Pulse Intravenous Clomipramine for Depressed Adolescents: Double-Blind, Controlled Trial

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Objective: *Major depressive disorder in adolescents is characterized as treatment resistant, but a previous open-label trial of pulse intravenous clomipramine demonstrated rapid relief of depressive symptoms. In the present study a single intravenous dose of clomipramine (200 mg) was compared with saline placebo in a randomized controlled trial for depressed adolescents. The hypothesis was that adolescents who were treated with pulse clomipramine would exhibit lower scores on the Hamilton Depression Rating Scale at endpoint than would adolescents who received saline and that clomipramine would be superior to saline in terms of antidepressant response.* *Method:* *Sixteen nonsuicidal outpatient adolescents (mean age=16.2 years, SD=1.0) who met the DSM-III-R criteria for major depression (score on 21-item Hamilton scale, ≥18) were randomly assigned to receive either clomipramine (200 mg i.v., N=8) or saline (N=8). Assessments of depression severity were completed 36 hours and 6 days thereafter.* *Results:* *The adolescents who received pulse clomipramine treatment demonstrated significant decreases in Hamilton depression scores from baseline at 6 days but not at 36 hours. A similar decrease from baseline was found in Clinical Global Impression severity at 6 days but not 36 hours. Seven of the clomipramine-treated patients and three of the saline-treated patients had drops of 50% or more from baseline in Hamilton depression score.* *Conclusions:* *Pulse clomipramine (200 mg i.v.) is associated with dramatic reduction in depressive symptoms at day 6 after infusion, which is significantly different from the effect of placebo.*

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Major depressive disorder in adolescents is a chronic and debilitating condition and has a prevalence of 3.5% among adolescents between the ages of 14 and 19 years (1, 2). It is believed to be a major contributing factor in adolescent suicide (3). Treatment of the adolescent with major depressive disorder is difficult; 20%–50% of these patients respond to tricyclic antidepressants (4–6), whereas the response rate for adults with major depression is 60%–80% (7). Several theories explaining this resistance to tricyclic antidepressants in biologic terms suggest developmental delay of the noradrenergic system or interference in antidepressant response from high ketosteroid levels (8). The resistance to tricyclic antidepressants has led to the assertion that major depression in adolescents is relatively serotonergic (8–10), and the use of selective serotonin reuptake inhibitors (SSRIs) has been advocated, yet the literature supporting their efficacy is limited (11). Alternative theories of resistance invoke phenomenologic characteristics, such as a low frequency of the endogenous subtype and a high frequency of atypical subtypes (12) although endogenous features may also be associated with treatment resistance among adolescents (5). Longitudinal studies point to protracted recovery in adolescent major depressive disorder; in the first 8 weeks of contact, recovery is one-tenth as likely as for major depressive disorder in adults (13). Because there is a substantial lag time from initiation of therapy with either tricyclic antidepressants or SSRIs to onset of clinical response, a rapidly acting treatment would potentially decrease morbidity in the adolescent population.

Intravenous clomipramine given in a pulse has been compared to oral loading of the same drug for adult major depressive disorder, which is associated with rapid and significant decreases in scores on the Hamilton Depression Rating Scale (14) (decrease of 35%) regardless

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of route of administration (15). There is, however, a decided advantage in bioavailability as the area under the plasma concentration/time curve for clomipramine is four times as great with intravenous administration as with oral administration (16), and the serotonergic clomipramine is not converted to the noradrenergic metabolite desmethylclomipramine for up to 40 hours with the intravenous route (17). The only pulse clomipramine study of adolescent major depression of which we are aware was open label (17); an intravenous 75-mg test dose followed by 200 mg (1 mg/minute) was given to five patients. Intravenous pulse clomipramine was well tolerated, and three of the five patients had 58%–96% reductions in Hamilton depression scale scores from baseline at 36 hours postinfusion. The score on the affective subscale of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (18) was significantly different from baseline at 36 hours and at 7 days postinfusion. Although dramatic changes in depression ratings were evident in this open-label study, several questions remained because of the shorter lag time for depressed adolescents than for depressed adults (36 hours versus 5–7 days in the study by Pollock et al. [19]), a potential placebo effect, and the inclusion of three (out of five) patients with comorbid obsessive-compulsive disorder, calling into question the specificity of the antidepressant effect. To address these issues we designed a double-blind, placebo-controlled trial for adolescents with major depressive disorder, which allowed comorbid diagnoses but was not heavily weighted with obsessive-compulsive disorder. The hypothesis was that depressed adolescents treated with pulse clomipramine would have lower Hamilton depression scores than saline-treated patients at endpoint and that clomipramine would be superior to saline in terms of antidepressant response.

