

Panic Provocation Studies with Placebo

M. Erkan Özcan M.D.¹, Louise R. Levine M.D.², William Z. Potter M.D., Ph.D.²

SUMMARY:

PANIC PROVOCATION STUDIES WITH PLACEBO

Objective: We intended to review studies investigating panic provocation tests using placebo and active drugs in panic disorder patients or in healthy controls. **Method:** A manual and computerized (MEDLINE) search was performed to examine the English-language literature on panic provocation studies.

Results: Sodium lactate, cholecystokinin and carbon dioxide challenge tests are the most frequently used tools. These challenge tests generally seem sensitive, safe, and reliable.

Conclusions: The results of these tests may or may not prove the efficacy of both novel compounds and drugs already marketed for indications other than anxiety disorders. Panic provocation studies may contribute to our understanding of anxiety disorders.

Key words: *panic disorder, provocation tests, carbon dioxide, cholecystokinin, sodium lactate, placebo*

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ÖZET:

PLASEBO KONTROLLÜ PANİK PROVOKASYONU ÇALIŞMALARI

Amaç: Bu makalede, panik bozukluğu olan hastalarla ya da sağlıklı bireylerle, plasebo kontrollü olarak yapılmış olan panik provokasyonu çalışmaları gözden geçirilmiştir. **Yöntem:** İngilizce yazılmış dergiler ve medline taranarak konu ile ilgili makalelere ulaşılmış ve bu çalışmalarda elde edilen sonuçlar derlenmiştir. **Bulgular:** Sodyum laktat, kolesistokin ve karbon dioksit panik provokasyonu amacı ile en çok kullanılan maddelerdir. Bu maddelere genel olarak bakıldığında duyarlı, güvenli ve güvenilir görünmektedirler. **Sonuçlar:** Bu çalışmalarda elde edilen bulgular, panik provokasyon testlerinin, hem halen anksiyete bozukluklarının dışındaki endikasyonlarda kullanılmakta olan ilaçların, hem de yeni bulunacak ilaçların anksiyete bozukluklarındaki etkinliğini ölçebileceğini göstermektedir. Panik provokasyonu çalışmaları, anksiyete bozukluklarının oluş mekanizmalarının daha iyi anlaşılmasına katkıda bulunabilirler.

Anahtar sözcükler: *panik bozukluğu, provokasyon testleri, karbon dioksit, kolesistokin, sodyum laktat, plasebo*

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INTRODUCTION

In panic disorder (PD) and agoraphobia with panic attacks, periodic panic attacks occur, characterized by the sudden onset of such physical symptoms as paresthesia, dizziness, palpitations, etc and are accompanied by a sensation of extreme fear (1). Panic attacks may be provoked by using some probes. Procedures that provoke symptoms of a specific illness have obvious value as tools for the study of that illness and may have important clinical uses as well (2). Pharmacological challenges in anxiety disorders generally and in PD specifically may serve as a diagnostic test, as a predictor of treatment response, as a means of assessing treatment adequacy, and as a predictor of relapse (3). The use of pharmacological challenges in PD is unique in that the clinical phenomenon of central interest (i.e., the pa-

nic attack) can be readily provoked and assessed in the clinical laboratory setting (4).

Carbon dioxide (CO₂) both 5% and 35% have been reported to be anxiogenic in patients with PD (5,6,7). It has been shown that compounds which are effective in PD decrease CO₂ sensitivity and ineffective ones cannot (8). Another effective probe, cholecystokinin (CCK) is an octapeptide found regionally in the gastrointestinal tract and brain, where it acts as a neurotransmitter and neuromodulator. In some neurons, it is colocalized with other neurotransmitters, particularly dopamine (DA) and gamma-aminobutyric acid (GABA), and GABA seems to be involved in the regulation of CCK release. Interest in CCK's role in anxiogenesis arose from evidence that it stimulates rat cortical and hippocampal neurons, effects that are blocked by benzodiazepine agonists (9).

