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Brief Report

BRIEF REPORT

# Intravenous Clomipramine for Treatment-Resistant Obsessive-Compulsive Disorder

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## Abstract

**Background:** This open trial was conducted to evaluate the effectiveness of intravenous clomipramine (CMI) in refractory obsessive-compulsive disorder (OCD).
**Methods:** Thirty OCD poor responders to previous multiple trials of anti-obsessive medications were selected and admitted to the hospital. Severity of the illness and response to treatment were primarily assessed by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). CMI was gradually administered intravenously for one week. All patients were thereafter switched to oral CMI with a maximum dose of 225 mg/day.
**Results:** The Y-BOCS total score mean at admission was in the severe range (24–31), and dropped on discharge and follow-ups to the moderate range (16–23). At discharge, 23 patients (76.7%) had a decrease in Y-BOCS ≥25% and were considered responders, while only 18 (60%) were still responders at 24 weeks. No relevant persistent side effects were reported.
**Conclusion:** Intravenous clomipramine could be of benefit for severe OCD cases that have not adequately responded to several therapies, including oral clomipramine.

**Keywords:** clomipramine, intravenous clomipramine, obsessive-compulsive disorder, treatment-resistant OCD

## Introduction

Selective serotonin reuptake inhibitors (SSRIs) are the primary drugs for treating obsessive-compulsive disorder (OCD), due to their efficacy and safety profile (Stein, 2002; Koran and Simpson, 2013). The percentage of responders to SSRIs in placebo-controlled studies is typically 40% to 60%. A decrease of 25% to 35% in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), acknowledged as the pivotal scale for measuring the severity of OCD symptoms over time, is considered to be an adequate treatment response.

However, even with this maximum response to therapy of 35%, many patients may still present with severe uncontrolled symptoms. Patients who do not respond to their first SSRI may have their medication switched to a different SSRI or to venlafaxine.

They may also be good candidates for treatment augmentation strategy, by adding an antipsychotic medication to an SSRI or by combining cognitive behavioral therapy, such as exposure and response prevention, with an SSRI (Koran and Simpson, 2013). Little practical advice is available to clinicians on next-step treatment strategies for patients who have shown either a partial response or who have not responded to this strategy. According to the latest guidelines of the American Psychiatric Association, this group of patients may benefit from an augmentation of SSRIs with clomipramine, buspirone, pindolol, riluzole, or once-weekly morphine sulfate (Koran and Simpson, 2013). In certain selected patients, a single drug therapy may also be used, such as tramadol, ondansetron, monoamine oxidase inhibitor, or D-amphetamine. Transcranial magnetic stimulation or deep brain stimulation is

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also an option in such cases. Ablative neurosurgery is rarely indicated, and it is reserved for severe and very treatment-refractory OCD patients.

Clomipramine (Anafranil) was the first drug to obtain Food and Drug Administration (FDA) approval for treating OCD. It is a tricyclic antidepressant (TCA) with a potent ability to inhibit serotonin reuptake; it also inhibits the reuptake of norepinephrine, and has dopamine-blocking effects (Bokor and Anderson, 2014). The first open-label study of clomipramine was done in the 1960s (Philpott, 1976). Clomipramine did not receive FDA approval for OCD until 1989. Head-to-head studies of SSRIs and clomipramine have found similar efficacy and better tolerance with a SSRI (Clomipramine Collaborative Study Group, 1991; Mundo et al., 2001).

Intravenous clomipramine (i.v. CMI) was proven to be effective for OCD in several studies, especially for patients who are nonresponsive to oral clomipramine (Warnecke, 1984, 1989). The largest randomized double-blind study was done by Fallon et al. in 1998 and showed the superiority of i.v. CMI over placebo in patients with inadequate response or intolerance to oral clomipramine. Some postulated theories of why CMI might be more effective than oral CMI include the better bioavailability, establishing a steady state by eliminating first pass metabolism in the liver (http://www.northshorelij.com/ccurl/810/560/winning_ paper_linder_09,0.pdf, accessed online May 2014). Many other studies showed that i.v. CMI can relieve symptoms in resistant OCD (Albert et al., 2013) and reported a faster and immediate improvement, noticed after few days of therapy rather than weeks (Koran et al., 1997).

