" is difficult, since data describing the time course of response in individual OCD patients are scarce. However, in a 3-arm selective serotonin reuptake inhibitor (SSRI) study, only about one third to one half of those who experienced a ≥ 35% decrease in YBOCS score by the end of week 10 did so by the end of week 4, compared with about 50% to 80% who did so by the end of week 6.[9]

Finally, we cannot predict which patient will respond to which SRI or will fail to respond to every SRI, and a treatment trial of 8 to 12 weeks is required to evaluate the response to each drug.[1,8,10]

Small controlled trials[11–13] and case series[14] suggest that intravenous clomipramine is often effective for OCD patients unresponsive to oral SRIs and produces a therapeutic response very rapidly. In view of the imperfect and delayed response to orally administered SRIs and the data concerning intravenous clomipramine in treatment-resistant OCD, we conducted a trial of intravenous administration of the SSRI citalopram. Orally administered

citalopram, in doses of 20, 40, and 60 mg/day, is effective in treating OCD but, like other SRIs, benefits only a limited proportion of OCD patients.[5,9] Intravenous citalopram has been found to be safe and effective in the treatment of major depression.[15,16] We hypothesized that intravenously administered citalopram would be effective for patients resistant to oral SRI treatment and would produce a therapeutic response more quickly than does oral dosing.

METHOD

Patients

We invited into the study all adult patients with treatment-resistant OCD (N = 46) seen at a private psychiatric clinic, the Institute for Neurosciences in Florence, Italy, during the period from August 1999 through July 2000. Thirty-nine patients (85%) accepted. All patients met DSM-IV criteria for OCD, established with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)[17] conducted by a psychiatrist (L.Q. or S.P.) certified for the use of this instrument.

No universally accepted definition of an OCD "nonresponder" or of "treatment-unresponsive," "resistant," or "refractory" OCD exists.[18,19] In the absence of an accepted definition, we defined "treatment-resistant OCD patients" as those who had failed at least 2 adequate (≥ 12-week) trials of oral SRI treatment conducted at our clinic at known effective doses, 1 trial with clomipramine (≥ 150 mg/day) and 1 with another SRI: fluoxetine (≥ 20 mg/day), fluvoxamine (≥ 200 mg/day), sertraline (≥ 150 mg/day), or paroxetine (≥ 40 mg/day) (Table 1). We defined "failure" as achieving a < 35% decrease from baseline in YBOCS score[20] and a score of "minimal improvement" or less on the Clinical Global Impressions-Improvement scale (CGI-I),[21] both rated by a clinician at our clinic. All 39 patients met this definition. The mean ± SD length of the 2 previous failed trials was 19.3 ± 4.6 weeks, during which each patient had been pushed to the maximum tolerated medication dose. No patient had had an adequate trial of behavior therapy.

We excluded potential patients with any of the following conditions: a concurrent DSM-IV Axis I diagnosis of major depressive disorder as indicated by a SCID-I interview and/or a score of > 18 on the 21-item Hamilton Rating Scale for Depression (HAM-D)[22]; schizophrenia or other psychotic syndromes; substance dependence in the last year or substance abuse, including alcohol, within the last 6 months; Tourette's disorder or other tic syndromes; bipolar I disorder; mental disorder due to a general medical condition; serious suicide risk; pregnancy; or nursing of an infant. No cognitive or behavioral psychotherapy was allowed during the intravenous or oral citalopram treatment periods.

After receiving an explanation of the potential risks and benefits of the citalopram treatment and of alternative treatments, each patient gave written informed consent in accordance with the Declaration of Helsinki.

Table 1. Baseline Demographic and Clinical Characteristics of 39 Treatment-Resistant OCD Patients[a]

Characteristic	Value
Age, y (range, 21–43 y)	29.2 ± 6.5
Education level, y	11.6 ± 3.5
Duration of OCD, y	6.1 ± 3.8
YBOCS score	30.3 ± 3.8
HAM-D score	12.7 ± 2.4
CGI score	5.3 ± 0.7
Short Form-36 (quality of life) score	
Physical activity (scale range, 0–20)	5.6 ± 3.2
Role and physical health (scale range, 0–4)	0.8 ± 0.9
Physical pain (scale range, 0–10)[b]	2.1 ± 1.6
General health (scale range, 0–20)	7.4 ± 3.7
Vitality (scale range, 0–20)	6.1 ± 2.8
Social activities (scale range, 0–8)	2.3 ± 2.1
Role and emotional state (scale range, 0–3)	0.6 ± 0.8
Mental health (scale range, 0–25)	7.9 ± 4.2
Previous adequate SSRI trials, N of patients	
Sertraline	15
Fluvoxamine	12
Fluoxetine	10
Paroxetine	9