TABLE 1. Baseline Characteristics of Adolescents With Major Depression Who Were Treated With Pulse Intravenous Clomipramine or Saline

Characteristic	Total (N=16)		Clomipramine (N=8)		Saline (N=8)	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
Age (years)	16.2	1.0	16.1	0.9	16.4	1.0
Height (cm)	169.8	8.3	169.8	9.3	169.9	9.4
Weight (kg)	63.4	10.6	58.4	9.6	67.7	11.6
Socioeconomic status[a]	43.7	12.5	44.0	12.5	43.4	11.6
Duration of episode (months)	6.8	7.1	6.5	7.4	7.1	6.2
	N		*N*		*N*	
Sex						
Male	11		6		5	
Female	5		2		3	
Type of major depression						
Single episode	13		7		6	
Recurrent	3		1		2	
Prior treatment						
No medication	10		7		3	
ECT	1		0		1	
Hospitalization	1		1		0	
Neuroleptic	1		1		0	
SSRI	4		1		3	
Tricyclic antidepressant	2		0		2	

[a]Determined according to the Hollingshead index (21).

METHOD

Subjects

Sixteen adolescent outpatients between the ages of 14 and 18 years were recruited from outpatient depression clinics without regard to race, gender, or ethnicity. After complete description of the study, all minors gave assent, and guardians or parents gave written informed consent before the adolescents' participation. Each potential subject received a comprehensive medical evaluation that included a physical examination, baseline electrocardiogram (ECG), urine drug screen, and, for the girls, measurement of serum human chorionic gonadotropin. The patients were evaluated by using the Structured Clinical Interview for DSM-III-R—Patient Version (20) and were found to meet the DSM-III-R criteria for current major depression. Baseline characteristics of the subjects are given in table 1. All patients previously treated with ECT, neuroleptics, tricyclic antidepressants, or SSRIs were admitted to the protocol a minimum of 4 weeks after discontinuation of previous therapy, with the exception of fluoxetine therapy, which ended 6 weeks before the current study.

The exclusionary criteria for the study included suicide risk or a DSM-III-R diagnosis of bipolar disorder, schizophrenia, anorexia or bulimia, or active substance or alcohol use disorder or dependence (within 3 months of protocol admission). Patients were also excluded if important medical disease, risk factors for seizure disorder, or contraindications to clomipramine were present. The comorbid diagnoses included attention deficit hyperactivity disorder (ADHD) (N=1), oppositional defiant disorder (N=1), generalized anxiety disorder (N=1), obsessive-compulsive disorder (N=2), panic disorder (N=3), social phobia (N=1), and prior (not current) alcohol and polysubstance use disorder ending 3 months before the protocol (N=1).

Design

Within 72 hours of clomipramine infusion, all patients were given baseline assessments with two physician-rated instruments, the 21-item Hamilton Depression Rating Scale (14) and the Clinical Global Impression (CGI) severity scale (22), and a self-rating of depressive symptoms, the 21-item Beck Depression Inventory (23). The patients were then randomly assigned in blocks: every set of two patients was assigned to clomipramine/placebo or placebo/clomipramine by coin toss. The patients were admitted to the General Clinical Research Center at the Medical University of South Carolina, to allow for continuous safety monitoring, the evening before infusion. All personnel except the research pharmacist were blind to treatment condition. Clomipramine, 200 mg (25 mg/2 cc), was filtered with a 0.22-μm glass filter and transferred to 500 cc of normal saline at the hospital pharmacy and transferred to the clinical research center. A similarly labeled 500-cc bag of normal saline constituted the saline placebo. Each infusion commenced at 6:30 p.m., was administered by means of an infusion pump at the rate of 1.1 mg/minute, and terminated at 9:30 p.m. Blood samples for measurement of plasma levels of clomipramine and metabolites were drawn immediately after the end of infusion (9:30 p.m.) and 12 hours later (9:30 a.m.), upon discharge from the research center. The patients were then seen again in the outpatient clinic at 9:30 a.m. 36 hours and 132 hours (day 6) after the end of infusion with no additional medication intervention. The Hamilton depression scale, CGI, and Beck Depression Inventory were readministered at each follow-up visit. The same physician performed the ratings at baseline, 36 hours, and 132 hours but was blind to treatment status, adverse events, and inpatient care of the patient. The

