Fluvoxamine Attenuates Panic Induced by 35% CO_2 Challenge

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Background: The authors investigated whether 6 weeks of treatment with fluvoxamine would decrease the anxiogenic response to the 35% CO_2 challenge in 11 patients with DSM-III-R panic disorder with agoraphobia.

Method: The patients underwent a 35% CO_2 challenge at baseline and again after 6 weeks of fluvoxamine treatment.

Results: The anxiogenic effect of CO_2 was significantly ($p < .05$) reduced during fluvoxamine treatment.

Conclusion: The results suggest a relationship between the anxiogenic effect of CO_2 and the therapeutic effect of fluvoxamine.

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Behavioral vulnerability to the inhalation of carbon dioxide–enriched gas mixtures has been repeatedly observed in panic disorders, although the method, dose, and duration of carbon dioxide inhalation throughout different studies vary considerably.[1–4]

The use of one vital capacity inhalation of 35% CO_2/65% O_2 as a challenge test typically provokes high levels of anxiety and somatic symptoms of panic in panic patients, but only limited somatic symptoms in healthy controls.[3,5] In addition, this behavioral vulnerability is absent in obsessive-compulsive patients,[6] patients with a phobia of animals,[7] and depressive patients[8] and appears to be independent of baseline anxiety level.[9]

Studies addressing the effects of anxiolytic drug treatments on the anxiogenic response to the 35% CO_2 challenge are yet limited. We have demonstrated that 5 weeks of treatment with the high-potency benzodiazepine clonazepam significantly decreased the anxiogenic response to the 35% CO_2 challenge in panic disorder patients.[10] Another study using the 35% CO_2 challenge evaluated the effect of 1 week of treatment with the reversible monoamine oxidase inhibitor toloxatone versus placebo on carbon dioxide vulnerability. Toloxatone significantly reduced the anxiogenic response to carbon dioxide, whereas the vulnerability during placebo treatment remained stable.[11]

Studies using other methods of CO_2 administration have also shown decreased anxiogenic response to CO_2 after long-term treatment with imipramine[12] and alprazolam.[2,13] Fluvoxamine, a serotonin selective reuptake inhibitor (SSRI), has shown efficacy in the treatment of panic disorder by decreasing the number of panic attacks, the level of overall and anticipatory anxiety, and the agoraphobic avoidance behavior in several controlled studies.[14,15] To study the effect of long-term fluvoxamine treatment on the anxiogenic response to the 35% CO_2 challenge in panic disorder patients, the following study was undertaken.

METHOD

Patients

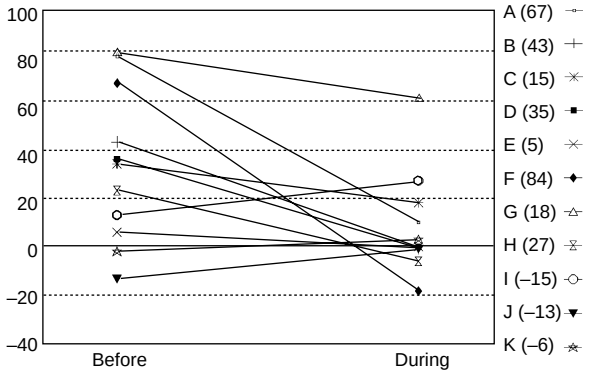
Eleven outpatients (9 women, 2 men: mean ± SD age = 35.6 ± 10.9 years; range, 24–59) were diagnosed by two experienced clinicians (J.A.M., E.J.G.) as meeting DSM-III-R criteria for a principal diagnosis of panic disorder with agoraphobic avoidance behavior. Two of the 11 carried an additional diagnosis of dysthymia. After giving informed consent, all patients underwent a 35% CO_2 challenge at baseline and subsequently entered a treatment program with fluvoxamine. Treatment was started with an initial dose of 50 mg/day for the first 4 days, increased to 100 mg/day for the following 4 days, and further increased to an effective dose of 150–200 mg/day for the remaining treatment period. During the initial 2 weeks of fluvoxamine treatment, concurrent medication with the benzodiazepine clonazepam, in a twice-daily dose of 0.5 mg, was allowed. In the third week of fluvoxamine treatment, this dose was tapered, and patients were free of any concurrent medication at Week 6. After a mean treatment period of 6 weeks (range, 5–7) with a mean daily fluvoxamine dose of 159 mg (± 20.2 mg; range, 150–200), the 35% CO_2 challenge was repeated.