In view of these findings, this study was conducted to explore the efficacy of i.v. clomipramine in improving symptoms in treatment-resistant OCD patients.

## Methods

Thirty patients were recruited from the outpatient clinic in the Department of Psychiatry at the American University of Beirut Medical Center (AUB-MC). All patients were diagnosed with OCD by an attending psychiatrist according to the DSM-IV criteria. For study inclusion, patients were required to have a duration of illness of at least 3 years, functional impairment with a Global Assessment of Functioning scale ≤70, a baseline Y-BOC total score of at least 16, and a poor response to at least two trials of anti-obsessional medications (each given at least for 8–12 weeks with at least 6 weeks at the maximum tolerated dose).

Patients with a history of psychosis, an unstable medical disease, evidence of cardiac conduction abnormalities, a history of seizures, and pregnant women were excluded from the study. The presence of lifetime or intraepisodic comorbidity with anxiety, mood, and personality disorders was not considered as exclusion criteria.

### Ethics

The study was approved by the Institute Review Board at the AUB-MC, and informed consent was obtained from every participant. The principal investigator met with each patient, read them the consent form, answered any questions they had, and asked them to sign in the presence of a witness. For minors (patients below 18 years), consent was obtained from the parents with the agreement of the minor.

### Study Design

The study was an open-label trial of 24 weeks duration. Clomipramine was administered intravenously in an inpatient setting at a dosage of 50 mg per day and titrated up to a maximum dose of 225 mg/d over 5–7 days. On discharge, all patients were given oral clomipramine (75 mg, ranging from ½ tablet twice daily to 1 tablet three times a day). No other drugs were permitted, except for low doses of benzodiazepines (Alprazolam or Lorazepam). The primary outcome measure was the effect of i.v. CMI on the Y-BOCS score. This score was assessed at baseline (admission), at discharge, and at follow-ups after 1, 2, 4, 12, and 24 weeks.

At baseline, a treatment-resistant OCD patient was defined as any OCD patient whose Y-BOCS total score has been reduced by less than 25% after at least 6 months of therapy with either a SSRI or clomipramine given at adequate dosages.

Responders were defined as patients showing a reduction of at least 25% in the Y-BOCS total score.

Apart from the Y-BOCS, a clinical assessment was done at baseline by means of the OCD questionnaire (checking list and severity rating), a semi-structured in-depth interview that collates relevant demographic data, family history, psychopathological features (DSM-IV 5 Axis), age of onset of illness, and past and current medications. The Hamilton rating scale for depression and anxiety was used at baseline, at discharge, and at every follow-up visit.

### Data Analysis

Data analysis was divided into two parts: descriptive, to display the basic characteristics of the patients and the mean of the Y-BOCS at admission and at every follow-up visit, and analytical, in which we used a *t*-test to look for significant clinical differences in Yale-Brown scale scores at baseline (before treatment) and after treatment (at discharge and at every follow-up visit). We used an analysis of variance test to compare the Y-BOCD scale at the different follow-up visits. We used Fisher's exact test to examine whether there was any difference in the Y-BOCD scale results between female and male patients. A *p*-value was considered significant if it was <0.005. The program used was the SPSS (Tofranil).

## Results

Thirty patients were enrolled in the study. Nineteen patients (63.3%) were male and 11 (36.7%) female. The mean age of the participants was 32 years (range 16–63); the mean age at onset of OCD was 15 years (range 8–35). Patients had experienced symptoms of the disease for a mean of 16.12 years (range 3–41).