[a]Values shown as mean ± SD unless otherwise noted. Abbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression, OCD = obsessive-compulsive disorder, SSRI = selective serotonin reuptake inhibitor, YBOCS = Yale-Brown Obsessive Compulsive Scale.
[b]Higher scores suggest lower quality of life.

Study Design

After a 2-week washout period from previous medications, patients began 21 days of open-label, intravenous citalopram infusions, started at 9 a.m. daily in the clinic's day hospital. Fluoxetine was not the preceding trial drug for any patient; thus, residual fluoxetine did not influence the results of the current trial. Citalopram was diluted in 250 cm^3 of physiologic saline solution and infused over 1.5 to 2 hours. Dosing was as follows: 20 mg on days 1 and 2, 40 mg on days 3 through 6, and 60 mg on days 7 through 21. From day 12 onward, the dose could be increased to 80 mg as tolerated if this increase seemed indicated in the investigators' clinical judgment. Patients had to be able to tolerate 40 mg of intravenous citalopram to continue in the study. After the 21 infusions, patients who showed at least minimal response to treatment (≥ 20% decrease in YBOCS score) continued open treatment with oral citalopram until day 84 (9 additional weeks) at the maximum dose received intravenously. Citalopram is not approved in Italy for the treatment of OCD. Therefore, we decided to drop from the study patients with less than a minimal response (< 20% decrease in YBOCS score) in order to treat them with approved medications or with an approved SRI plus risperidone.

From day 22 onward, oral citalopram was administered in divided doses, morning and evening. The mean ± SD maximum daily dose was 68.2 ± 12.7 mg/day,

with a range of 40 to 80 mg/day. During the study period, the only additional psychotropic medication permitted was a benzodiazepine (lorazepam, 1–2 mg daily, or temazepam, 20 mg daily), if needed to control sleep disturbances.

Assessments

At baseline, all patients were assessed with the SCID-I and SCID-II[23] diagnostic interviews, the Yale-Brown Obsessive Compulsive Checklist (YBOC checklist), the YBOCS, the CGI-I and CGI-Severity of Illness scale (CGI-S),[21] the self-administered Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)[24] for assessing quality of life, and the HAM-D. The YBOCS, HAM-D, CGI-I, CGI-S, and Dosage Record and Treatment Emergent Symptoms Scale[21] were administered at each preplanned assessment visit (days 7, 14, and 21 [end of infusions] and days 42, 63, and 84), rating patients' symptoms on average over the last week. Pulse rate and rhythm and blood pressure were monitored regularly before and after each infusion. At day 84, the SF-36 was administered again. Score on the YBOCS was the primary efficacy variable for evaluating OCD symptoms.

Statistical Analysis

Means, standard deviations, and ranges were calculated for all parametric variables. Interrater reliability was ascertained by means of a series of live, shared interviews with independent ratings by the raters (S.P. and L.Q.) and yielded intraclass correlation coefficients of 0.81 for the YBOCS and 0.88 for the HAM-D (Cronbach's α). Student t tests for independent variables, paired t tests, or Pearson rho correlation coefficients were calculated where appropriate to assess the significance of differences between groups, with α set at $p < .05$, 2-tailed. Data were analyzed using an SPSS-PC package (Release 10.0, SPSS, Inc., Chicago, Ill.).

RESULTS

Intravenous Citalopram

The patients' demographic and clinical characteristics are presented in Tables 1 and 2. Of the 39 patients enrolled (21 men, 18 women), 38 (97.4%) completed the 21 intravenous infusions. One patient stopped the trial in the first week because of adverse effects, particularly intolerable nausea, and was shifted to oral treatment with another SSRI.

