

CARBON DIOXIDE TEST AS AN ADDITIONAL CLINICAL MEASURE OF TREATMENT RESPONSE IN PANIC DISORDER

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ABSTRACT - Objective: We aim to determine if a treatment with a dose of clonazepam - 2 mg/day, for 6 weeks, blocks spontaneous panic attacks and the ones induced by the inhalation of 35% carbon dioxide (CO₂) in panic disorder (PD) patients. The CO₂ challenge-test may be a useful addition tool for measuring the pharmacological response during the initial phase (6 weeks) in the treatment of PD. **Method:** Eighteen PD patients drug free for a week participated in a carbon dioxide challenge test. Fourteen had a panic attack and were openly treated for a 6-week period with clonazepam. At the end of the 6-week period they were submitted again to the CO₂ challenge test. **Results:** After 6 weeks of treatment with clonazepam, 12 of 14 PD patients (85.7%) did not have a panic attack after the CO₂ challenge test. Just 2 of 14 patients (14.3%) had a panic attack after the CO₂ challenge test. Ten of 14 (71.4%) PD patients had panic free status after clonazepam treatment. The 2 patients who had a panic attack in the sixth week, after the CO₂ test, did not have panic free status after the treatment with clonazepam. **Conclusion:** The CO₂-test may be a valid tool for testing and predicting the drug response.

KEY WORDS: panic disorder, benzodiazepine, carbon dioxide, clonazepam.

O teste com dióxido de carbono como uma medida adicional na mensuração da resposta terapêutica no transtorno de pânico

RESUMO - Objetivo: Desejamos determinar se o tratamento com clonazepam – 2mg/dia, durante 6 semanas, bloqueia ataques de pânico espontâneos e os induzidos pela inalação de dióxido de carbono (CO₂) a 35% em pacientes com transtorno de pânico (TP). O teste com CO₂ talvez possa ser uma ferramenta adicional útil para medir a resposta farmacológica durante a fase inicial (6 semanas) do tratamento farmacológico no TP. **Método:** 18 pacientes com TP sem medicamento por uma semana participaram de um teste com CO₂ a 35%. 14 pacientes tiveram um ataque de pânico e foram tratados de forma aberta por um período de 6 semanas com clonazepam. Ao final das 6 semanas, os pacientes foram submetidos novamente ao teste com CO₂. **Resultados:** Após 6 semanas de tratamento com clonazepam, 12 (85,7%) dos 14 pacientes não apresentaram ataques de pânico no teste com CO₂ a 35%. Apenas 2 (14,3%) apresentaram ataques de pânico ao teste respiratório e não apresentaram remissão dos ataques de pânico espontâneos. 10 (71,4%) pacientes ficaram livres dos ataques de pânico espontâneos após o tratamento. **Conclusão:** O teste com CO₂ pode ser uma ferramenta válida para testarmos e predizermos a resposta terapêutica.

PALAVRAS-CHAVE: transtorno do pânico, benzodiazepínico, dióxido de carbono, clonazepam.

A panic attack is usually initiated by a sudden, surprising, unexpected rise of terror associated with many autonomic, especially cardio-respiratory symptoms¹. The description of the natural history of panic disorder (PD) makes clear the central importance of the acute panic attack as the basis for all features of the illness². A number of agents are reported to be capable of provoking acute panic attacks in PD pa-

tients under laboratory conditions: carbon dioxide³, sodium lactate⁴, caffeine⁵, isoproterenol⁶ and yohimbine⁶. These agents induce panic attacks in the laboratory that are very similar of spontaneous panic attacks. The understanding of the mechanism of action of a panicogenic agent may elucidate the underlying pathogenesis of panic disorder.