Half of the patients were married, and approximately one-fourth were university graduates. Demographic and baseline characteristics of the patients are shown in Table 1. Five patients showed lifetime comorbidities with at least one psychiatric disorder: four had recurrent depression and one had generalized anxiety disorder. Eight patients had personality disorders: three had obsessive compulsive disorder, one was antisocial, one was dependent, one was histrionic, one was schizotypal, and one had mixed disorders.

Twenty-six patients (86.6%) had failed a previous therapy, consisting of a combination of at least a SSRI and a TCA (oral anafranil or tofranil). The majority of the patients (73.3%) were taking a TCA directly before enrollment in the study (Table 2).

Two patients were lost to follow-up: the first after the first follow-up and the second after the third one.

### Efficacy

Treatment with i.v. clomipramine led to clinically and statistically significant reductions in the Y-BOCS total score. At discharge, the mean score was 18.10, which means a reduction of

30.74% and consequently reflects a response to the treatment. This improvement was maintained throughout the duration of the study: in fact, the mean score dropped to 16.32 (reduction of 36.81%) after 24 weeks of follow-up (Table 3).

The Y-BOCS total score mean at admission was in the severe range (24–31), and dropped on discharge and follow-ups to the moderate range (16–23).

At discharge, 23 patients (76.7%) had a decrease in Y-BOCS ≥25% and were considered responders, while only 18 (60%) were responders at 24 weeks.

The comparison of the response to treatment between males and females revealed a better statistically significant effect of i.v. CMI in female patients for compulsions but not obsessions ($p < 0.05$; Table 4).

No relevant side effects were reported, except for one patient who noted palpitations within the first few days of treatment, which then disappeared.

## Discussion

Our study found a significant effect for i.v. clomipramine in improving OCD symptoms. This effect was more pronounced in females and persisted through the 8 week follow-up period. At the end of the study, 60% of the patients were responders, with a mean decrease in Y-BOCS of 36%.

The limitations of our study were the small sample size (30 patients), the lack of a control group, and the fact that the investigators were not blinded to the conditions of therapy.

**Table 1.** Distribution of Study Participants by Basic Demographic Characteristics

| | n | % |
|---|---|---|
| Gender | | |
| Male | 19 | 63.3 |
| Female | 11 | 36.7 |
| Marital Status | | |
| Single | 15 | 50 |
| Married | 15 | 50 |
| Education | | |
| University | 8 | 26.6 |
| High school | 13 | 43.3 |
| < High school | 9 | 30 |
| Employment | | |
| Professional | 6 | 20 |
| Employee | 8 | 26.67 |
| Student | 5 | 16.67 |
| Don't work/House wife | 11 | 36.67 |
| | Mean (standard deviation) | |
| Age | 31.76 (12.27) | |
| Yale-Brown Obsessive Compulsive Scale | 26.2 (5.05) | |

However, certain aspects must be emphasized with respect to results. Our group of patients had severe obsessive compulsive symptoms (baseline mean of 26.2 on Y-BOCS), long durations of symptoms (mean of 16 years), and had a history of nonresponse to different previous treatments. In our sample, the current medication before admission was oral CMI alone in 22 (73.3%) patients.

Fallon et al. (1992) tested the efficacy of i.v. clomipramine in comparison with placebo in a group of 54 patients who were considered treatment resistant or could not tolerate clomipramine oral therapy. Their study was in part a double-blind study, until the end of 14 infusions, when it became single-blind for a week and then changed to a complete non-blind study for final 4 weeks.

By the end of the study (24 weeks), 18 patients (60%) were responders. This percentage was the same obtained in the study by Fallon et al. (1998), in which 58.1% of subjects who had received i.v. CMI were deemed responders.

The mean reduction of Y-BOCS at 4 weeks was 33.2%, which is slightly more than that reported by Fallon et al. (1998) but less than the 40% reduction reported by Koran et al. (1994).

Our study replicates the results of a series of studies reported by Warneke (1984, 1989), in which i.v. CMI was administered to subjects non-responsive to previous multiple medications, including oral CMI, and in which all patients reported significant and dramatic improvement in OCD symptoms.

