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Intravenous Clomipramine in Severe and Refractory Obsessive-Compulsive Disorder

To the Editors:

Severe and incapacitating obsessive-compulsive disorder refractory to antiobsessive medications and behavior therapy remains a challenge in clinical practice. Intravenous (IV) clomipramine (CMI) have been suggested in this context, and has been used as a series of infusions¹⁻⁶ or as pulse therapy.^{7,8} The response seems to be faster than that obtained with oral CMI: 36 hours⁷ to 5 days,⁸ and with a minimum of side effects.^{1,2} Patients with a history of poor response to oral CMI and behavior therapy eventually respond to IV CMI.^{4,5} Because IV CMI avoids the first-pass hepatoenteric metabolism, bioavailability to the central nervous system of the serotonergic parent compound (non-desmethylated clomipramine) may be greater by IV route than orally.^{5,6} Peak plasma levels of patients given intravenous pulse loading are 4 to 14 times higher than those of patients given oral pulse loading.⁸ Studies have, however, failed to demonstrate any statistically significant relationship between clinical response and levels of CMI, desmethyl-clomipramine, or the ratio between them.^{5,8} As far as we know, there has been no specific study of the response to IV CMI in a special group of obsessive-compulsive patients, those with severe and incapacitating symptoms, not responding to previous pharmacologic treatments. Our objective is to describe the response of a group of such patients to this treatment.

METHOD

Six hospitalized obsessive-compulsive disorder patients (DSM IV), 3

men and 3 women, aged between 19 and 42 years, with severe (Y-BOCS > 30) and incapacitating obsessive-compulsive symptoms, refractory or not tolerating previous pharmacologic treatments or behavior therapy were included in the study. All were in good health, with normal physical and neurologic exam, hemogram, urine, blood biochemistry, electrocardiogram, and CT scan. The symptoms had started between the age of 10 and 18 years (mean: 13.5 years) and lasted from 2 to 32 years (mean: 14 years). The patients had previously used oral CMI in doses between 175 to 300 mg/d for periods of 3 months to 9 years, with the exception of 1 patient who used oral CMI for less than 3 months and interrupted the treatment due to side effects. This patient also did not tolerate the use of fluoxetine and sertraline. In addition to oral CMI, 3 patients had not responded to the use of selective serotonin reuptake inhibitors for more than 3 months, 2 to fluoxetine in doses of 40 and 100 mg/d, respectively, and 1 to fluvoxamine in doses of 100 mg/d. Of the 6 patients, 3 had undergone and not responded to behavior therapy.

Patients were treated for 2 weeks, in an open clinical trial, with 14 daily IV infusions of CMI diluted in 500 mL of saline solution, in increasing doses, starting at 25 mg/d and reaching 250 mg/d after day 7. The series of infusions were followed with oral CMI at the maximum tolerated dose (mean: 150 mg/d). They were evaluated weekly by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)⁹ and the 17-item Hamilton Depression Scale¹⁰ over a period of 12 weeks, being 2 weeks of treatment and 10 weeks of follow up. All patients gave their written informed consent before treatment began.

RESULTS

The patients presented a modest reduction in the Y-BOCS scores at the end of treatment and over the 12-week

follow-up period and 1 presented no reduction. Reductions varied from 6% to 23% at the 2nd week, from 6% to 57% at the 4th week, from 13% to 51% at the 8th week, and from 0% to 43% at the 12th week. Mean reduction at the end of the series of the 14 intravenous infusions in the 2nd week was 11%, which was not significant. There was a significant reduction between the 5th and 7th weeks of the study (Friedman Test = 37.502; $g1 = 12$; $P < 0.05$). Maximum effect was observed at the 5th week, 3 weeks after the end of the administration of IV CMI. From the 8th to the 12th week, a mild increase was observed in the severity of the symptoms that rendered the difference of the Y-BOCS scores in relation to baseline statistically nonsignificant. These results are summarized in Table 1.