At the end of the 21-day infusion period, 7 patients were receiving intravenous citalopram, 40 mg/day; 12 patients, 60 mg/day; and 19 patients, 80 mg/day. The mean ± SD maximum citalopram dose received by these 38 patients was 66.3 ± 15.5 mg/day. The 21-day mean daily citalopram dose (i.e., total dose/21) was 54.3 ± 18.5 mg/day.

Table 2. Lifetime Comorbidity of DSM-IV Disorders for 39 Treatment-Resistant Obsessive-Compulsive Disorder Patients

Disorder	N	%
Axis I		
Major depressive disorder	7	17.9
Cyclothymic disorder	2	5.1
Panic disorder	6	15.4
Generalized anxiety disorder	2	5.1
Social phobia	5	12.8
Somatoform disorder	3	7.7
Alcohol abuse	2	5.1
Substance abuse	1	2.6
Axis II		
Avoidant personality disorder	1	2.6
Obsessive-compulsive personality disorder	2	5.1
Passive-aggressive personality disorder[a]	2	5.1
Narcissistic personality disorder	1	2.6

[a]Listed in DSM-IV under "Criteria Sets and Axes Provided for Further Study."

After 21 days of intravenous citalopram, the mean ± SD YBOCS score for the 38 patients who completed the infusion period decreased significantly from 30.2 ± 3.9 at baseline to 22.5 ± 4.0 (N = 38) (paired $t = 12.1$, $df = 37$, $p < .001$). (Table 3 presents the intent-to-treat results, N = 39.) The range for YBOCS scores decreased from 24 to 38 at baseline to 14 to 30 at day 21. The mean decrease in YBOCS score was –7.8 ± 4.0 (range, +2 to –15 points), or, in percentage terms, a mean decrease of –25.3% ± 12.8% (range, +8.0% to –51.7%). Twenty-seven patients experienced a decrease in YBOCS score of ≥ 20%, 23 (59% of the intent-to-treat sample, N = 39) had a decrease of ≥ 25%, and 4 (10%) had a decrease of ≥ 35%. Eighteen patients (46%) were rated much or very much improved on the CGI-I at day 21 compared with their baseline status.

The amelioration of OCD symptoms was also reflected in a mean reduction in CGI-S score of the 38 patients who completed the infusions (mean ± SD at baseline = 5.3 ± 0.7, mean at day 21 = 4.2 ± 0.8; paired t test, $t = 8.1$, $df = 37$, $p < .001$). Depressive symptoms also decreased significantly from a baseline mean HAM-D score of 12.6 ± 2.4 to a day 21 mean of 9.3 ± 2.1 (N = 38; paired t test, $t = 6.7$, $df = 37$, $p < .01$). The decreases in YBOCS and HAM-D scores from baseline to day 21 were not significantly correlated (Pearson rho = 0.144, N = 38, $p > .10$); the percent changes in YBOCS and HAM-D scores were also nonsignificant (Pearson rho = 0.175, N = 38, $p > .10$).

The maximum daily intravenous citalopram dose showed a positive correlation with the reduction in YBOCS score at day 21 that just missed statistical significance (Pearson rho = 0.31, N = 38, $p > .05$ [Pearson rho = 0.32 needed for $p = .05$]).

The most common adverse events, affecting ≥ 20% of patients in the intravenous phase, were dry mouth, somnolence, anxiety, decreased appetite, nausea, delayed

Table 3. Yale-Brown Obsessive Compulsive Scale (YBOCS) Scores (mean ± SD) for the Intent-to-Treat (N = 39) and the Intravenous at Least Minimal Response (N = 27) Groups

Treatment Group	Baseline	Day 7	Day 14	Day 21	Day 42	Day 63	Day 84
Intent to treat	30.3 ± 3.8	29.5 ± 3.2	26.3 ± 4.1	22.7 ± 4.3	21.9 ± 4.4	21.0 ± 4.6	20.2 ± 4.8
At least minimal response	31.4 ± 3.7	29.8 ± 3.5	25.8 ± 4.4	21.6 ± 4.1	20.4 ± 3.9	19.2 ± 3.6	18.0 ± 3.4

Table 4. Emergent Adverse Effects During the Intravenous Citalopram (days 1–21) and Oral Citalopram (days 22–84) Treatment Periods