patients were again evaluated 2 weeks after infusion (while medication free if possible), and a clinical decision was made at that time as to whether the patient continued to meet the criteria for major depression and whether oral treatment with an antidepressant was indicated. Intervention was possible before 2 weeks postinfusion but only if the patient became suicidal or if there was a substantial increase (>25%) from baseline in Hamilton depression score. At week 8 formal follow-up was again performed for all patients, in both the pulse clomipramine and saline treatment groups, and an assessment was made as to whether the criteria for major depression were still met and, for patients who were receiving oral antidepressants, whether the patient was responding to antidepressant treatment. No patient dropped out either during infusion or during the follow-up procedures. The final outcome measure was the score on the Hamilton depression scale, which was also used to identify treatment responders. A responder was defined as a patient who had experienced a decrease of 50% of more from baseline in Hamilton depression scale score at day 6.

Infusion Procedures

Each vial of clomipramine used for intravenous administration contained 25 mg of clomipramine, 54 mg of glycerin as an excipient, and 2 ml of distilled water. All intravenous solutions were prepared by the hospital pharmacy and administered in a blinded fashion. The subjects remained supine throughout the entire procedure and remained at bed rest. An ECG and a urinalysis for determination of RBC were performed immediately before and after infusion. Blood pressure and pulse were monitored every 20 minutes with an automated machine and by nursing staff.

Laboratory Methods

Blood samples for measurement of clomipramine and metabolite concentrations were drawn into disposable polypropylene syringes and immediately transferred to EDTA-containing Vacutainer tubes and centrifuged, and the plasma was stored at –70°C until assay. The samples for clomipramine measurement were obtained immediately after the end of infusion from the arm opposite that of the infusion site, and additional samples for clomipramine measurement were obtained 12 hours thereafter. Plasma clomipramine and desmethylclomipramine and their respective hydroxylated metabolites were measured by using high-performance liquid chromatography with ultraviolet detection. The lower limit of quantitation was 1.0 ng/ml for clomipramine, 2.5 ng/ml for desmethylclomipramine and 8-hydroxyclomipramine, and 5.0 ng/ml for 8-hydroxydesmethylclomipramine. The intra-assay and interassay coefficients of variation were between 2% and 10%.

Statistical Analyses

The two treatment groups' changes in score on each assessment measure between baseline and day 6 were compared by means of Student's t tests. Since matching of male and female patients in the saline- and clomipramine-treated groups was achieved, sex was not used as a cofactor in the analysis. The null hypothesis that the mean score of the saline-treated group was equal to the mean score of the clomipramine-treated group was tested against the alternative, i.e., that the mean scores of the two populations were not equal. Type 1 errors for these tests were controlled at 5%.

The responses to the two treatments were compared by Fisher's exact test of independence, with the counts in the four cells representing the responders to clomipramine, responders to saline, nonresponders to clomipramine, and nonresponders to saline. A responder was defined as a patient who experienced a decrease of 50% or more in Hamilton depression scale score from baseline to day 6. The null hypothesis that the proportion of responders in the clomipramine-treated group was equal to the proportion of responders in the saline-treated group was tested against the alternative, that the proportions were not the same. A Yates-corrected chi-square test was also performed for these data. Type 1 errors for these tests were controlled at 5%.