Table 1. Mean ± SD Scores on Self-Rating Scales at Baseline and After 6 Weeks of Fluvoxamine Treatment in 11 Patients With Panic Disorder With Agoraphobia*

	Baseline		After Fluvoxamine Treatment		Paired t Test (df = 10) t, p Value	
Scale	Mean	SD	Mean	SD	t	p
SAS[15]	54.4	5.2	41.2	13.7	3.34	.05
SDS[16]	52.1	6.4	41.8	11.6	3.33	.05
STAI-I[17]	50.0	9.2	43.1	16.0	1.71	NS
STAI-II[17]	57.9	6.0	46.9	8.8	4.07	.05
FQ[18]	56.8	26.7	46.5	24.9	1.41	NS
FQ-Ag[18]	27.3	12.0	21.9	12.5	1.66	NS

*Abbreviations: SAS = Zung Self-Rating Anxiety Scale, SDS = Zung Self-Rating Depression Scale, STAI = State-Trait Anxiety Inventory, FQ = Fear Questionnaire, FQ-Ag = Fear Questionnaire agoraphobia subscale, NS = not significant.

Figure 1. Individual Scores on the Visual Analogue Scale of Anxiety (VAS-A) Before and During Fluvoxamine Treatment



*For patients A to K, the change on the VAS-A is given in parentheses.

35% CO_2 Challenge

The 35% CO_2 challenge is extensively described elsewhere.[6] In short, patients were informed before performing the test that they would inhale two different gas mixtures containing different percentages of CO_2 and O_2, and that during the challenge they might experience some discomfort, ranging from a few physical symptoms to a definite sensation of anxiety. No reference to a panic attack was made in the instruction. The order of the administration of gases, a 35% CO_2/65% O_2 mixture or compressed air, was random. Patients were asked to take one vital capacity inhalation of the gas mixture and to hold their breath for 4 seconds. Before and after each inhalation (air or CO_2), patients were asked to fill in a visual analogue scale of anxiety (VAS-A), which is a 100-mm scale ranging from 0 (no anxiety at all) to 100 (worst anxiety ever imaginable). In addition, patients had to fill in a panic symptom list (PSL-III-R), which is a self-administered questionnaire assessing the 13 panic symptoms, as described in DSM-III-R, on a 5-point scale (0 = absent to 4 = very intense), resulting in a total score (PSL-III-R, range, 0–52). The net score of the 35% CO_2 challenge test was calculated by subtracting the difference of the postinhalation minus preinhalation values of the air condition from the difference in postinhalation minus preinhalation values.

Clinical Assessment

The Clinical Global Impressions scale for Severity of Illness[16] (CGI-S), a 7-point scale ranging from 1 = not at all ill to 7 = among the most extremely ill patients, was scored by the treating physician at baseline and after 6 weeks of treatment. In addition, a Clinical Global Impressions-Improvement scale[16] (CGI-I), a 7-point scale ranging from 1 = very much improved to 7 = very much worse, was scored after 6 weeks. At baseline and after 6 weeks, self-rating scales for anxiety (Zung Self-Rating Anxiety Scale [SAS], State-Trait Anxiety Inventory-I and -II [STAI-I, STAI-II]), depression (Zung Self-Rating Depression Scale [SDS]), and phobias (Fear Questionnaire [FQ] and its agoraphobia subscale [FQ-Ag]) were administered.[17–20] Clinical assessments were made prior to CO_2 testing.

RESULTS

Fluvoxamine Treatment

Mean ± SD ratings on the CGI-S at baseline and during 6 weeks of fluvoxamine treatment were 4.9 ± 0.53 versus 3.72 ± 1.00, respectively (paired t = 3.35, df = 10, p < .05). Ten of the 11 patients were considered fluvoxamine responders in the judgment of the treating physician. On the CGI-I, 1 patient was rated as "no change," 4 were rated as "minimally improved," 5 were rated as "much improved," and 1 was rated as "very much improved."

On self-rating scales for anxiety and depression, significant improvement was observed (Table 1). On self-rating measures for phobias, no significant effect was observed.

35% CO_2 Challenge

Mean ± SD net scores on the VAS-A at baseline and after 6 weeks of fluvoxamine treatment were 33.2 ± 31.7 versus 9.5 ± 21.1, respectively (paired t = 2.46, df = 10, p < .05), and for the PSL-III-R were 9.1 ± 6.5 versus 5.3 ± 5.9, respectively (paired t = 2.02, df = 10, N.S.). The 35% CO_2 challenge results are graphically illustrated in Figure 1.