	Intravenous Citalopram (N = 39)		Oral Citalopram (N = 27)	
Adverse Effect	N	%	N	%
Nausea	10[a]	25.6	4	14.8
Headache	7	17.9	2	7.4
Tremor	5	12.8	0	0
Insomnia	8	20.5	0	0
Somnolence	11	28.2	4	14.8
Anxiety	11	28.2	2	7.4
Asthenia	10	25.6	0	0
Dry mouth	12	30.8	11	40.7
Constipation	3	7.7	1	3.7
Delayed orgasm	8	20.5	7	25.9
Decreased libido	7	17.9	4	14.8
Blurred vision	1	2.6	0	0
Carbohydrate craving	4	10.3	6	22.2
Loss of appetite	11	28.2	2	7.4
Weight gain	3	7.7	5	18.5
Weight loss	5	12.8	2	7.4

[a]One patient dropped out because of this adverse effect.

orgasm, and insomnia (Table 4). No patient experienced troubling cardiovascular adverse effects or cardiac arrhythmia, felt faint, or had symptoms of postural hypotension.

Oral Citalopram Continuation Phase

All 27 patients who completed the citalopram infusion period with a ≥ 20% decrease in YBOCS score completed the 63-day oral citalopram treatment period. A patient who was intolerant of citalopram capsules took the equivalent dose of citalopram oral drops. Of these 27 patients, 13 (33% of the initial 39 patients) experienced a ≥ 35% decrease in YBOCS score by day 42 (6 weeks); 19 (49%), by day 63; and 25 (64%), by day 84, of whom 4 experienced a ≥ 50% decrease. The 27 patients' mean decrease in YBOCS score from baseline to day 84 was –13.4 ± 2.2 (range, –10 to –20 points), which represented a percentage reduction of –42.9% ± 6.4% (range, –29.4% to –55.6%). For the entire patient sample (N = 39), including the 12 who received various treatments other than citalopram after the 21 intravenous infusions, the mean decrease in YBOCS score from baseline to day 84 was –10.1 ± 45.5 (range, +2 to –20 points), which represented a mean percentage reduction of –32.7% ± 17.1% (range, +8% to –55.6%). Table 3 displays the trajectories of YBOCS scores for the intent-to-treat group (N = 39) and those with at least a minimal response to intravenous citalopram (N = 27).

Oral citalopram continuation treatment was associated with significant further reduction in OCD symptoms compared with the end of intravenous citalopram treatment (Table 3). For the 27 patients with a ≥ 20% decrease in YBOCS score after intravenous citalopram, the mean CGI-S score fell from 4.0 ± 0.8 at day 21 to 3.1 ± 1.1 at day 84 (paired t test, $t = 4.7$, $df = 26$, $p < .01$).

These 27 patients also reported a significant increase (paired t tests, all $df = 26$) compared with baseline on 7 of the 8 quality of life subscales of the SF-36: physical activity ($t = 2.36$, $p < .05$), role-physical ($t = 2.91$, $p < .01$), vitality ($t = 3.42$, $p < .01$), general health ($t = 2.78$, $p < .01$), role-emotional ($t = 3.38$, $< .01$), social activity ($t = 3.88$, $p < .001$), and mental health ($t = 3.54$, $p < .01$).

With the exception of dry mouth, delayed orgasm, and carbohydrate craving with weight gain, all of the adverse events noted in the intravenous treatment phase decreased in frequency during the oral treatment phase. At the end of this phase, carbohydrate craving and weight gain (≥ 7% of baseline weight) affected 6 (22.2%) of 27 patients (Table 4).

DISCUSSION

Our study is limited by its open-label design, the absence of a placebo control group, and the absence of blinded outcome ratings. Still, the results suggest that intravenous citalopram in doses of 40 to 80 mg/day is well tolerated and rapidly effective for many patients with treatment-resistant OCD. Without a placebo intravenous infusion group, however, we cannot exclude a therapeutic role for the "drama" of the 21 daily intravenous infusions.