RESULTS

Demographic and clinical characteristics of the two treatment groups are listed in table 1. The mean score on the 21-item Hamilton depression scale was 22.6 (SD=4.6). This score and the duration of symptoms suggest that the adolescents recruited were severely depressed and had been so for a considerable time. No factor listed in table 1 was significantly different between the depressed adolescents assigned to clomipramine and those given saline, and there also was no significant difference in baseline score on the Hamilton depression scale, CGI, or Beck Depression Inventory. Three patients in the clomipramine group had comorbid diagnoses: panic disorder plus obsessive-compulsive disorder (N=1), panic disorder plus social phobia (N=1), or oppositional defiant disorder (N=1). Anxiety diagnoses were also frequent in the saline treatment group—obsessive-compulsive disorder (N=1), panic disorder (N=1), and generalized anxiety disorder (N=1)—and one patient had ADHD plus a previous diagnosis of alcohol abuse (not active in the 3 months before the study). All of the clomipramine-treated patients received the full 200-mg dose and tolerated the procedure well. The resultant mean plasma concentration of clomipramine immediately after infusion was 173 ng/ml (SD=17), and the mean concentration was 247 ng/ml (SD=245) 12 hours later, at 9:30 a.m. The concentration of the metabolite desmethylclomipramine was 8.1 ng/ml (SD=3.8) immediately after infusion and 22.6 ng/ml (SD=8.2) 12 hours later. No relationship between clinical outcome and plasma concentration of clomipramine or desmethylclomipramine could be detected. The plasma concentration of 8-hydroxyclomipramine was 8.5 ng/ml (SD=4.1) immediately after infusion and 15.5 ng/ml (SD=4.6) 12 hours later. The plasma concentration of 8-hydroxydesmethylclomipramine was largely undetectable both after infusion and at 12 hours. Adverse events were reported by three of the eight clomipramine-treated patients and two of the eight saline-treated patients, and all reports were of little clinical consequence. The three patients who experienced clomipramine-related adverse events complained of dizziness (N=2), sedation (N=2), and nausea (N=1). No alteration in the Qt, Qtc, QRS, or PR interval was found from the ECGs, and these values were not significantly different from baseline after pulse clomipramine administration. No significant differences between the clomipramine and saline groups could be detected in the ECG variables. The mean PR interval at the end of infusion was 129 msec (SD=11) for clomipramine and 149 msec (SD=27) for saline. The mean Qtc interval for clomipramine after infusion was 410 msec (SD=20) and 413 msec (SD=20) for saline. Pulse and systolic and diastolic blood pressure were also unchanged from baseline.

Scores on the Hamilton scale, CGI, and Beck Depression Inventory at baseline, 36 hours, and day 6 are shown in table 2. In general, the patients did not worsen between baseline and 36 hours, and there appears to be a tendency for improvement, particularly in the clomi-

TABLE 2. Clinical Depression Ratings of Adolescents With Major Depression Who Were Treated With Pulse Intravenous Clomipramine or Saline

	Clomipramine (N=8)						Saline (N=8)					
	Baseline		36 Hours		Day 6		Baseline		36 Hours		Day 6	
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Hamilton Depression Rating Scale score	22.9	6.0	11.0	4.7	7.9[a]	5.1	22.4	4.0	13.4	7.4	13.4	7.3
Clinical Global Impression severity score	5.7	0.7	4.0	0.8	2.5[b]	0.8	5.4	0.7	4.5	1.3	4.0	1.5
Beck Depression Inventory score	20.4	9.8	15.7	6.7	7.7	7.9	24.4	11.2	18.0	19.1	15.0	12.9

[a]Significant difference in change from baseline to day 6 between clomipramine and saline groups (t=2.3, df=14, p=0.04, two-tailed).
[b]Significant difference in change from baseline to day 6 between clomipramine and saline groups (t=3.6, df=14, p=0.003, two-tailed).

