Cerebral blood flow in obsessive–compulsive patients with major depression: effect of treatment with sertraline or desipramine on treatment responders and non-responders

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Abstract

We examined the effects of sertraline and of desipramine on patients with OCD and comorbid major depressive episodes at study entry. Sixteen patients, 9 receiving sertraline and 7 desipramine, received HMPAO SPECT scans while free of medication and after 12 weeks of treatment. Patients on sertraline showed significantly reduced regional cerebral blood flow (rCBF) in the right prefrontal and temporal regions. Patients on desipramine showed more diffuse rCBF reductions in frontal and temporal regions, more so in the left side. In a second analysis, patients who had a symptom reduction on the Yale–Brown Obsessive Compulsive Scale (YBOCS), irrespective of the type of medication, were retrospectively classified as ‘responders’ to treatment. Eleven patients were ‘responders’ and 5 ‘non-responders’. Before being medicated, responders differed from non-responders through higher rCBF in prefrontal regions, mostly on the left, and higher rCBF in the cingulate and basal ganglia bilaterally. After 12 weeks of treatment, responders showed a diffuse reduction of rCBF in prefrontal regions while non-responders showed only...
a few scattered low-frequency responses. Thus, higher prefrontal and subcortical activity was associated with better response to drug treatment. In addition, clinical change, but not the administration of medication as such, was associated with a decrease of prefrontal rCBF. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

The most consistent findings in imaging studies of obsessive–compulsive patients are increased blood flow or glucose metabolism in the orbitofrontal and anterior cingulate cortex as well as the caudate nucleus, which is accentuated during symptom provocation (for review see Insel, 1992; Hoehn-Saric and Benkelfat, 1994; Saxena and Rauch, 2000). This hyperactivity attenuates after treatment with fluoxetine (Hoehn-Saric et al., 1991), clomipramine (Benkelfat et al., 1990; Molina et al., 1995) or behavior therapy (Schwartz et al., 1996). Changes in regional cerebral activity during depression are more varied, although the majority of studies found anterior hypoactivity (Ketter et al., 1997). Consistent decreases in CBF or metabolism were found in the prefrontal, cingulate and amygdala regions (Kennedy et al., 1997). While the majority of studies reported a baseline decrease in prefrontal activity in depressed patients, which increased during treatment with antidepressants (for review see Marsh et al., 1996; Mayberg et al., 1997; Schlaepfer and Pearlson, 1997), some studies found the opposite, namely an increase in prefrontal activity during depression that decreased during treatment (Drevets, 2000). However, in the latter study, pure familial depressed patients were ruminating and possibly obsessing, which may have caused hyperfrontality in their scans. Increases as well as decreases in other brain regions have been observed with treatment (Mayberg et al., 1997; Drevets 2000). Thus, the relationship between depression and regional cerebral blood flow (rCBF) is more complex than in OCD, probably because of the more heterogeneous nature of depression.

Recently we conducted a study in which we compared the effects of sertraline with desipramine in chronic obsessive–compulsive patients who, at the time of the study, also suffered from major depression (Hoehn-Saric et al., 2000). We demonstrated that, while both medications reduced depression and obsessive–compulsive symptoms, sertraline was more effective than desipramine in reducing symptoms of both disorders. However, only 48% of patients receiving sertraline and 31% of patients receiving desipramine showed a 40% or greater reduction of obsessive–compulsive symptoms. To examine the effects of sertraline and desipramine on rCBF in OCD patients with comorbid depression, we obtained SPECT scans in a subsample of the study population before they were placed on medication and at the end of the 12-week treatment period. We predicted a stronger reduction of hyperfrontality after treatment with sertraline than with desipramine. In addition, we examined in this subgroup the characteristics of rCBF and its changes in patients who were retrospectively divided into responders and non-responders to treatment. The responders and non-responders were compared at pretreatment baseline. In addition, comparisons were made between rCBF changes in each group before and at the end of treatment. We predicted that responders would show, at the end of treatment, greater rCBF reduction in prefrontal areas and the caudate than non-responders.