We computed whether there was a correlation between the decrease in carbon dioxide–induced anxiety—before and during fluvoxamine treatment—and the decrease in clinical symptomatology. The Pearson correlation coefficients between carbon dioxide–induced anxiety (VAS-A) and the SDS, SAS, STAI-I, STAI-II, FQ, FQ-Ag, CGI-S, and CGI-I were 0.37, 0.30, 0.22, 0.39, 0.36, 0.59, 0.14,

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and 0.13, respectively. None reached statistical significance. The correlation coefficients between the decrease in carbon dioxide–induced panic symptomatology (PSL-III-R) and the mentioned scales were 0.28, 0.03, 0.004, 0.37, 0.35, 0.30, 0.22, and 0.19, respectively. None reached statistical significance.

DISCUSSION

The present study indicates that the anxiogenic response in patients with panic disorder with agoraphobia to the 35% CO_2 challenge decreases after a 6-week treatment period with fluvoxamine. Because the group of patients responded to fluvoxamine, as measured by clinical and self-rating assessments, it is suggested that the decrease in anxiogenic response is related to the clinical improvement under fluvoxamine treatment. The number and severity of carbon dioxide–induced panic symptoms, as reflected by the scores on the PSL-III-R, did not significantly decrease. This, however, may be of limited importance since a recent study found that the scores on the PSL-III-R do not discriminate between two closely linked anxiety disorders, panic disorder, and generalized anxiety disorder. The typical feature by which these two disorders differ upon 35% CO_2 challenge is the sudden crescendo increase in anxiety that is present only in panic disorder patients.[21] Therefore, it is likely that this feature is also the most relevant in investigating treatment effects in laboratory models of panic, and one should not rely too much upon changes in carbon dioxide–induced somatic symptomatology.

One has to acknowledge that overall improvement during the 6-week fluvoxamine treatment period was relatively modest. A CGI-S score of 3.72 indicates that patients were more moderately ill than mildly ill. Also when more conservative criteria for response on the CGI, "much improved" or "very much improved," were used, only 6 of the 11 were treatment responders. Nevertheless, a more conservative definition would not alter the present results. The effects might have been more robust if the tests had been repeated after 8 to 12 weeks.

A limitation of the present study is the fact that it was not placebo-controlled given that CO_2 vulnerability may wane in the natural course of the disorder. A recent study, however, has demonstrated that the anxiogenic response to the 35% CO_2 challenge remains stable under placebo medication.[11]

Another limitation is the relatively small number of patients included. Of the 11 patients included, only 1 was considered to be a nonresponder to fluvoxamine treatment by the treating physician. This patient also showed a slight decrease in carbon dioxide–induced anxiety upon rechallenge. Overall, there was a poor correlation between the quantitative decrease in carbon dioxide–induced anxiety and the quantitative improvement upon clinical assessment. This outcome might suggest that reduced carbon dioxide vulnerability precedes treatment outcome and that altered response to carbon dioxide might be used as a predictor for later treatment outcome. To determine whether vulnerability to carbon dioxide inhalation is qualitatively as well as quantitatively related to clinical improvement, a larger number of treatment nonresponders are needed. In addition, absolute criteria for carbon dioxide responsiveness have to be set.

From a biochemical point of view, there may be a link between the action of antipanic medication on serotonergic pathways and carbon dioxide–induced panic. Preclinical studies indicate that the utilization of 5-HT is increased during CO_2 exposure[22]; furthermore, serotonin system activation decreases carbon dioxide–stimulated respiration.[23] Clinical studies have shown that the behavioral vulnerability to carbon dioxide is decreased upon treatment with effective antipanic drugs, like alprazolam,[2,13] imipramine,[12] and clonazepam.[10] In addition, studies where chemoreceptor sensitivity to carbon dioxide was evaluated, before and during treatment with antipanic drugs like alprazolam,[2,13] clomipramine,[24] and imipramine,[4] indicate that antipanic medication may work by resetting chemoreceptor sensitivity to a lower level.

Another explanation for the decrease in anxiogenic response to carbon dioxide might be an effect of CO_2 on 5-HT uptake mechanisms. When blood platelets were used as a model for serotonergic neurons, it was found that 5-HT uptake is increased in panic patients.[25] In addition, it was demonstrated that lactate and lowering pH increases 5-HT uptake in vitro in the blood platelet. It has been suggested that lactate as well as carbon dioxide might be panicogenic by increasing 5-HT uptake.[26] If these processes were active in vivo, there might be a direct antagonism between the 5-HT-uptake increasing properties of classical panicogens, like lactate and CO_2, and the 5-HT-reuptake inhibiting properties of fluvoxamine. In conclusion, large-scale placebo-controlled studies are needed to address the effects of therapy evaluated within laboratory models of panic.

Drug names: alprazolam (Xanax), clomipramine (Anafranil), clonazepam (Klonopin), fluvoxamine (Luvox), imipramine (Tofranil and others).

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