pramine group, but this did not reach statistical significance. At day 6 there were substantial differences between treatment groups in the Hamilton depression and CGI severity ratings. The change in Hamilton depression scale score from baseline to day 6 differed significantly between the patients given clomipramine (mean=15.0, SD=4.1) and saline (mean=9.0, SD=6.1). The change in CGI severity rating between baseline and day 6 also differed significantly between the groups treated with clomipramine (mean=3.2, SD=1.0) and saline (mean=1.4, SD=1.1). Although the change in Beck inventory score between baseline and day 6 was greater for the clomipramine treatment group (mean=12.6, SD=4.6) than for the saline group (mean=9.4, SD=4.5), this difference was not statistically significant. Taken together, the clinical severity ratings demonstrate a decrease for the clomipramine group by day 6 to levels approximating the nonclinical range (e.g., Hamilton depression scale score of 7 or lower and a CGI rating of 2 or less).

When responders were defined by a decrease of 50% or more from baseline in Hamilton depression scale score at day 6, there were three responders to saline and seven responders to clomipramine. Fisher's test of two-way tables revealed a difference between the clomipramine and saline treatment groups, although the difference did not reach statistical significance (p=0.06, one-tailed Fisher's exact test; χ^2=2.4, df=1, p=0.12, with Yates's correction).

No oral antidepressant treatment was required for any subject before week 2 of follow-up. At week 2 postinfusion, three of the seven responders to pulse clomipramine had either complete resolution of depressive symptoms (N=2) or a reduction large enough that the criterion for response continued to be met (N=1). These same clomipramine responders continued to be free of depressive symptoms (N=2) or to have subclinical depressive symptoms (N=1) at week 8 without further intervention. One of these patients with dramatic responses to pulse clomipramine had recurrent depression and previously had been treated without success with the combination of a neuroleptic and sertraline. One responder to pulse clomipramine who had comorbid obsessive-compulsive disorder had a concomitant decrease of 50% in Yale-Brown Obsessive Compulsive Scale rating between baseline and day 6. This patient had reemergent depressive symptoms at week 2 and was treated clinically until week 8 with open-label sertraline, 200 mg/day, with positive results. The lone clomipramine nonresponder at day 6, who was followed medication free until week 2, was found at that time to have complete resolution of depressive symptoms. This patient was followed up until week 8 while still medication free, and at that time the depressive symptoms had resumed and the patient was treated clinically with paroxetine. The remaining three responders to pulse clomipramine exhibited depressive symptoms that were clinically significant at week 2 despite being improved at day 6. These patients were treated in an open-label fashion with paroxetine (N=1) or sertraline (N=2) until week 8. Only one of these three failed to improve, despite receiving sertraline, 200 mg/day, with lithium augmentation at week 8. Seven of the eight saline-treated patients were clinically depressed at week 2, regardless of whether they had shown responses at day 6 (N=3). Only one saline-treated patient was symptom free at week 2. The seven saline-treated patients with depression at week 2 were treated in open-label fashion with various SSRIs, and five of the seven failed to show a response at week 8 despite adequate doses and duration of therapy (e.g., 200 mg/day of sertraline for 6 weeks).

DISCUSSION

The present study of pulse intravenous clomipramine for depressed adolescents demonstrated dramatic and rapid symptom improvement from a single 200-mg dose. The conclusions of this study are that 1) clomipramine administered parenterally appears to be more efficacious (88% response rate) than placebo (38% response), 2) response to pulse clomipramine is apparent at 132 hours (day 6), and 3) response to pulse clomipramine may persist in some patients (three of seven, 43%) for up to 8 weeks. The strength of these conclusions and the generalizability of the findings are limited, however, by the small number of subjects. The placebo response rate in the present study is not unlike that reported in the literature (7), but the rate of response to pulse clomipramine was robust. In contrast to our previous open-label study (N=5) (17), in this study there was no significant difference between clomipramine and saline treatment at 36 hours postinfusion. This inconsistency may be attributed to a general reduction of symptoms after the intravenous procedure itself, which