The inhalation of high concentrations of carbon

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dioxide (CO₂) has consistently been shown to increase anxiety and induce panic attacks in PD patients⁷⁻¹⁰. CO₂ induced panic attacks closely resemble the panic attack in PD patients experience outside the laboratory. Of the numerous agents capable of inducing panic attacks in patients with PD, CO₂ offers significant advantages. It is easily administered, well tolerated, and one of the most reliable panicogenic agents¹¹. The two most common methods used are the prolonged (15 minutes) inhalation of 7% CO₂ and the one or two vital capacity inhalation of 35% CO₂ and 65% O₂. The 35% CO₂ technique was found to differentiate between PD patients and controls, displaying enough specificity for PD^{11,12}. The provocation of anxiety by CO₂ may be a reliable marker of panic. Gaining insight into the mechanisms of CO₂ provoked anxiety may in turn shed light on the pathophysiology of PD. This agent probably triggers some vulnerability that may represent the predisposition to the development of panic. CO₂ challenge appears to be a possible biological marker for PD patients¹³. Klein¹⁴ proposed that many spontaneous panic attacks occur when the brain's suffocation monitor erroneously signals a lack of useful air, maladaptively triggering an evolved suffocation alarm system. Such a dysfunction would make an individual vulnerable to "false suffocation alarms", namely panic attacks. CO₂ sensitivity would be an aspect of a hypersensitive suffocation detector.

Alprazolam¹⁵ and clonazepam¹⁶ are efficacious drugs for the treatment of panic disorder and 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 sites¹⁷. This possible particular mechanism of action may help to explain its efficacy in panic disorder.

We aim to determine if a treatment with a dose of clonazepam - 2 mg, for 6 weeks, blocks spontaneous panic attacks and the ones induced by the inhalation of 35% carbon dioxide in panic disorder patients. We also expect that the CO₂ challenge-test could be a useful addition tool for measuring the pharmacological response during the initial phase (6 weeks) in the treatment of PD patients. It is expected that clonazepam should block CO₂ induced anxiety attacks and other studies have reported similar results with chronic administration of clonazepam¹⁸ and acute¹⁹ and long term administration of alprazolam.²⁰ In a preliminary report²¹ clonazepam

was effective in blocking CO₂ panic attacks after 10 days of treatment.

METHOD

We randomly selected at the Laboratory of Panic & Respiration in the Federal University of Rio de Janeiro 18 PD subjects with agoraphobia who agreed to participate in this protocol. The diagnosis was obtained using the Structured Clinical Interview²² (SCID-I) for DSM-IV²³. 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.

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 the two weeks before the first challenge test day. All patients were free of psychotropic drugs for at least one week and have a negative urine test for benzodiazepines and other medications. All patients underwent physical examination and laboratory exams to ensure they were healthy enough to participate in a CO₂ challenge test. They had no respiratory or cardiovascular abnormalities and were free of caffeine for one day.

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 were informed that one inhalation was likely to induce unpleasant sensations, while the other was harmless.

As a part of the challenge test, patients received both 35% CO₂ and atmospheric compressed (placebo test) air 20 minutes apart each other under double-blind conditions. The subjects were asked to exhale as fully as possible, place the mask on their face, take a fast vital capacity breath, inhaling either the 35% CO₂ mixture or the atmospheric compressed air, holding their breath for 8 seconds and afterwards exhale. Immediately after, they were asked to repeat the fast vital capacity breath and hold it again for 8 seconds. The same procedure was repeated after 20 minutes using the gas not used before.

To measure the presence of a panic attack subjects were asked to complete the Diagnostic Symptom Questionnaire²⁴ adapted for DSM-IV²³ in which the presence and level of discomfort of panic symptoms experienced after the inhalations were rated on a 0 - 4 point scale (0 = none, 4 = very severe). On the basis of the Diagnostic Symptom Questionnaire, a CO₂-induced panic attack was defined as the following: 1) the presence of four or more DSM-IV panic attack symptoms where either the presence or the increase in DSM-IV symptomatology was used for diagnosis; 2) at least one DSM-IV cognitive panic symptom (i.e. fear of dying, losing control, or going crazy); 3) sensation of panic or fear, resembling real-life panic attacks; and 4) an agreement of two medical doctors that the patient had a clini-

cal panic attack. This criteria made the diagnosis of a panic attack reliable and with clinical significance.