The underlying neurophysiological explanation for the potentially superior efficacy of i.v. CMI remains incompletely understood. It has been hypothesized that this effect may be due to the higher bioavailability of CMI, which has a more serotonergic effect compared to its metabolite, dysmethylclomipramine, which has a higher noradrenergic effect. This is mainly explained by the ability of intravenous CMI preparation to bypass the entero-hepatic metabolism (Fallon et al., 1998).

**Table 2.** Distribution of Patients by Past and Current Medications.

| | n | % |
|---|---|---|
| Past medication | | |
| TCA | 2 | 6.6 |
| SSRI | 2 | 6.6 |
| TCA + SSRI | 16 | 53.3 |
| TCA + SSRI + Others | 10 | 33.3 |
| Current medication | | |
| TCA | 22 | 73.3 |
| SSRI | 1 | 3.3 |
| TCA or SSRI +others | 3 | 10 |
| Multiple | 3 | 10 |
| None | 1 | |

SSRIs were recorded in the data by class. The dose used was the maximal tolerated dose for each drug. TCAs used by the patients were Anafranil or Tofranil. SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant.

**Table 3.** Results of the Repetitive Measures for Obsessions and Compulsions

| | Admission | Discharge | F/U 1 | F/U 2 | F/U 3 | F/U 4 | F | *p* |
|---|---|---|---|---|---|---|---|---|
| O Y-B scale (obsession score) | 15.28 | 11.64 | 10.14 | 10.56 | 10.36 | 10.07 | 42.31 | 0.000 |
| C Y-B scale (compulsion score) | 10.68 | 6.71 | 5.96 | 7.07 | 6.57 | 6.25 | 26.24 | 0.000 |
| Y-BOCS | 25.96 | 18.35 | 16.1 | 17.63 | 16.93 | 16.32 | | |

The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) total score mean at admission was in the severe range (26), and dropped on discharge to 18 (30.7% reduction). This response was maintained during all the follow-ups. The mean score dropped to a moderate range (16.3; 36.8% reduction) at the end of the study. F, final; F/U, follow-up.

**Table 4.** Distribution of Males and Females by Score on Obsessions and Compulsions

| | Total Mean/SD | Male Mean/SD | Female Mean/SD | *p*-value |
|---|---|---|---|---|
| Admission | | | | |
| Obs Y-B scale | 15.34 (2.48) | 15.10 (2.86) | 15.82 (1.66) | 0.458 |
| CompY-B scale | 10.83 (4.40) | 11.89 (4.01) | 9.00 (1.39) | 0.082 |
| Discharge | | | | |
| Obs Y-B scale | 11.37 (2.86) | 11.53 (3.40) | 11.09 (1.64) | 0.695 |
| CompY-B scale | 6.73 (3.30) | 7.79 (3.05) | 4.91 (3.01) | 0.018 |
| F/U 1 | | | | |
| Obs Y-B scale | 10.07 (3.60) | 10.74 (4.31) | 8.91 (1.37) | 0.101 |
| CompY-B scale | 6.03 (4.37) | 7.79 (4.10) | 3.00 (3.00) | 0.002 |
| F/U 2 | | | | |
| Obs Y-B scale | 10.54 (3.31) | 11.17 (3.82) | 9.27 (1.85) | 0.138 |
| CompY-B scale | 7.03 (4.40) | 8.89 (3.85) | 4.00 (3.58) | 0.002 |
| F/U 3 | | | | |
| Obs Y-B scale | 10.21 (3.37) | 11.11 (3.80) | 8.73 (1.85) | 0.064 |
| CompY-B scale | 6.48 (4.01) | 8.06 (3.76) | 3.91 (3.05) | 0.005 |
| F/U 4 | | | | |
| Obs Y-B scale | 10.07 (3.52) | 11.12 (3.84) | 8.45 (2.25) | 0.048 |
| CompY-B scale | 6.25 (3.84) | 7.88 (3.53) | 3.73 (2.87) | 0.003 |

The table shows a better statistically significant effect of i.v. CMI in female patients for compulsions, but not obsessions.
CMI, clomipramine; comp, compulsions; F/U, follow-up; obs, obsessions; SD, standard deviation; Y-B, Yale-Brown Obsessive Compulsive Scale.