Most patients tolerated daily intravenous citalopram doses of 60 or 80 mg/day. Only 1 patient (of 39) discontinued intravenous treatment because of adverse effects (nausea). At day 21, intravenous citalopram produced a high "response" rate (59% with a decrease in YBOCS score of ≥ 25%; 10% with YBOCS score decrease of ≥ 35%; 46% much or very much improved on the CGI [all percentages of the intent-to-treat group]) more quickly than one would expect. For example, an identically defined response rate (YBOCS decrease of ≥ 25%) after oral citalopram 20 mg for 3 days, 40 mg for 4 days, and 60 mg for 14 days (total = 21 days) was only about 27%[5]; even after continuing at 60 mg/day for 28 days (total

treatment period: 35 days), the response rate was only about 48%.[5]

Intravenous followed by oral citalopram also produced a "response" rate higher than one would expect in patients who had failed 2 adequate SRI trials. For example, after 12 weeks of fluoxetine treatment, only 11% to 27% of OCD patients who had been previously treated with at least 1 SSRI were "responders" (YBOCS decrease of ≥ 35%).[25] By this 35% criterion, we observed response rates of 33% (intent to treat) at the end of week 6 (3 weeks of intravenous citalopram and 3 of oral citalopram) and of 64% at the end of week 12. The proportion of week 12 responders who responded by week 6 (13 of 25, or 52%) is within the range reported by others,[9] even though ours was a treatment-resistant group. Unfortunately, we do not have responder ratings at the end of treatment weeks 4 or 5.

The rapid improvement associated with intravenous citalopram has several advantages for treatment-resistant OCD patients. First, those who experience at least a 20% decrease in YBOCS score at day 21 are highly likely (in the present study, 25 of 27 patients [93%]) to experience the commonly utilized "response" criterion of a ≥ 35% decrease from their baseline YBOCS scores if they undergo oral citalopram treatment. Thus, some patients can be identified early as highly likely to be treatment responders. Whether those with smaller day 21 YBOCS score decreases have a similar chance of reaching the 35% criterion with oral citalopram treatment remains unknown. Second, patients are more likely to comply with a treatment that brings rapid symptom relief. Finally, the value of rapidly reducing the suffering of patients and of their families, although difficult to measure in monetary terms, should not be underestimated.

Although intravenous clomipramine also appears to be effective in treatment-resistant OCD, it carries a much higher risk of troubling cardiovascular adverse events.[11,12] Moreover, the side effect profile of oral citalopram is more benign, e.g., characterized by lower risk of cardiovascular and anticholinergic side effects. The weight gain reported in 18.5% of our patients is unusual. Weight gain has been reported in some small citalopram treatment trials,[26] but was not observed in a large 6-month, placebo-controlled trial in more than 200 depressed patients[27] or in studies reported to the U.S. Food and Drug Administration for approval of citalopram in the treatment of depression.[28] Additional study of this issue in patients with resistant OCD is indicated.

The improvement in our patients' quality of life by day 84 reminds us that symptom ratings do not capture the full benefit of treatments. These quality of life improvements also indicate that treatment was associated with a wide array of benefits. Future studies comparing the outcomes of different treatments for OCD should incorporate quality of life measurements in addition to symptom ratings.

The neurophysiologic mechanisms by which intravenous citalopram might bring about a more rapid and a greater likelihood of response in treatment-resistant OCD remain unknown. Although orally administered citalopram is 80% bioavailable,[29] intravenous administration over 90 minutes should produce somewhat higher brain concentrations. Given the evidence suggesting that the pathophysiology of OCD involves deficient serotonergic neurotransmission,[30] the higher brain concentrations of citalopram may either more rapidly desensitize serotonergic receptors or initiate changes in postsynaptic serotonergic neurons that oral citalopram can then maintain.

CONCLUSION

Intravenous citalopram appears to be a safe, reasonably well-tolerated, and rapidly effective treatment for treatment-resistant OCD. The benefits of intravenous treatment can be maintained and extended by subsequent treatment with oral citalopram. A double-blind, double-dummy design that compares intravenous citalopram, oral citalopram, and intravenous and oral placebo in treatment-resistant OCD is warranted. Future investigations should explore the safety and effectiveness of different intravenous starting doses and rates of dose escalation, combining intravenous administration with simultaneous behavior therapy, and the predictive value of patients' baseline clinical characteristics.

Drug names: citalopram (Celexa), clomipramine (Anafranil and others), fluoxetine (Prozac and others), fluvoxamine (Luvox), lorazepam (Ativan and others), paroxetine (Paxil), risperidone (Risperdal), sertraline (Zoloft), temazepam (Restoril and others).

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