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Research Articles

NEUROENDOCRINE PREDICTORS OF RESPONSE TO INTRAVENOUS CLOMIPRAMINE THERAPY FOR REFRACTORY OBSESSIVE–COMPULSIVE DISORDER

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The current study examines the neuroendocrine response to intravenous clomipramine (IV CMI) in oral CMI-resistant obsessive-compulsive disorder (OCD) patients on day 1 and day 14 of treatment to identify predictors of response. Forty-four OCD patients with an inadequate response or poorly tolerant to oral CMI were begun at 25 mg IV CMI, increasing to 250 mg by day 10, and continuing on that dose to day 14. On day 1, plasma levels of prolactin (PRL), growth hormone (GH), and cortisol were obtained immediately before the 25 mg IV infusion, and at five 30-minute time points after the infusion. On day 14, hormonal samples were obtained in a similar fashion. Response was assessed by the Clinical Global Impressions (CGI). Low PRL_{MAX} to IV CMI and low cortisol levels overall on day 1 were both significantly associated with clinical response at day 14. An overall increase in growth hormone (GH) secretion during the day 14 testing was associated with positive response. A pronounced PRL response to IV CMI on day 14 was exhibited by the nonresponders, whereas a smaller and later but significant increase in PRL was noted in the responders. The findings suggest that in this sample of oral CMI-resistant patients with OCD, neuroendocrine measures derived from pharmacological challenge with IV CMI are capable of distinguishing IV CMI treatment responders from nonresponders. The limitations of IV CMI as a specific probe of serotonin function are discussed. Depression and Anxiety 14:199–208, 2001. ***© 2001 Wiley-Liss, Inc.***

Key words: ***obsessive compulsive disorder; intravenous clomipramine; pharmacological challenge; prolactin; growth hormone; cortisol***

INTRODUCTION

The interpretation of pharmacological challenge studies in obsessive-compulsive disorder (OCD) is complicated by differences in challenge agent, gender response [Monteleone et al., 1997a; Mundo et al., 1999], route of challenge administration [Pigott et al., 1993], and dosing and its relevance to the dissociation between anxious and specific OCD symptoms [Erzegovesi et al., 2001]. Pharmacological challenge strategies have focused on the serotonin (5-HT) system, since controlled studies have demonstrated the unequivocal superiority of serotonin reuptake inhibitors (SRIs) in reducing symptoms of OCD [see Greist et al., 1995 for review]. Although many patients improve with SRIs, approximately 40% to 60% of patients experience minimal or only partial improvement after an adequate trial of these drugs and cognitive-

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behavioral therapy [see Mathew et al., 2000 for review]. No challenge studies to our knowledge have investigated this relatively large medication-refractory population of patients with OCD.

An advantage of utilizing intravenous clomipramine (IV CMI) as a pharmacological probe is that this medication is also an effective treatment in oral CMI refractory OCD [Fallon et al., 1998; Koran et al., 1997], and can thus be incorporated into the treatment protocol. Why is a challenge study in a refractory population important? While IV CMI is effective in certain subsets of patients with OCD refractory to oral CMI, it is costly, time-intensive, fatigue-inducing, and is not effective for the majority of patients. Early dissection of likely treatment responders and nonresponders to IV CMI might prove valuable in light of costs, time, and associated morbidity.

CMI appears to have multiple, complex neurochemical effects which differ over the course of treatment [Pallota et al., 1999a,b]. CMI stimulates several 5-HT receptors, including 5-HT 2 receptors [Attar-Levy et al., 1999], exhibits potent in vitro 5-HT reuptake inhibition, and its metabolite desmethylclomipramine hydrochloride (DCMI) is a potent norepinephrine uptake inhibitor [Hyttel, 1982]. Acute CMI treatment was found to decrease cortical extracellular dopamine (DA) in rats, while chronic treatment increased DA levels by affecting N-methyl-D-aspartate (NMDA)-evoked release of DA [Pallota et al., 1999b]. The parenteral route of CMI administration has a virtual absence of the DCMI metabolite as a result of bypassing first-pass hepatoenteric metabolism [Sallee et al., 1989]. We have suggested that the preferential efficacy of IV CMI over oral CMI relates to the greater bioavailability of the more serotonergic parent compound CMI versus the more noradrenergic metabolite DCMI [Fallon et al., 1998]. In this study, sample treatment response was not related to drug bioavailability, since plasma drug levels were similar in responders and nonresponders [Fallon et al., 1998].

Although several IV CMI challenge studies have been performed in OCD [Mundo et al., 1995, 1999; Sallee et al., 1998b], their relevance to refractory OCD is questionable because this patient population was not assessed. In both adolescent and adult normal controls, parenteral CMI administration has been shown to result in rapid and reliable increases in prolactin (PRL), cortisol, and growth hormone (GH) [Golden et al., 1989; Laakmann et al., 1984; Sallee et al., 1998a]. In a study of nonrefractory OCD patients, Sallee [1998b] found that the initial GH response to 12.5 mg IV CMI challenge differentiated nonresponders to 8 weeks of oral CMI treatment from responders. Likewise, in challenge studies employing d-fenfluramine, a presynaptic 5-HT releaser [Monteleone et al., 1997b], and m-chlorophenylpiperazine (m-CPP), a 5-HT_{2C} agonist [Hollander et al., 1993], blunted levels of PRL in OCD patients differentiated response status to oral SRI treatment, although the studies yielded opposite findings. Thus, although there is precedent in the OCD literature for neuroendocrine response to pharmacologic challenge predicting treatment response status, the studies to date have used nonrefractory populations and none have assessed response to IV CMI treatment.