was indistinguishable from drug effect in the first study because of the lack of placebo control. These placebo effects are most apparent soon after the procedure, and so the best point of comparison may be day 6, not 36 hours. Although spontaneous resolution of depressive symptoms unrelated to pulse clomipramine is possible, the pretreatment duration of illness (mean=6.8 months) and the lack of similar resolution in the saline-treated group make spontaneous resolution unlikely. A community sample of adolescents with major depression had a mean duration of illness of 26.4 weeks (median=8 weeks) (24). All adolescent patients with major depression who received pulse clomipramine experienced dramatic decreases in depressive symptoms either at day 6 (seven of eight) or at week 2 (the one patient receiving pulse clomipramine who was a nonresponder at day 6). This is a strong argument for the ability of adolescent depression to respond to antidepressant treatment. In contrast, seven of the eight saline-treated patients were clinically depressed at week 2. Although our study group as a whole does not appear to be skewed by either treatment resistance or chronic depression (25), it is remarkable that open-label treatment to week 8 resulted in a lower response rate (29%, two of seven patients) among the saline-treated patients than among those receiving clomipramine (88%, seven of eight). It is possible that pulse intravenous clomipramine may allow for response to oral antidepressants. This is suggested by the report of Koran et al. (26) on patients with treatment-resistant obsessive-compulsive disorder, for whom reintroduced oral antidepressants induced a response only after administration of pulse intravenous clomipramine.

Although the clinical utility of pulse clomipramine for adolescents with major depression is not demonstrated by this small study, it has heuristic value in determining whether major depressive disorder among adolescents is truly treatment resistant or whether other factors (27, 28) contribute to the lack of demonstrated treatment efficacy. In a meta-analysis of the literature on treatment of adolescent major depressive disorder, Ambrosini et al. (7) found that double-blind, controlled studies have demonstrated a recovery rate with antidepressants (tricyclic antidepressants or SSRIs) of 55% (30 of 55 patients), while 41% of patients (27 of 66) recover with placebo. At least five well-controlled studies (4–6, 29, 30) have failed to demonstrate either a relationship between plasma level and response or the superiority of tricyclic antidepressants to placebo. Information concerning response to SSRIs in adolescent major depression is only now starting to accumulate (11, 31). Controlled studies (31, 32) and open-label trials (33, 34) of SSRIs for this patient population are limited and demonstrate mixed results. A retrospective chart review of 38 patients treated with fluoxetine (20–80 mg/day) suggested improvement in 74% of the patients surveyed, but 26% showed minimal or no change (35). Clinical predictors of antidepressant response in adolescent major depression have been limited, with the exception of delusional subtype, which is predictive of nonresponse and protracted course (13). A biologic measure that has been shown to predict antidepressant response is number of lymphocyte glucocorticoid type II receptors (36), which is lower than normal at baseline, increases with response, and accurately classifies 90% of SSRI responders, but such a biologic measure may not be practical in clinical settings. To date, the best predictor of antidepressant response appears to be clinical response itself, such that pulse clomipramine may find utility as an adjunctive clinical tool for both predicting and, perhaps, producing response. The present findings suggest that major depression in adolescents is not treatment resistant, at least not when the treatment is pulse intravenous clomipramine.

Although clomipramine has a number of pharmacologic actions (i.e., noradrenergic and muscarinic), intravenous administration creates a selective SSRI effect for 40 hours of body transit time (17). Intravenous pulse clomipramine also immediately provides a potentially therapeutic plasma concentration (mean, 173 ng/ml). Pulse intravenous clomipramine is fundamentally different from intravenous use previously described in the literature (37–39). Typically, intravenous clomipramine has been administered gradually in 25–50-mg increments up to 150–200 mg/day over 7–10 days, nullifying any selective serotonergic advantage. Serotonergic treatments may be particularly effective for adolescent major depressive disorder, as serotonergic augmentation of tricyclic antidepressants with lithium or tryptophan (40, 41) dramatically improves response. Adolescent depression has been characterized as hyposerotonergic on the basis of fewer serotonin binding sites on platelets than in depressed adults (42) and indirect demonstration by means of prolactin blunting on challenge with low-dose parenteral clomipramine (43). It is possible that pulse intravenous clomipramine may be more effective for adolescent depression than gradually administered clomipramine because of its rapid enhancement of serotonergic transmission and that the apparent lack of response in adolescent major depression is related to the limited number of studies that have examined use of SSRIs for this population.

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