2. Methods

2.1. Subjects

Subjects were chosen from patients enrolled in a larger study (Hoehn-Saric et al., 2000). The subgroup that received SPECT scans consisted of the first 16 enrolled patients who consented to be scanned and finished treatment. They had to be at least 3 weeks free of medications affecting the central nervous system and 5 weeks free if they
Fig. 1. Changes in rCBF from before to end of treatment with sertraline (Weeks 0–12).

Fig. 2. Changes in rCBF from before to end of treatment with desipramine (Weeks 0–12).
Fig. 3. Differences in rCBF between responders and non-responders before medication (Week 0).

Fig. 4. Change in rCBF in all responders to medication from before to end of treatment (Weeks 0–12).
had been on fluoxetine, and had to meet inclusion criteria at the time of randomization before they were included in the study. Patients of this subgroup were of both sexes and between the ages of 18 and 65. They were diagnosed using the SCID for DSM-III-R (Spitzer et al., 1992) as having long-standing OCD and, at the time of the evaluation, Major Depression. They had to score 20 or above on the YBOCS (Goodman et al., 1989) and 18 or above on the 24-item Hamilton Scale for Depression (HAM-D) (Hamilton, 1967). Patients with health problems or additional comorbidity were excluded. All scanned patients were right-handed. The institutional review board approved the study and patients signed an informed consent.

2.2. Treatment

Suitable patients were randomly assigned to a sertraline or desipramine group, using a double-blind parallel design. Medications were gradually increased to the highest level tolerated by the patient, with a maximum dose of 200 mg/day for sertraline and 300 mg/day for desipramine. The length of treatment was 12 weeks. Patients were assessed weekly during the first 8 weeks and thereafter every 2 weeks, using the YBOCS for obsessive–compulsive symptoms and the HAM-D for depression. At the end of the study, we divided patients whose YBOCS score had decreased 30% or more into a responder group and those with lesser responses into a non-responder group. A 30% symptom reduction was chosen on clinical grounds, representing changes from severe to moderate or from moderate to mild symptoms, and was a compromise between the more stringent definition of a 35% improvement (McDougle et al., 1994) and the more modest 25% improvement seen in other studies of drug treatment of OCD, for instance, Saxena et al. (1999).

2.3. Imaging

Patients were scanned at the end of the drug-free period and again at the end of 12 weeks on the study medication. Image analysis was performed according to a previously reported method (Schlaepfer and Pearlson, 1995). Approximately 20 mCi of the SPECT blood flow tracer $^{99m}$Tc-HMPAO was injected intravenously. Fifteen minutes before the injection of the tracer, subjects were blindfolded and their ears covered with a silencer in order to minimize auditory and visual stimulation. SPECT scans were performed using a triple-headed (TRIONIX TRIAD) gamma camera 30–60 min after HMPAO administration. Each SPECT scan was individually examined for possible artifacts and overall image quality. Image data were analyzed using the statistical parametric mapping (SPM) program ‘SPM 94’ (Friston et al., 1989, 1990, 1991). Significant regional cerebral blood flow (rCBF) decreases from pre-treatment to end of treatment and between responders and non-responders were calculated by averaging subjects’ images for each respective drug (sertraline or desipramine) after correcting for the injected dose of radioactivity. The exact localization of the voxels with the most significant differences was found using the brain atlas of Talairach (Talairach and Tournoux, 1988). The significance levels cited for the above SPM analysis are ‘corrected’ for the problem of multiple-dependent comparisons by a statistical technique based on Gaussian random field theory (Adler, 1981). Roughly speaking, the SPM test-statistic is the peak height of a contiguous set of voxels exceeding a given threshold (Worsley et al., 1992; Friston et al., 1995).

3. Results

3.1. Clinical changes

Out of the first 18 enrolled study patients, 16 participated in the imaging study. One patient refused participation and one patient dropped out before completion of the study. Toxicology screens on days of scanning were negative for prohibited
substances. None of the 32 SPECT scans had to be excluded from the analysis for artifacts or problems with image quality.