The present study is one component of a larger placebo-controlled treatment study of IV CMI in OCD refractory to oral CMI [Fallon et al., 1998]. This study is unique by virtue of being the first in our knowledge to employ IV CMI as a neuroendocrine probe in a refractory patient population. As has been demonstrated in nonrefractory populations utilizing 3 different challenge agents [Sallee et al., 1998b; Monteleone et al., 1997b; Hollander et al., 1993], we sought to determine whether neuroendocrine measures derived from IV CMI challenge predicted response to IV CMI treatment.

MATERIALS AND METHODS

SUBJECTS

The IV CMI neuroendocrine challenge was one component of a larger treatment study, a double-blind placebo study of IV CMI in OCD patients with a history of inadequate response or intolerance to oral CMI [Fallon et al., 1998], conducted between 1989 and 1995. Entry criteria, treatment, and ratings from the larger study are described in detail elsewhere [Fallon et al., 1998]. Fifty-four subjects aged 18 to 55 years whose obsessions and compulsions were poorly responsive to oral CMI enrolled in the IV CMI treatment study. Of the 54 patients in the treatment study, 44 consecutively treated patients participated in the neuroendocrine challenge. To maximize the number enrolled in the neuroendocrine challenge component, both patients given IV CMI in the double-blind phase and those who subsequently were treated with IV CMI in an open fashion (patients originally randomized to IV placebo who were nonresponders at the end of the study) were included. The diagnosis of OCD was made by Diagnostic and Statistical Manual, Third Edition, Revised (DSM-III-R) criteria as determined by the intake psychiatrist, confirmed by the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) [Goodman et al., 1989] Symptom Checklist, and by discussion with the referring psychiatrist. Eligible subjects had a Y-BOCS total score of at least 16, which is considered a moderate in severity score. A patient was considered to be "oral clomipramine refractory" or "poorly responsive" if they had received an adequate trial of oral CMI, defined as 8 weeks in duration with at least 2 weeks at 200 mg/day or more, and continued to show no or only partial improvement or an inability to tolerate drug side effects, preventing an adequate trial. Patients retrospectively evaluated their prior response to oral CMI based on the percentage reduction in symptoms.

All subjects received a comprehensive medical examination including a baseline electrocardiogram

(ECG), urine drug screen, and routine laboratory tests, including a serum human chorionic gonadoptropin (HCG) for all women subjects. Patients were taken off all centrally acting medications for 2 weeks prior to participation (or 4 weeks if taking fluoxetine hydrochloride), and were instructed to abstain from other medications for the duration of the study. Patients were excluded from the study if they had unstable medical disease, evidence of cardiac conduction abnormalities, a history of seizures, or were pregnant or nursing. Psychiatric exclusion criteria included mania, psychosis, eating disorder, panic disorder, Tourette's disorder, substance abuse, and moderate to severe depression (Hamilton-D [Hamilton, 1960] score greater than 20) that preceded the onset of OCD. Patients with major depression deemed secondary to the OCD were entered into the study.

After the study was explained, subjects provided written informed consent. The protocol was approved by the institutional review board of the New York State Psychiatric Institute.

CHALLENGE AND TREATMENT PROTOCOL

Patients were placed on a low monoamine diet for all 14 infusions to maintain uniformity, and were in a fasting state from 12:00 a.m. until shortly after the infusions. Patients received 14 consecutive weekday clomipramine (Anafranil, Ciba Geigy, Summit, NJ) infusions either as an outpatient or inpatient (there were 2 weeks without medication). The CMI dosage schedule for the 14 days was as follows: 25 mg × 2 days, 50 mg × 1 day, 75 mg × 1 day, 100 mg × 1 day, 125 mg × 1 day, 150 mg × 1 day, 175 mg × 1 day, 200 mg × 1 day, and 250 mg daily for 5 days. This regimen was not rigidly followed if the patient had certain adverse effects. Thus, the 2 challenge dosages by which neuroendocrine measures were obtained were 25 mg IV on day 1 and 250 mg IV on day 14.

Subjects were supine throughout and were instructed to remain awake throughout the procedure (although with 250 mg of IV CMI, nearly all patients were sleeping). Thirty min prior to the challenge dose of IV CMI, patients had a venous cannula placed. The dose of CMI was administered in 500 ml of 0.9% isotonic over 1 hr, infused at a rate of 0.81 mg/minute. On day 1 and day 14 of the protocol, timed serial blood samples were obtained through the heparin lock immediately prior to drug infusion (time 0), and at 120, 150, 180, 210, and 240 minutes after the infusion. At baseline before the infusion (time 0), 6 cc of blood was obtained for CMI/DCMI levels, and 5 cc were obtained each for cortisol, PRL, and GH. Blood pressure and pulse were recorded every 15 min, and cardiac rhythm was monitored by telemetry.

LABORATORY ASSESSMENT

Blood samples were centrifuged, placed on ice, and stored at –20°C to be assayed as a batch. All samples were assayed in duplicate with the use of previously described methods [Sinha et al., 1973]. Laboratory technicians were blind to the results of clinical assessments. PRL and GH were assayed with the use of a double-antibody radioimmunoassay. The intraassay variability for PRL was 2.0%, while the interassay variance was 3.5%. For GH, within-run and between-run relative standard deviations were 9.62% and 12.38% at 1.54 ng/ml, and 3.17% and 3.75% at 7.49 ng/ml, respectively. Cortisol was measured by radioimmunoassay after denaturation of the binding proteins by heat. The intraassay coefficient of variation ranged from 2.0% to 3.0%, while the interassay coefficient of variation ranged from 2.9% to 6.0%. Plasma CMI and DCMI levels were obtained 23 hr after the last dose and were measured using gas-liquid chromatography (Hewlett-Packard, Sunnyvale, CA) fitted with a nitrogen detector. The extraction method is a minor modification of the method of Cooper et al. [1975] used for imipramine and DCMI. There was a coefficient of variation for CMI of 3.9% at a plasma concentration of 40 ng/ml, 3.4% at 120 ng/ml and 320 ng/ml, while there was a coefficient of variation for DCMI of 6.0% at a plasma concentration of 40 ng/ml, 3.2% at 120 ng/ml, and 4.7% at 320 ng/ml.