¹Inönü University Medical School, Department of Psychiatry, Malatya, 44069, Turkey.

²Lilly Research Laboratories, Indianapolis, Indiana, 46285, USA.

Yazışma adresi / Address reprint requests to: Yrd. Doç. Dr. M. Erkan ÖzcanTurgut Özal Tıp Merkezi Psikiyatri Bölümü Malatya, 44069, Turkey

Tel: +90 422 3410660/5403

Fax: +90 422 3410728

E-mail: ozcane@usa.net

Panicogenic effect of sodium lactate, another efficacious agent in provoking panic attacks, was first shown in 1967 (10). The challenge probe generally consists of 0.5-M sodium lactate (10 ml/kg) given iv over 20 min (3). Lactate-induced anxiety appears specific to PD (11) and is antagonized by treatment with anti-panic agents (4).

In this review article, we intended to review panic provocation studies in which a placebo and at least an active agent were used for treatment of PD.

METHOD

A manual and computerized (MEDLINE) search was performed to examine the English-language literature on panic provocation studies. The following key words were used in the computer search: panic disorder, panic provocation studies, CO₂, sodium lactate, CCK, placebo studies. Only double-blind, placebo-controlled studies were included. (Table-1,2).

RESULTS

Imipramine, either alone (12) or in comparison with paroxetine and sertraline (8) has been studied and all three of these drugs have been found to be effective and superior to placebo in two trials using CO₂ as a probe. Alprazolam has been found to be effective in one similar study (13) and ineffective in another (14). The results of CO₂ challenging studies in PD are outlined in Table 1.

A study comparing alprazolam and placebo by Carr et al (15) showed that alprazolam treatment reduced panic attacks induced by sodium lactate Table 2. The results with L-365,260 (16,17), treatment failure with the cholecystokinin-B receptor antagonist CI-988 (18) and a treatment efficacy of fluvoxamine (19) were found in studies using CCK (Table-3). Some other double-blind, placebo-controlled studies are summarized in (Table-4).

Table 1. Double-blind, placebo-controlled studies using 35% CO₂

Reference	N	Active Drug(s)	Percent Pts. Blocked	Results/Comments
Sanderson et al 1994 (13)	10	Alprazolam	P: 30 A: 90	70% had panic attack on placebo; 10% had panic attack on alprazolam
Pols et al 1996 (14)	20	Alprazolam	P: 36.2 A: 32.9	Alprazolam failed to protect against CO ₂ -induced effects versus placebo
Bertani et al 1997 (8)	70	Imipramine Paroxetine Sertraline	P: 10 Im: 45.0 Pa: 66.6 Se: 47.3*	All three drugs showed reduced reactivity compared to placebo

* Percentage of patients with at least 50% decrease of _ % VAS-A score (Visual Analogue for Anxiety)

Table 2. Double-blind, placebo-controlled studies using sodium lactate

Reference	N	Active Drug(s)	Percent Pts. Blocked	Results/Comments
Carr et al 1986 (15)	25 10*	Alprazolam	P: NA A: NA *P: NA *A: NA	Alprazolam treatment reduced panicogenic effects of sodium lactate

* healthy subjects, NA: Not available from the article or the abstract.

Table 3. Double-blind, placebo-controlled studies using CCK

Reference	N	Active Drug(s) (dose)	Percent Blocked	Results/Comments
Bradwejn et al 1994 (16)	29	L-365,260 (10 mg, 50 mg)	P: 12 L10: 67 L50: 100	The CCK-antagonist (50 mg dose) significantly reduced frequency of a provoked panic attack with CCK-4 versus placebo (88% on placebo; 33% on 10 mg L-365,260; and 0% on 50 mg L-365,260 panicked)
Westenberg et al 1994 (17)	24	L-365,260 (50 mg)	P: 50 L50: 75	The CCK-antagonist (50 mg dose) significantly reduced the frequency of a provoked panic attack with CCK-4 versus placebo (50% on placebo; 25% on L-365,260 panicked)
Cowley et al 1996 (18)	5	CI-988 (100 mg)	P: 0 C: 0	CI-988 was ineffective in preventing a panic attack provoked with CCK-4
van Meegen et al 1997 (19)	26	Fluvoxamine (150 mg daily)	P: 44 F: 71	Patients treated with fluvoxamine showed a decreased response to CCK-4 as compared to placebo treatment