Nine patients received sertraline. Their average age was 38.5 (22–65) years, 2 were male, 8 white and 1 African–American. They received an average daily dose of 194 (150–200) mg of sertraline. Their mean sertraline blood levels were 99.3 (26–211) μg/l at Week 12. Their mean pretreatment YBOCS score was 25.1 (20–28) and the mean HAM-D score was 26.8 (19–34). End of study scores were 13.9 (2–29) and 10.7 (1–24), respectively.

Seven patients received desipramine. Their average age was 40.2 (25–50) years, 4 were male, 6 were white and 1 East Asian. They received an average daily dose of 228.5 (150–300) mg of desipramine. Their mean desipramine blood level was 322 (108–545) μg/l at Week 12. Mean scores on the YBOCS and the HAM-D were 24.0 (22–26) and 23.6 (19–27), respectively, before treatment, and 9.6 (1–20) and 7.9 (3–17), respectively, at the end of the study.

Eleven of the 16 patients were responders with a mean age of 41.1 (28–65) years; 3 were male, 9 were white, 1 was African–American and 1 East Asian. They had a mean education of 16.1 (14–20) years. Six of the patients had received sertraline (all 200 mg/day), with mean plasma drug level of 111.8 (46–140) μg/l at Week 12. Three patients had received desipramine, with a mean dose of 250 (200–300) mg/day, and mean plasma level of 305.2 (108–545) μg/l at Week 12. Mean HAM-D scores were 25.4 (19–29) at Week 0 and 6.8 (1–17) at Week 12; mean YBOCS scores were 25.1 (22–28) at Week 0 and 7.0 (1–16) at Week 12.

The remaining 5 patients were non-responders with a mean age of 35.0 (22–41) years; 3 were male, all were white, with a mean education of 16.4 (13–19) years. Three had received sertraline, with a mean dose of 175 (150–200) mg/day with a mean plasma level of 74.3 (26–166) μg/l at Week 12, 2 had received desipramine, 150 and 300 mg/day, with plasma levels of 367 and 455 μg/l at Week 12. Mean HAM-D scores were 25.4 (19–29) at Week 0 and 15.4 (6–24) at Week 12; mean YBOCS scores were 23.6 (22–28) at Week 0 and 23.0 (19–27) at Week 12.

3.2. Changes in rCBF on sertraline and desipramine

Fig. 1 shows changes in rCBF in patients receiving sertraline. From before to after 12 weeks of treatment, patients had significant reductions of CBF in both frontal lobes with a clear maximum in the right lobe and smaller reduction of rCBF in a right temporal area (all $P < 0.01$).

Fig. 2 shows the changes in rCBF in patients who received desipramine. Patients also showed a widespread and very large rCBF decrease in both frontal lobes that was slightly more prominent on the left (all $P < 0.01$).

3.3. Differences in rCBF between responders and non-responders before treatment

Fig. 3 depicts differences between responders and non-responders at the time when they were drug-free at baseline. Responders had higher CBF in prefrontal regions, including the orbital cortex, with an accentuation on the left and higher activity in the basal ganglia and cingulate compared to the CBF of non-responders.

3.4. Differences in rCBF between responders and non-responders after 12 weeks of treatment

Figs. 4 and 5 depict changes in rCBF from before to the end of treatment, whereby each group included responders or non-responders who had received either sertraline or desipramine. Responders showed a diffuse decrease in rCBF in the prefrontal regions, slightly stronger on the left than the right side and increased activity in parietal regions. Changes in non-responders showed only a relatively few scattered low-frequency decreases.

4. Discussion

Both sertraline and desipramine treatment was associated with reduced rCBF in frontal regions, but the distribution of the reduction differed. Reductions after sertraline were predominately on the right side. This area corresponded to regions that have been found hyperactive in unmed-
Fig. 5. Change in rCBF in all non-responders to medication from before to end of treatment (Weeks 0–12).
iated OCD patients (Harris et al., 1994; Hoehn-Saric and Greenberg, 1997) and may be specifically involved in the pathology of OCD since transcranial magnetic stimulation led to a temporary reduction of obsessive–compulsive symptoms after stimulation of right but not left prefrontal areas (Greenberg et al., 1997) and neurosurgical intervention improved chronic OCD patients by interrupting right- but not left-sided fronto-thalamic connections (Lippitz et al., 1997).