RATING MEASURES

Clinical evaluations were performed at baseline (before the day 1 infusion) and 24 hr after the day 14 infusion. This delay in day 14 ratings enabled the independent evaluator to avoid guessing the blinded randomization through observation of CMI's sedating effects. Specific measures included Y-BOCS, the National Institute of Health Obsessive-Compulsive (NIMH-OC) Scale, the Hamilton Depression Scale, and the Clinical Global Impressions (CGI) severity and change scales. For the CGI, subjects with no improvement or minimal improvement were classified as "nonresponders," and subjects with much or very much improvement were classified as "responders." The severity of illness measure corresponded highly with change in Y-BOCS score; we determined that the CGI nonresponders showed a reduction of 3 points or less on the Y-BOCS, and CGI responders showed an average decrement of 13.5 points in Y-BOCS ($t = -8.2$; df = 42; $P < .001$). Side effects were assessed by the Systemic Assessment for Treatment Emergent Events (SAFTEE) checklist.

STATISTICAL ANALYSES

Associations were examined with the use of both the maximal hormonal level (i.e., "prolactin-max") and the maximal minus baseline (Δ max) criteria. We then used a repeated-measures analysis of covariance (ANCOVA-RMs) to compare subject group scores on CGI and hormonal values, where sex and age served as covariates in all analyses. These analyses were applied to 5 change-from-baseline postinfusion values (120, 150, 180, 210, 240 minutes postinfusion) to assess overall group, time, and group-by-time interactions. The

maximum change from baseline (Δ max) for each hormone sampled was compared by two-way ANOVA with age as covariate and group and sex as cofactors. For this analysis, the baseline hormonal value was the level at time 0 (at the start of CMI infusions). Analyses of variance (ANOVAs) were performed in which CGI change was the dependent variable, while gender and hormonal response to challenge were independent variables. When an overall ANOVA yielded significant results, post-hoc pairwise comparisons using Fisher Least Square Differences were performed to identify specific group differences.

Responders were compared to nonresponders in terms of Δ max values by two-way ANCOVA (gender and sex as covariables). To better characterize the neurohormonal secretion in response to challenge, we also inspected by relationship between baseline PRL, cortisol, and GH levels and the area under the curve (AUC) using the trapezoidal rule. All tests were two-tailed, and the alpha was fixed at the $P < 0.05$ level.

RESULTS

SAMPLE CHARACTERISTICS

The mean age of all subjects was 33 ± 9.7, with 25 males and 19 females. The mean age of onset of OCD was 17.20 ± 8.2, and the mean duration of illness was 15 ± 10.5 years. At day 1, the mean Y-BOCS score was 27.9 ± 5.4, and the mean Hamilton Depression Rating Scale (17-item) was 10.9 ± 5.3. There were 30 nonresponders and 11 responders with complete neuroendocrine data available for analysis, per response criteria outlined above. There were no statistical differences found between nonresponders and responders in age, age of onset, illness duration, sex distribution, or baseline Y-BOCS or HAM-D scores.

CMI BLOOD LEVELS

There were no statistical differences in CMI plasma levels between responders and nonresponders obtained for the infusions on day 1 and day 14, with ANOVA not revealing a correlation between plasma CMI value and any hormonal level. Regarding CMI and desmethylated metabolite DCMI plasma levels, there was no responder group effect ($F = 1.09$, df = 1,27, $P = .30$), suggesting that responder status was not a function of plasma drug levels.

NEUROENDOCRINE ANALYSES: PROLACTIN (PRL)

Baseline PRL levels and PRL MAX analyses. There were no significant differences in baseline PRL between responders (8.27 ± 2.96 ng/mL) and nonresponders (8.72 ± 4.0 ng/mL; $t = .34$; $P = .74$). Since there were no baseline differences in PRL levels, we did not covary for baseline PRL value in our initial analyses. In responders, baseline PRL correlated strongly with PRL max (8.61 ± 2.25 ng/mL; Pearson's $r = .72$; $P = .01$). For nonresponders, there was a much less robust correlation between baseline PRL and PRL max (12.21 ± 5.689 ng/mL; Pearson's $r = .31$; $P = .09$).

At day 1 CMI challenge, patients who would respond had a lower overall PRL max (8.61 ± 3.15 ng/mL) in comparison to nonresponders (12.21 ± 5.68 ng/mL, $U = 97.00$, $Z = –2.00$, $P = .045$), per nonparametric Mann-Whitney U test, performed because of a nonnormal distribution. There were no significant differences in PRL max for sex: males (10.54 ± 4.85 ng/mL), versus females (12.25 ± 5.97 ng/mL, $t = –1.01$, df = 39, $P = .31$). When PRL max was covaried for sex, a significant effect for responder status was still noted ($F = 4.19$, df = 38, $P = .048$), suggesting that both male and female responders had blunted PRL max compared to nonresponders. At day 14 treatment with 250 mg IV CMI, the PRL max remained blunted in responders (13.1 ± 13.16 ng/mL) compared to nonresponders (25.40 ± 16.4 ng/mL, Mann-Whitney $U = 62.5$, $Z = –2.47$, $P = .013$), suggesting a preservation of the attenuated PRL status in treatment responders.