After the CO₂ challenge test, 14 PD patients who had a panic attack were selected to participate in the study. In an open trial, they received clonazepam (2mg/day, taken once a day) for 6 weeks, then the CO₂ challenge test was repeated. The patients who did not have a panic attack after the first CO₂ challenge test were excluded at baseline. They were treated with antipanic drugs by medical doctors of the Laboratory of Panic & Respiration.

RESULTS

The PD patients were 9 female and 5 male with a mean (\pm SD) age of 36.9 ± 8.7 years. Of this sample, 12 of 14 (85.7%) PD patients had agoraphobia and 2 (14.3%) had not. The mean (\pm SD) time duration of PD in the sample was 45.8 ± 71.4 months. After 6 weeks of treatment with clonazepam (2mg/day), 12 (85.7%) of 14 PD patients did not have a panic attack after the CO₂ challenge test. Just 2 (14.3%) of 14 patients had a panic attack after the CO₂ challenge test. Ten (71.4%) of 14 PD patients had panic free status after clonazepam treatment. Both of the 2 patients who had a panic attack in the sixth week, after the CO₂ test, did not have panic free status after the treatment with clonazepam.

DISCUSSION

The original data of our trial is that the blockade of CO₂ induced panic attacks was related to a clinical improvement of the PD patients, since 10 (71.4%) of 14 patients had panic free status after clonazepam treatment. We also observed that this open trial with clonazepam confirmed that when taken in a regimen of 6 weeks, blocked panic attacks evoked by inhalation of 35% CO₂ in PD patients. After 6 weeks of treatment with clonazepam (2mg/day), 12 (85.7%) of 14 PD patients, who had had a panic attack after the CO₂ challenge test at baseline, when were free of psychotropic drugs, did not have a panic attack after the second CO₂ challenge test. Curiously, the 2 patients who had a panic attack after the CO₂ challenge test, in the sixth week of the study, did not have panic free status, after using clonazepam (2mg/day) for 6 weeks.

Our finding is consistent with the observation that acute alprazolam¹⁹, 10 days treatment with clonazepam²¹, long term alprazolam²⁰ treatment and 5-week treatment with clonazepam^{18,25} are effective in reducing CO₂ induced panic attacks. Perhaps the most essential point in every CO₂ study is the criteria used to define laboratorial panic attacks and the CO₂ concentrations.

The chronic administration (11 weeks) of alprazolam (mean dose 3.1 mg) to eight panic disorder patients attenuated the anxiety induced by 5% CO₂ inhalation.²⁰ In a previous study²⁶ it was found that a single dose of clonazepam blocked CO₂ induced panic attacks significantly over placebo. A single dose of alprazolam (1 mg) as a pretreatment reduced anxiety and panic provoked by the inhalation of 35% CO₂ in patients with panic disorder¹⁹. These patients did a 35% CO₂ challenge test in two different occasions, with one week of interval between them, and received 1mg of alprazolam or placebo 90 minutes before the CO₂ test. It was found that 7 in 10 patients had a panic attack after using placebo and only 1 in 10 patients had a panic attack after using alprazolam. Mono-amino-oxidase inhibitors²⁷, tricyclic antidepressants^{28,29} and selective serotonin reuptake inhibitors^{28,29} are also able to reduce CO₂ reactivity.

It is possible that the response to antipanic treatment is correlated with a reduction to CO₂ sensitivity. The 35% CO₂ challenge test is an interesting neurobiologic probe into the pathophysiology of panic anxiety and an ideal way for the observation and experimental manipulation of different components of panic in a controlled setting.

CONCLUSION

The CO₂-test may be a valid tool for testing and predicting the drug response. This trial provides evidence for the positive effect of clonazepam in carbon dioxide-induced panic attacks. The CO₂ challenge test might be a laboratory instrument able to predict the efficacy of an antipanic medication in PD patients.

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