Desipramine had a wider effect on rCBF, involving both hemispheres but more the left than the right one. In this study, desipramine also was found to reduce OC symptoms. However, because of the double-blind design of the study, demanding an increase of the study medication to the maximum tolerated level, desipramine blood levels were high; in 5 out of 7 patients they were above recommended therapeutic levels, although they were well tolerated. Since desipramine has some serotonin reuptake inhibiting properties (Chen and Reith, 1994) and reduces serotonin-2 receptor binding (Yatham et al., 1999), it is possible that high doses of desipramine led to the reduction of OC symptoms via serotonergic mechanisms.

An alternative explanation is that the reduction of rCBF reflects clinical improvement rather than a specific effect of the medications on the brain in depression as well as in OCD. Therefore, greater changes are seen in improving patients, irrespectively of intervention. There is good evidence for the latter explanation. In depressed patients a greater reduction of rCBF or metabolism has been found after fluoxetine (Mayberg et al., 2000) and after ECT (Milo et al., 2001). In OCD patients responders showed greater changes after fluoxetine (Baxter et al., 1992; Schwartz et al., 1996), clomipramine (Swedo et al., 1989; Benkelfat et al., 1990), paroxetine (Saxena et al., 1999) and behavior therapy (Schwartz et al., 1996). We also found that, irrespective of the medication, responders showed significant blood flow changes while non-responders did not.

In depressed patients most imaging studies have shown decreased (Mayberg et al., 1997) but some have shown increased frontal activity (Drevets, 2000) in addition to altered activity in the anterior cingulate (Mayberg et al., 1997), the amygdala and related parts of the striatum and thalamus (Drevets, 2000). Moreover, reports of the effects of antidepressants on brain activity in depression are inconsistent. In several studies, treatment of depressed patients with antidepressants tended to reverse baseline abnormalities, leading to an increase (Baxter et al., 1985) or to a decrease in some but an increase in other regions (Mayberg et al., 1997; Kocmur et al., 1998; Kennedy et al., 2001) of metabolism or perfusion. Treatment may reverse some abnormalities while not affecting others (Martinot et al., 1990; Goodwin et al., 1993; Drevets, 2000) or fail to induce changes (Hurwitz et al., 1990). It is conceivable that antidepressants normalize brain activity in different ways, depending on the etiology or stage of depression. In our OCD patients with depression, a reduction of prefrontal cerebral activity was associated with a reduction of depression. However, the diagnosis of major depression includes disorders of a heterogeneous nature. Some of our patients with OCD may have had endogenous depressions while others may have suffered from secondary depressions such as being demoralized by chronic OCD symptoms.

The division of patients into responders and non-responders yielded two sets of results: (1) Untreated patients whose obsessive–compulsive symptoms subsequently improved on medications differed from patients who failed to improve by having higher rCBF in the left prefrontal region, basal ganglia and cingulate. (2) As discussed above, patients who improved on either sertraline or desipramine showed a reduction of rCBF in prefrontal and parietal regions, while patients who failed to improve in spite of adequate doses of medication showed no significant changes in cerebral blood flow.

In several studies, improvement of treated unipolar depression has been associated with an initially increased activity of prefrontal regions. Wu et al. (1999) found that unipolar depressed patients who responded to sleep deprivation had higher relative metabolic rates in the medial prefrontal cortex, ventral anterior cingulate, and posterior subcallosal gyrus at baseline. Buchsbaum et al. (1997) reported a significant correlation
between metabolic activity in the left rectal gyrus and improvement. Individuals who had high values at baseline more likely improved on sertraline and showed lower metabolic rates after treatment. Mayberg et al. (1997) found patients with high pretreatment rostral anterior cingulate metabolism to respond better to antidepressants than patients with low metabolism who remained significantly depressed after 6 weeks of treatment. Pizzagalli et al. (2001), using low-resolution electromagnetic tomography, found depressed patients to respond better to nortriptyline when showing hyperactivity in the rostral anterior cingulate. On the other hand, others have reported lower baseline pregenual anterior cingulate (Brody et al., 1999) and bilateral medial frontal metabolism (Little et al., 1996) to predict superior response to antidepressants.