ANOVA-RM analyses. To explore the data further so that findings would not be reliant on maximal measures alone, analysis of variance with repeated measures (ANOVA-RM) was performed for day 1 and day 14 or neuroendocrine sampling. For the ANOVA-RM analysis, responder status was the group factor, and the repeated measures were time within the CMI challenge, and day of sampling (day 1 or day 14). At day 1, subjects who would eventually respond to IV CMI treatment at day 14 had lower overall levels of PRL ($F = 6.9$; df = 1,33; $P = .012$). The future responder group on day 1 showed a slight decrease from the baseline value of PRL, while the future nonresponders had a slight increase overall, a strong time effect ($F = 2.36$; df = 5,165; $P = .04$; [Fig. 1]). There was a highly significant responder-by-time interaction ($F = 5.75$; df = 5,165; $P = .00006$), suggesting that the subjects who would be treatment responders remained relatively impervious to the PRL-releasing effects of CMI.

Subjects generally had higher PRL levels overall for the day 14 testing ($F = 11.5$; df = 1,33; $P = .0018$), presumably an effect of the greater dosage of CMI (250 mg). Day 14 ANOVA-RM revealed significant responder, time, and responder-by-time interactions ($F = 3.93$; df = 5,210; $P = .001$), such that despite treatment at high dosages, responders continued to have attenuated increases in PRL compared with the group of nonresponders (Fig. 1).

For the overall day 1 and day 14 ANOVA-RM, which measured changes from day 1 of treatment to day 14, responders continued to have significantly lower PRL levels than nonresponders over both visits. The significant interaction of group-by-visit (day 1 versus day 14) by-time showed that despite massively higher dosages of CMI (10-fold increase), the responders to treatment continued to have attenuated PRL responses across nonbaseline time measurements

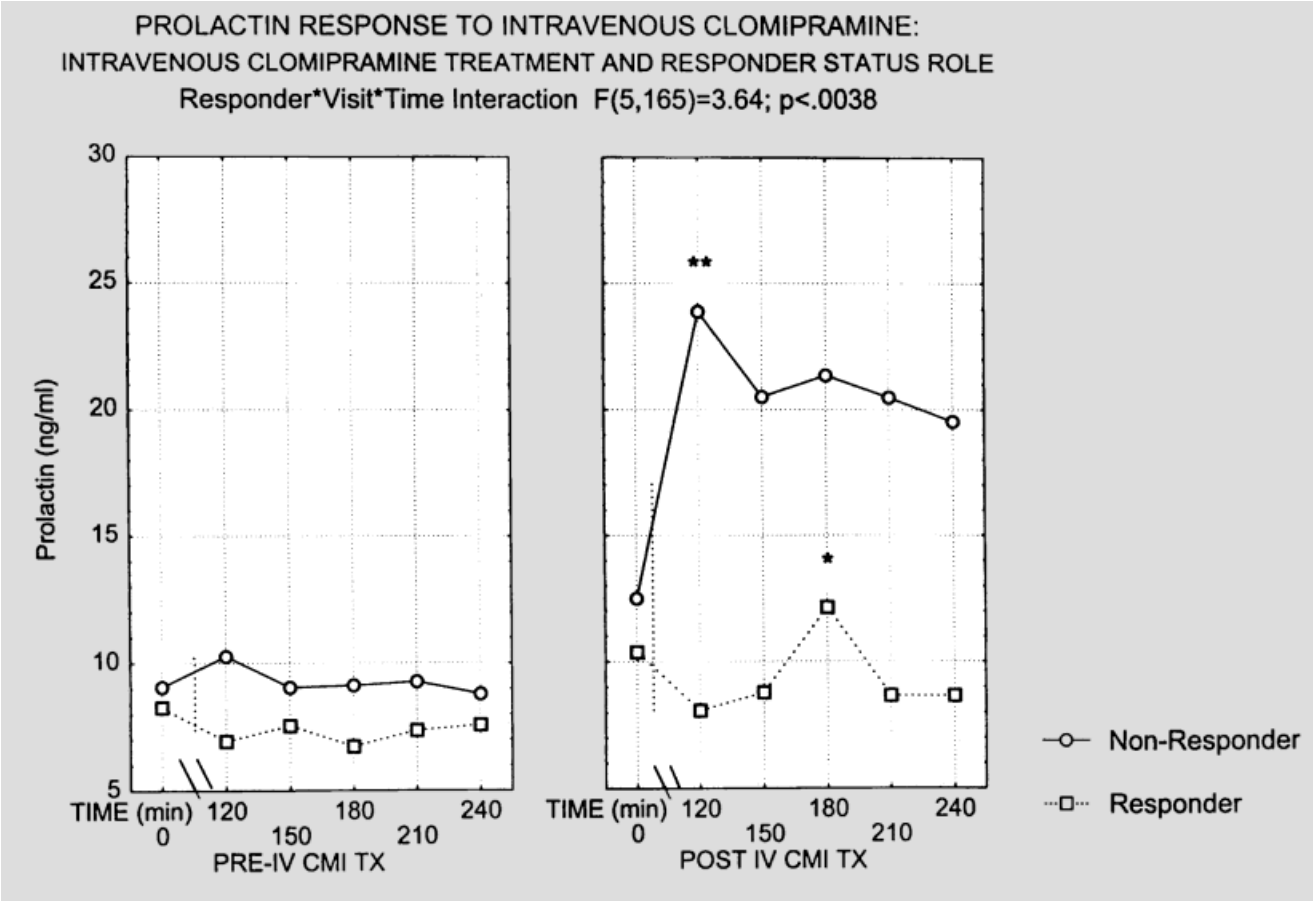

Figure 1. Plasma prolactin (PRL) concentration (ng/ml) illustrated at baseline (0 min), and 120, 150, 180, 210, 240 min after intravenous clomipramine (IV CMI) infusion (25 mg pre-treatment and 250 mg post-treatment). There was a significant responder-by-visit-by-time interaction (analysis of variance with repeated measures [ANOVA-RM]: F = 3.64; df = 5,165; *P* < .0038), with continued blunted PRL levels in treatment responders versus treatment nonresponders for both days of testing. **P* < .05; ***P* < .05.

