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Brief report

Double-blind acute clonazepam vs. placebo in carbon dioxide-induced panic attacks

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Abstract

The inhalation of 35% carbon dioxide has consistently been shown to provoke panic attacks in panic disorder patients. We aim to determine if an acute dose of clonazepam (2 mg) attenuates the panic attacks induced by an inhalation of 35% carbon dioxide in panic disorder. Twenty-two panic disorder patients who had been drug-free for 1 week participated in a carbon dioxide challenge test 1 h after a dose of either 2 mg of clonazepam or placebo with a randomized double-blind method. Also in a double-blind design during the tests the patients inhaled either atmospheric compressed air ('placebo control') or the carbon dioxide mixture. All patients participated in both tests which were done with a 20-min interval. Immediately before and after the inhalation, the anxiety levels and the symptoms of panic were always assessed. In the clonazepam group ($n = 11$) two patients (18.2%) had a mild panic attack and in the placebo group ($n = 11$) nine patients (81.8%) had a moderate to severe panic attack in the CO₂ challenge test. No patient had panic attacks during inhalation of atmospheric compressed air although anticipatory anxiety levels tended to be higher than in the CO₂ tests. After the CO₂ test anxiety levels were significantly greater in the CO₂ group (three-way ANOVA with Geisser–Greenhouse adjustments, $F(31.92, 1.86) = 17.15$, d.f. = 7, $P = 0.013$). Although a small sample was studied, the findings suggest the efficacy of an acute dose of clonazepam in attenuating panic attacks induced by carbon dioxide inhalation. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Panic disorder; Benzodiazepine; Carbon dioxide

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1. Introduction

The inhalation of high concentrations of carbon dioxide (CO₂) has consistently been shown to provoke anxiety and panic attacks in patients with panic disorder (Sanderson and Wetzler, 1990; Papp et al., 1993a; Sanderson et al., 1994). The two most common methods used are the prolonged (15 min) inhalation of 5% CO₂ and the one or two vital capacity inhalation of 35% CO₂ and 65% O₂. The 35% CO₂ technique was found to differentiate between panic disorder patients and normals (Griez et al., 1987), to display enough specificity for panic disorder (Griez et al., 1990) and to mimic naturally occurring panic attacks (Chouinard et al., 1982; Fontaine and Chouinard, 1984; Papp et al., 1993b).

The effect of antipanic drugs on the anxiogenic response to 35% CO₂ may help to elucidate the mechanism of CO₂-induced panic attacks. It is important to determine if pretreatment with antipanic drugs would alter the anxiogenic response to CO₂. Different antidepressants — imipramine, paroxetine, sertraline (Bertani et al., 1997), fluvoxamine (Pols et al., 1996a) and fluoxetine (Bocola et al., 1998) — have been used as an effective control for CO₂-induced panic attacks. Serotonin seems to have a role in the mechanisms mediating the antipanic effects of antidepressants, but these antipanic drugs effects might be expressed clinically only after some weeks (Bertani et al., 1997).

Alprazolam (Chouinard et al., 1982) and clonazepam (Fontaine and Chouinard, 1984) are effective drugs for the treatment of panic disorder and are mostly studied in association with CO₂-provoked panic attacks. Clonazepam has some atypical features in comparison with other benzodiazepines, including the demonstration of elevated serotonin levels in the brain, suggesting that this drug may also act by increasing the concentration of the neurotransmitter at synaptic receptor sites (Fennessy and Lee, 1972). This possible particular mechanism of action may help to explain its effectiveness in panic disorder. In a preliminary report (Nardi et al., 1999), clonazepam was effective in blocking CO₂-induced panic attacks after 10 days of treatment.

We aim to determine if an acute dose of clonazepam (2 mg) attenuates the panic attacks induced by the inhalation of 35% carbon dioxide in panic disorder. It is expected that clonazepam should block CO₂-induced anxiety attacks, and other studies have reported similar results with the chronic administration of clonazepam (Pols et al., 1991) and acute (Sanderson et al., 1994) and long-term administration of alprazolam (Woods et al., 1986). The acute administration of alprazolam (Pols et al., 1996b) also has some effects in attenuating CO₂-induced panic attacks. However, this replication in a different design using a double-blind acute dose of clonazepam or placebo with the CO₂ test and atmospheric compressed air test is a worthwhile addition.

2. Patients and methods

We randomly selected at the Laboratory of Panic and Respiration in the Federal University of Rio de Janeiro 22 panic disorder subjects with agoraphobia who agreed to participate in this protocol. The diagnosis was obtained using the Structured Clinical Interview (First et al., 1997) for DSM-IV (American Psychiatric Association, 1994). The study design of the investigation was explained to the patients, and a signed voluntary written informed consent for their participation in this study was obtained. The protocol complying with the principles laid down in the Declaration of Helsinki was approved by our local Ethics Committee.

The subjects were informed that the test could either cause sinus head pressure, dizziness, a mild headache or an increase in anxiety levels and that the symptoms would be quickly relieved when the test was finished. The possibility of a panic attack was not mentioned in order to avoid a bias linked to anticipatory anxiety features. The patients knew they were to receive either a benzodiazepine or placebo as they were informed that one inhalation was likely to induce unpleasant sensations, while the other was harmless.

To participate in the study, the subjects were required to be between the ages of 18 and 55 years and to report at least three panic attacks in

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