Table 4. Other double-blind, placebo-controlled studies

Reference	N	Active Drug(s) (dose)	Percent Not Blocked	Results/Comments
Nutt et al 1990 (20)	10 and 10*	Flumazenil (2 mg)	P: 0 F: 80	Subjective anxiety responses after flumazenil infusion were significantly higher in the patient group with panic disorder than in the controls, and eight patients with panic disorder but no controls had panic attacks.
Klein et al 1991 (21)	7	m-CPP (0.5 mg/kg) caffeine (480 mg)	P: 0 M: 70 C: 70	Both m-CPP and caffeine had significantly greater anxiogenic and panic-inducing effects than placebo, although caffeine produced nonsignificantly greater increases on all anxiety rating scales than m-CPP.

among them.

* healthy subjects.

DISCUSSION

In studies of neuropsychiatric disorders, the ideal challenge probe should have a mechanism of action that is well-characterized at the preclinical level, be pharmacologically selective for the system under investigation, have no active metabolites, and induce responses that are sensitive, reliable, accessible to clinical measurement, and reflective of brain function. Safety and convenience are desirable qualities (3).

In this concept, all three challenge tests seem to be safe and useful, but 35% CO₂ challenging seems to be the best - maybe not the ideal -

Klein (22) has advanced a comprehensive theory suggesting that both CO₂ and lactate induce panic by triggering a suffocation false alarm in individuals with a hypersensitive suffocation detector.

Carbon dioxide-induced panic attacks are phenomenologically similar to lactate-induced attacks and involve similar biochemical and physiological changes (6). Infusion of sodium lactate itself, differs significantly from placebo in provoking panic attacks (15). Strohle et al (23) challenged 10 patients with PD with infusions of saline, sodium lactate, and flumazenil in randomized order. Eight of 10 patients experienced a panic attack after sodium lactate, but none did after the benzodiazepine

receptor antagonist flumazenil or saline. However, Nutt et al (20) found that subjective anxiety responses after flumazenil infusion were significantly higher in the patient group with PD (n:10) than in the controls (n:10), and eight patients with PD, but no controls had panic attacks in their crossover study.

Another method that has been used in panic provocation studies is the infusion of cholecystokinin tetrapeptide (CCK-4). Studying the CCK-B antagonist L-365,260 and placebo in 24 patients, Westenberg et al (17) found that the frequency of panic attack was 25% in patients with L-365,260 and 50% in patients with placebo. These findings also give tentative support to the hypothesis that central CCK pathways may mediate pathological anxiety. Benkelfat et al (24) reported that CCK-4 but not placebo, elicited a marked anxiogenic response, reflected by robust increases in subjective anxiety ratings and heart rate.

Abelson and Nesse (25) have also found that the CCK-B agonist pentagastrin (0.6 g/kg iv) provokes panic symptoms in four out of five drug-free

panic patients and one out of four controls. Cholecystokinin tetrapeptide's anxiogenic effects have been found reliable and dose-dependent, with 25 g iv of CCK-4 producing panic responses similar to 35% CO₂ inhalation in patients and controls, in another study (26).

The results that show the anxiogenic effects of CO₂ were significantly reduced during long-term imipramine treatment suggest that the mechanisms underlying carbon dioxide-induced anxiety perhaps similar to those involved in the pathophysiology of panic disorder (12).

Carbon dioxide, sodium lactate and CCK appear to constitute useful neurobiological probes into the pathophysiology of panic disorder. Findings of panic provocation studies give support to the assertions that panic disorder arises from an abnormally low suffocation alarm threshold and that respiratory symptoms are therefore the core phenomena of panic attacks among patients with true panic disorder.

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