(F = 3.64; df = 5,165; *P* = .0038) compared to treatment nonresponders (Fig. 1).

Post-hoc testing. Based on the significant overall group-by-visit-by-time interaction, post-hoc testing using least square differences were employed to further characterize the PRL response at day 1 and day 14. Post-hoc analysis for day 1 revealed that for both responders and nonresponders, there were no significant differences in PRL levels for the five time points measured after baseline. On day 14, significant differences between responders and nonresponders were observed (*P* < .05). Figure 1 reveals that at time 2 (120 min), the nonresponder group PRL level is greater than all other time points (*P* < .05). For the responder group, the PRL level at time 4 (180 min) was greater than all other responder PRL levels (*P* < .05). Thus, a pronounced early PRL response to IV CMI on day 14 was exhibited by the nonresponders, whereas a smaller and later but nevertheless statistically significant increase in PRL was noted in the responders. AUC values were determined for each subject using the trapezoidal rule in order to correlate PRL max values with AUC; these did not reveal significant differences between groups.

NEUROENDOCRINE ANALYSIS: CORTISOL

Baseline cortisol levels (measured from the zero time point) did not appear affected by insertion of needle for venipuncture, with values within the normal range in human studies. For day 1 sampling, responders were found to have lower overall cortisols, a group effect (F = 6.58; df = 1,41; *P* = .014) by ANOVA. There was a time effect on day 1 (F = 4.26; df = 5,200; *P* = .001), with both groups showing decreases in cortisol levels from baseline, but no group-by-time interaction (F = .72; df = 5,200; *P* = .605) per ANOVA-RM (Fig. 2). On day 14, the only significant effect was a time effect (F = 7.64; df = 5,185; *P* < .0001) by ANOVA-RM, with both groups showing decreased cortisol values from baseline in response to the 250 mg IV CMI (Fig. 2). Visual inspection of the day 14 plots for cortisol revealed a dramatic decrease in value

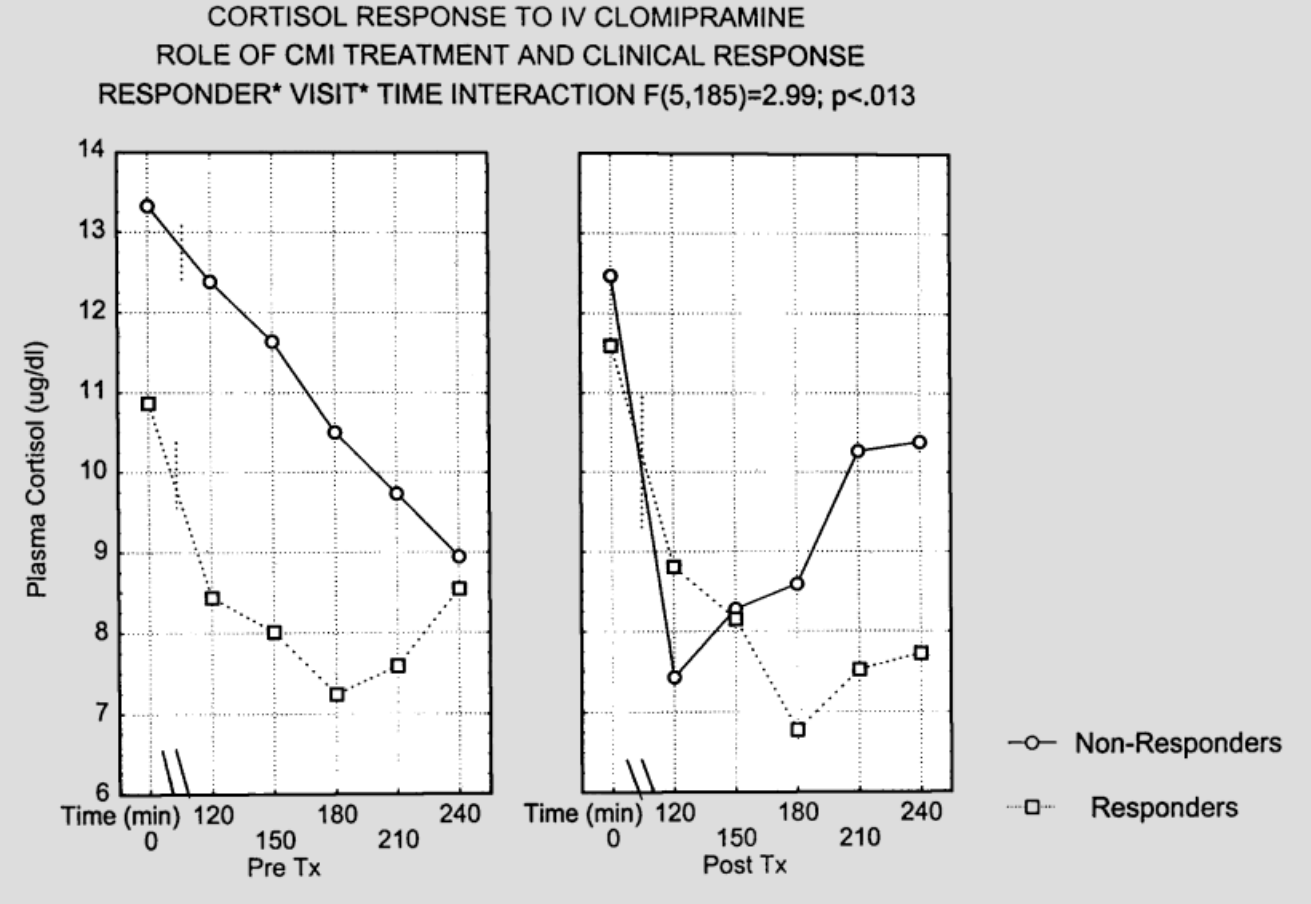

Figure 2. Plasma cortisol concentration (μg/dl) represented at baseline (0 min), and 120, 150, 180, 210, 240 min after IV CMI infusion (25 mg pre-treatment and 250 mg post-treatment). There was a significant responder-by-visit-by-time interaction (ANOVA-RM: F = 2.99; df = 5,185; *P* < .013).