DISCUSSION

The interpretation of the results of the present study is limited by the small sample size, the absence of a control group and evaluators who were not blind to the treatment conditions. Some aspects of the results, however, should be highlighted. Our patients presented severe and incapacitating obsessive-compulsive symptoms (baseline mean of 34.5 on Y-BOCS) and had a history of nonresponse to different previous treatment. The majority presented a modest reduction in symptom severity with the treatment, which reached a maximum value around the 5th week, in the follow-up period. The mean reduction of Y-BOCS scores at the 2nd week, after the series of infusions, of 11%, was identical to that reported by Fallon et al⁵ with similar treatment. The mean reduction at the 4th week of 28% was within the range of results reported by other studies using IV CMI, less than the 40% reduction reported by Koran et al⁶ and similar to 26% reported by Fallon et al.⁵ The baseline Y-BOCS scores of our patients, however, were higher than

TABLE 1. Individual Scores in the Yale-Brown Obsessive-Compulsive Scale and Hamilton Rating Scale for Depression*

Patient	Baseline		Week 2		Week 4		Week 8		Week 12	
	Y-BOCS	HAM-D	Y-BOCS	HAM-D	Y-BOCS	HAM-D	Y-BOCS	HAM-D	Y-BOCS	HAM-D
1	31	20	24 (23%)	14 (30%)	29 (6%)	13 (35%)	25 (19%)	18 (10%)	33 (0%)	17 (15%)
2	36	14	33 (8%)	10 (29%)	26 (28%)	10 (29%)	23 (36%)	05 (64%)	27 (25%)	06 (57%)
3	37	15	34 (8%)	12 (20%)	16 (57%)	11 (8%)	18 (51%)	09 (40%)	21 (43%)	08 (47%)
4	30	15	28 (7%)	11 (27%)	17 (43%)	10 (67%)	26 (13%)	14 (7%)	21 (30%)	09 (40%)
5	35	01	30 (14%)	01 (0%)	29 (17%)	06 (0%)	27 (23%)	03 (0%)	25 (29%)	05 (0%)
6	36	20	34 (6%)	16 (20%)	30 (17%)	13 (35%)	30 (17%)	13 (35%)	30 (17%)	11 (45%)
Mean	34.2	14	30.5 (11%)	11 (21%)	24.5 (28%)	11 (21%)	24.8 (27%)	10 (9%)	26.2 (23%)	09 (36%)

Y-BOCS: Yale-Brown Obsessive-Compulsive Scale; HAM-D: 17-item Hamilton Rating Scale.

*Percentages show reduction in relation to baseline value.

those of the patients of the mentioned studies.

An increased and delayed reduction of symptoms was also observed in the period between the end of the infusions and 5th weeks, in agreement with Fallon et al,⁵ who observed a better response 4 weeks after the end of infusions. However, it contradicts the results of other authors, who reported an immediate reduction in the symptoms occurring a few days after the infusions.^{7,8} The patients of those studies were general obsessive-compulsive disorder patients, and did not have a history of refractoriness, like our patients. This may be one of the reasons for the different speed of response that we observed. Future studies comparing the response to IV CMI of refractory and nonrefractory patients could clarify this question.

We can question the cost effectiveness of IV CMI, and the inclusion in the options for severe and incapacitating obsessive-compulsive disorder patient's refractory to usual treatments, since the

results seem to be modest, no matter which criteria are used. On the other hand, we should stress, however, that for those patients, although their symptoms may continue in the severe level after the treatment, a reduction of 8 to 10 points on the Y-BOCS scale, can represent a considerable increase in their capacity for work and interpersonal relationships, and, consequently, an improvement in their quality of life.

Aristides Volpato Cordioli, MD*

Marcelo Basso de Sousa, MD†

Daniela Braga Bochi‡

*Department of Psychiatry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; †Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; ‡Hospital Mãe de Deus, Porto Alegre, Brazil
acordioli@terra.com.br

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