In spite of the success in the treatment of OCD with serotonin reuptake inhibiting drugs, 20–40% of OCD patients do not respond adequately to treatment (Pigott and Seay, 1997). Imaging studies have been only moderately successful in identifying brain activity associated with clinical improvement. Studies associated lower activity in the right (Baxter et al., 1992) or left caudate nucleus (Benkelfat et al., 1990), the right orbitofrontal cortex and cingulate gyrus (Swedo et al., 1989; Brody et al., 1998) or the right and left orbitofrontal cortex (Saxena et al., 1999) with a more favorable response to medication. However, in one study (Benkelfat et al., 1990) the difference in caudate metabolism between responders and non-responders failed to reach significance. In another study (Swedo et al., 1989), the association between response and lower activity on orbitofrontal and cingulate cortex was not confirmed when patients were re-examined at a later point (Swedo et al., 1992). In the study of Saxena et al. (1999) correlations between prefrontal metabolisms, while significant, were low. Interestingly, Brody et al. (1998) associated low orbitofrontal metabolism with patients receiving fluoxetine but with poorer outcome in those given behavior therapy. Mindus et al. (1986) found lower global metabolism in OCD patients who were treatment failures and became candidates for neurosurgery. Since our patients were also depressed, it is possible that some observed brain activities were associated with depression and differed from findings in ‘pure’ OCD or depression. However, non-responders were classified on the basis of changes in OCD symptoms, which in all cases preceded the depression. Moreover, regions that changed during treatment corresponded to regions, which have been found in previous studies to be hyperactive in OCD rather than depression (Hoehn-Saric and Greenberg, 1997).

A possible explanation for the diverse findings may be that in OCD regional cerebral activity in basal ganglia and prefrontal cortex reflects attempts to compensate for dysfunction and manifests itself, according to severity of the disorder, in an inverted U shape. Mild cases may need less compensatory activity than more severe cases. However, the most severe and treatment-resistant cases may have suffered sufficient localized neuronal damage to exhibit lower regional activity which makes compensatory responses impossible. Recent studies, measuring N-acetyl-aspartate with magnetic resonance spectroscopy, suggest neuronal loss in the cingulate gyrus and the right striatum of OCD patients (Ebert et al., 1997). Comparisons of striatal N-acetyl-aspartate levels in responders and non-responders with magnetic resonance spectroscopy may clarify the validity of the above hypothesis.

In conclusion, our findings confirm other studies that showed greater changes in brain metabolism or rCBF in patients who responded to treatment than non-responders, irrespective of the therapeutic interventions. Thus, changes in cerebral activity correspond with changes in psychopathology rather than reflecting response-independent effects of treatment modalities. The findings also suggest biological differences between patients who respond and patients who fail to respond to pharmacological treatment. However, our study has various limitations and the results need to be seen as preliminary. Unfortunately, because of a crash of the computer disk we had to rely on an older method of image analysis and were unable to reanalyze the data with more advanced programs. Another methodological limitation is that our patients suffered
from OCD and comorbid major depression and the number of patients was small. Studies of treatment response need to compare cerebral activity changes in OCD patients with and without depression. Another limitation is that our study and other studies defined non-responders as patients who failed to improve on a single treatment modality. To exclude the possibility of the biological inability of the brain to respond to a specific medication, non-responders should be defined as patients who have failed several treatment regimes. Finally, in our study, patients took clinically adequate doses; however, drug plasma levels varied considerably at the end of the study, ranging from low to excessively high. In most studies plasma drug levels have not been reported and variation in drug levels may account for some variations in the results. Therefore, in future studies plasma levels of the medications need to be controlled.

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