at the 120-min time interval in nonresponders, corresponding to the large increase in PRL level at day 14 in nonresponders at the same time point. At the 120-min time interval, there was an overall inverse correlation noted (r = –.49, *P* = .001), with all contribution to the inverse correlation from nonresponders.

For the overall day 1 and day 14 ANOVA-RM analysis, lower cortisol values were observed in responders (F = 5.94; df = 1,37; *P* = .02; [Fig. 2]) with the day 1 group effect evidently contributing significantly to the overall results. There was a continued strong time effect overall (F = 10.5; df = 5,185; *P* < .001), and an overall group-by-visit-by-time interaction (F = 2.99; df = 5,185; *P* < .013), suggesting that the lower cortisol levels at day 1 in the future treatment responders was sufficiently blunted relative to the nonresponders to maintain overall group differences, and that the marked early decrement in nonresponder cortisol levels for the day 14 visit accounted for the visit interaction (Fig. 2). Gender and age were not significant factors in the responder group differences at day 1. ANCOVA analysis using gender as a covariate was insignificant. AUC analyses did not reveal significant group differences.

NEUROENDOCRINE ANALYSIS: GROWTH HORMONE (GH)

Day 1 revealed no significant group differences in GH response to 25 mg IV CMI challenge (Fig. 3). However, at day 14 infusion, the mean plasma GH during IV CMI infusion was significantly greater in responders than in nonresponders (F = 6.61; df = 1,37; *P* < .015), a group effect that was present when covaried for gender (Fig. 4). At day 14 sampling, ANOVA-RM showed a trend towards a group-by-time interaction (F = 2.14; df = 5,185; *P* = .06), with GH levels in responders showing a massive increase, then decrease over the last two time points (Fig. 3). These results were not effected by baseline GH, as both high (> 4) and low baseline levels showed the same effect. When gender was entered as a covariate in the day 14 analysis, ANCOVA-RM revealed no gender-by-group interaction, with a still significant group effect (F = 5.66; df = 1,35; *P* = .022).

Day 1 and day 14 overall MANOVA-RM analyses using gender as an independent factor were consistent with the day 14 ANOVA-RM in that there was still a