In our study, the reduction of the symptoms was immediate: it was detected after one week of the first dose of i.v. treatment. This rapid improvement on the Y-BOCS score was also reported by Fallon et al. (1992) and Koran et al. (1997, 1998). In their study, Koran et al. (1997) detected a more rapid effect of the i.v. pulse therapy versus the oral one. After being randomly distributed, the subjects were given a dosage of either oral or intravenous CMI for 2 days, followed by CMI oral for another 8 weeks. Improvement was noticed within 1 week after pulse loading treatment in six out of seven patients in the group receiving the i.v. CMI but in only one patient in the group receiving the oral formulation.

When comparing pulse loading versus gradual dosing of i.v. CMI in OCD patients, Koran et al. (1998) reported a rapid and dramatic response 5 days after pulse-loading.

Our results also support those of Koran et al (1997, 2006) by showing that patients who responded to CMI will continue to improve during several weeks of oral clomipramine therapy. In 1997, Koran et al. showed that following the 8-week oral maintenance period, the proportion of responders was similar, with a minimum improvement of at least eight points in the Y-BOCS score. In their more recent study comparing oral versus i.v. pulse loading administration of CMI for patients with treatment-resistant OCD, Koran et al. (2006) once again showed a significant improvement in Y-BOCS scoring after one week of therapy; however, the clinical improvement was noted in only a small percentage of treated patients.

In our study, we noted consistent improvement on oral clomipramine during 24 weeks of follow-up.

In our study, we did not measure blood levels of clomipramine to correlate the concentration with the clinical response. However, other studies did not find any correlation between peak plasma CMI levels and a clinical response (Koran et al., 1997, 2006)

Negative predictors of response have been identified: earlier onset, comorbid disorders (such as tic disorder), social phobia, schizotypal personality disorder, obsessive compulsive personality disorder, presence of hoarding obsessions, and a higher baseline severity of OCD symptoms (Erzegovesi et al., 2001). One study (Mundo et al., 1997) suggested that female subjects show a better anti-obsessional response, especially when treated with CMI. Another study confirmed that poor insight is the best predictor of poor drug response, and a family history is the best predictor of good drug response (Erzegovesi et al., 2001).

Neuroendocrine response can also have a clinical utility to distinguish treatment responders to i.v. CMI treatment in refractory OCD. Recently, Mathew et al. (2001) showed that a good response at 2 weeks was directly related to low levels of cortisol and prolactin at baseline but to a high level of growth hormone as well.

Our results confirmed what had been shown in previous studies: that being female is a positive predictor variable for response to CMI. However, it was only significant with respect to compulsions, and not obsessions.

Warneke (1984) had previously noted that patients are more tolerable to i.v. CMI than oral CMI. This was doubted by others until several controlled trials showed a superior tolerability profile of i.v. formulation compared to oral. Side effects were minor, infrequently noted, and decreased with time. Knowing that the sample size in those controlled trials was small, and taking into account the cardio toxicity of the i.v. molecule, this treatment should be avoided in cardiac patients, as well as in those with a history of seizure and previous contraindications to tricyclics (Ravindron et al., 2010). Our study showed similar findings concerning the tolerability profile of the drug. There were no side effects reported, except for one case of palpitation.

In conclusion, our study presents more reasonable preliminary evidence to suggest that i.v. CMI is a good alternative therapy for drug-resistant OCD patients that previously showed poor or no response to oral medications, especially oral CMI.

More and longer-term studies should be considered in the future to study the effectiveness of i.v. CMI and the persistence of its effect over time in comparison to a rapidly escalating regime of oral CMI as well as to other medications.

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None

## Statement of Interest

None.

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