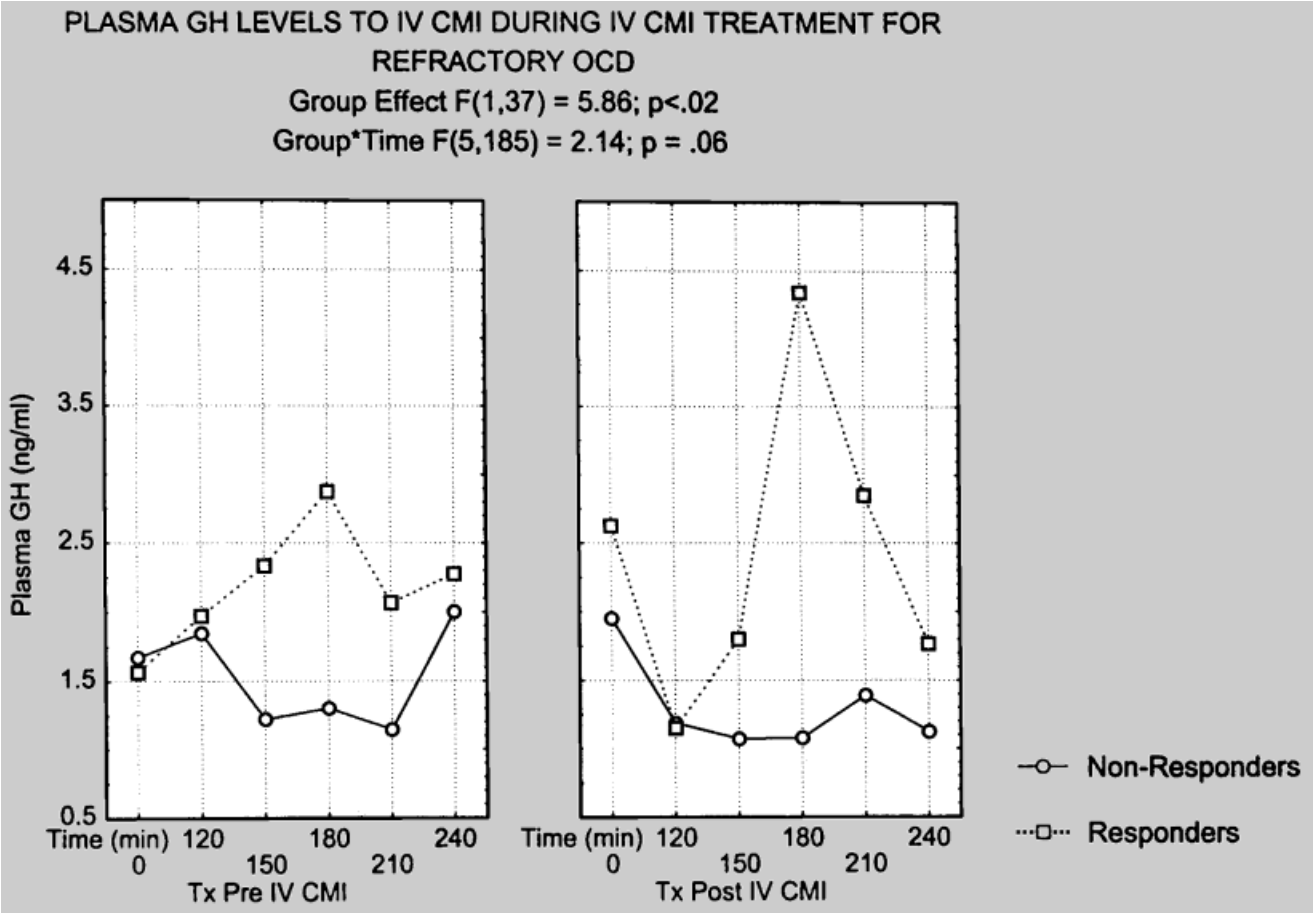

Figure 3. Plasma growth hormone (ng/ml) illustrated at baseline (0 min), and 120, 150, 180, 210, 240 min after IV CMI infusion (25 mg pre-treatment and 250 mg post-treatment). There was an overall group effect, with treatment responders showing increased growth hormone (GH) (ANOVA-RM: F = 5.86; df = 1,37; *P* < .02). OCD, obsessive–compulsive disorder.

significant group effect (F = 5.86; df = 1,37; $P < .02$) and group-by-time interaction (F = 2.14; df = 5,185; $P = .06$), meaning that IV CMI responders showed an overall increased GH response than nonresponders for both visits (Fig. 3). On day 1 and day 14, GH max levels overall were elevated in responders compared to nonresponders, a significant group effect of response status (F = 5.51; df = 1,38; $P < .025$). Post-hoc testing using least square difference revealed a significant elevation of GH max in responders versus nonresponders ($P < .005$) at day 14, which accounted for the higher levels in the overall analysis. In summary, day 1 GH analyses revealed no significant predictors of response status, while on day 14 an overall increase in GH secretion was associated with positive response.

DISCUSSION

This report is the first description to our knowledge of neuroendocrine response to IV CMI in oral CMI-resistant OCD patients, both prior to and during treatment. The principle finding is that low PRL max and low cortisol levels on day 1 of IV CMI infusion were predictive of clinical response to treatment at day 14. In contrast, GH values at day 1 were unable to differentiate responders versus nonresponders. Although it is difficult to infer specific neurochemical system effects of IV CMI given its multiple neurochemical effects on both serotonin and nonserotonergic systems [Pallota et al., 1999a,b], it is noteworthy that the oral CMI-resistant patients who displayed low PRL and cortisol to initial challenge, measures that have been suggestive of abnormal serotonergic function in other studies [Monteleone et al., 1997b; Sallee et al., 1998b], were more likely to respond to IV CMI treatment. Given the refractory nature of our cohort, our results cannot be readily compared to other samples; nevertheless, this study builds on earlier reports that distinguish treatment response in OCD by neuroendocrine challenge measures.

Despite the above findings, there are several limitations to this study. First, the neuroendocrine challenge findings, both on day 1 and day 14, might be affected by prior and intercurrent psychopharmacological treatment. The day 14 neurohormonal findings in particular might by unduly reflective of a "rechallenge effect,"

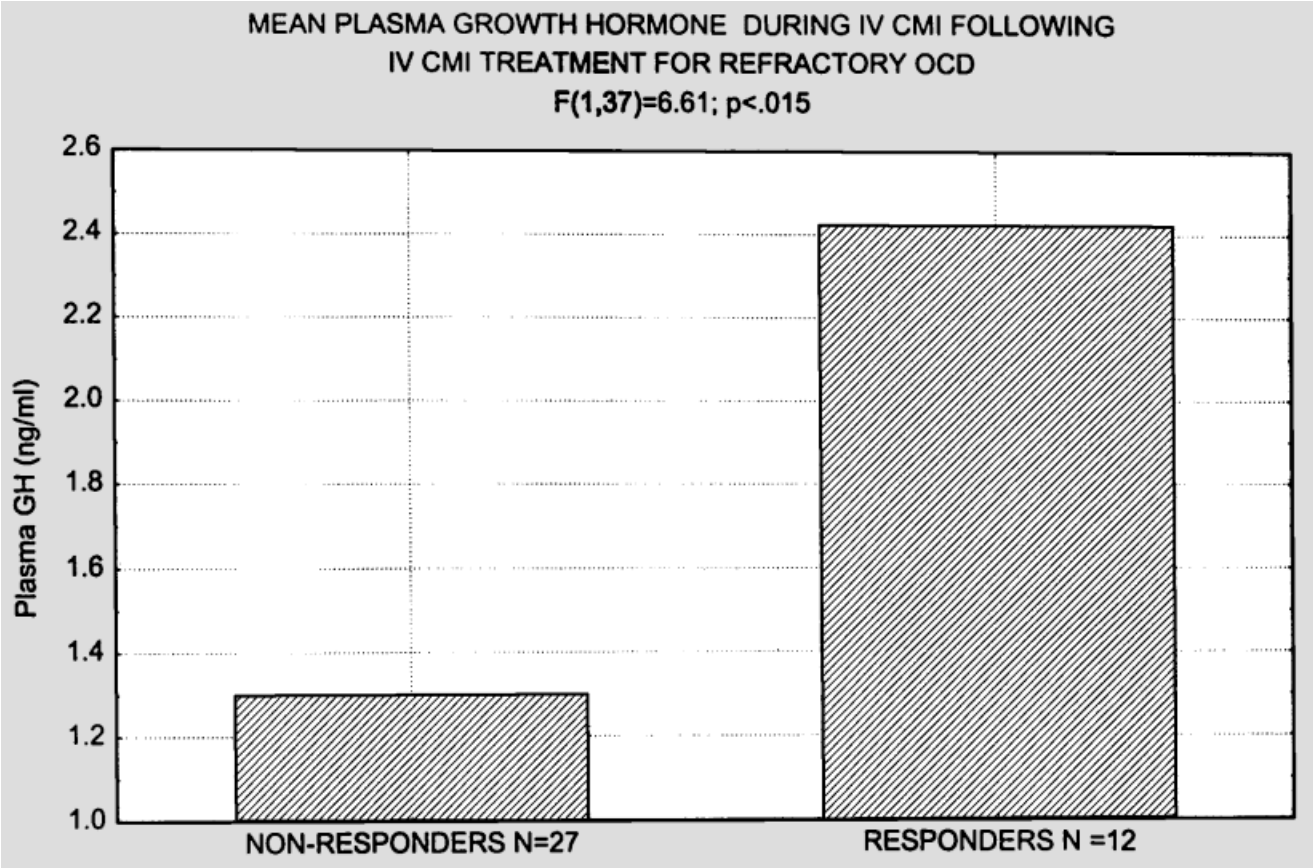

Figure 4. Mean plasma growth hormone levels at day 14 testing, demonstrating a significantly greater response in IV CMI responders than nonresponders (ANOVA-RM: F = 6.61; df = 1,37; *P* < .015).

whereby a prior exposure to IV CMI may cause neuroreceptor changes that effect neuroendocrine measures 2 weeks later [Gilmore et al., 1993]. In our study, not only were the patients in the sample "rechallenged" at a 10-fold higher dose of CMI, but they were treated with ascending dosages of medication in the 2-week interim period between hormonal sampling. Thus, the day 14 results in particular should be viewed with caution in attempting to understand potential neurochemical differences between groups. Second, OCD is a heterogeneous condition with increasing evidence for clinical subtypes and symptom clusters [Mataix-Cols et al., 1999] that are associated with regional blood flow differences [Rauch et al., 1998]. For example, a recent study showed that higher scores on a hoarding symptom dimension predicted poorer outcome with SSRIs [Mataix-Cols et al., 1999]. Thus, subtype and not neuroendocrine profile may in fact account for our findings. Related to this issue, it is questionable whether patients resistant to oral CMI can be considered a clinically distinguishable category, as we know little about previous responses to other SRI treatments. Further, the entry criteria did not differentiate between patients intolerant to oral CMI's side effects and those who were poorly responsive, likely an important neurobiological distinction. A final limitation is the absence of a control group, but given the refractory nature of the patients' OCD, an appropriate control group might not be readily feasible or apparent.

The acute hormonal effects of IV CMI are generally attributed to presynaptic 5-HT action, or to altered postsynaptic receptor responsivity [Sallee et al., 1998b], although the binding profile and multiple neurochemical effects of CMI do not allow for simple interpretations of the neuroendocrine findings. Various 5-HT receptor subtypes, as well as nonserotonin systems, mediate the PRL response, each possibly endowed with different adaptive properties. The only previous assessment of PRL response in OCD with IV CMI challenge showed no difference from controls in a nonrefractory sample [Sallee et al., 1998b]. Curiously, in the current study there was a dramatic increase in PRL levels observed at day 14 challenge for the nonresponder group. One interpretation of this finding, with the above limitations in mind, is disorder heterogeneity, in that the serotonin system is presumably rendered functional (as manifest by the very robust PRL response to IV CMI) but essentially irrelevant to disorder pathophysiology.

The GH response might have limited utility in assess-

ing neurochemical functioning in OCD [Golden et al., 1989], given the pharmacological nonspecificity of both CMI and the multiple determinants of GH response. In our study, the treatment responders when covaried for sex had significantly greater elevations in GH values to 250 mg CMI (day 14) than nonresponders. It should be noted that the directionality of our GH findings at day 14 as an index of treatment response differ from Sallee et al.'s [1998b], although their study used a nonrefractory sample and a different dosage of CMI, making relevant comparisons difficult.

The augmented GH response to IV CMI at high dose in responders in our study raises questions about the role of 5-HT1D receptors in OCD [see Sallee et al., 1998b for review]. Sumatriptan, a selective ligand of the 5-HT1D autoreceptor, has been shown to improve OCD symptoms with chronic administration [Stern et al., 1998]. Using sumatriptan as a 5-HT1D probe, Mota et al. [1995] found that sumatriptan had a stimulatory effect on GH levels, by probable inhibition of hypothalmic somatostatin release. Neuroanatomically, 5-HT1D receptors are densely localized to basal ganglia and caudate, regions important in neuroimaging studies of OCD [Baxter, 1999]. A possible increased inhibitory autoreceptor 5-HT1D sensitivity would be consistent with previous suggestions of low 5-HT tone in responders [Monteleone et al., 1997b], although we did not find differences in GH response to low dose initial challenge.

Our report's finding that low cortisol levels in response to IV CMI challenge predicted treatment response status, similar to the PRL results, could be interpreted as impaired 5-HT function predicting response to IV CMI, although any neurochemical inferences must be tentative given the nonspecificity of CMI as a probe of serotonergic function. Our finding might reflect differentially subsensitive 5-HT2 receptor activity in refractory patients, as CMI has been shown to enhance 5-HT-mediated cortisol release, which is regulated partly by 5-HT2 receptors [Sargent et al., 1998].

In summary, this paper lends support to the notion that neuroendocrine response can be used to distinguish responder status to IV CMI treatment in oral CMI refractory patients with OCD. The present report also suggests the limitations of utilizing IV CMI as a specific probe for 5-HT function.

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