Eur Psychiatry (1994) 9, Suppl 1, 86s–87s

S40. Anxiolytic drugs

POTENTIAL SIGNIFICANCE OF CCK-B RECEPTORS AND CCK-B ANTAGONISTS IN PANIC DISORDER.

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An increasing body of evidence suggest that CCK-B receptors are involved in biological processes that regulate anxiety. Previous investigations revealed that CCK-4 and the CCK-4 analogue pentagastrin are able to induce panic attacks in patients with panic disorder (PD). Advantages of administration of CCK-4 in the provocation of panic are: 1) that it rapidly induced panic which lasts only about 2 minutes and 2) the point of panic is relatively easily to define, compared with other challenge paradigms (e.g. lactate).
In the present studies we investigated the ability of the CCK-B receptor antagonists L-365,260 and CI-988 to block CCK-4 induced panic. **Methods**: In two double-blind studies using an unbalanced incomplete block design we compared the effects of placebo, and the CCK-B receptor antagonists L,365,260 and CI-988 on panic attacks induced by CCK-4. PD patients were treated with either placebo or 10 or 50mg L-365,260 before receiving an i.v. bolusinjection of 20μg CCK-4. In the case of CI-988, before being injected with an i.v. bolus injection of 20 μg CCK-4 patients received either a) two placebo capsules b) 50mg CI-988 or c) 100mg CI-988. **Results**: The level of anxiety and panic were measured with a Visual Analogue Scale and the Panic Symptom Scale respectively. Pretreatment with placebo produced panic attacks in 86% of the patients, whereas pretreatment with L-365,260 led to a dose dependent statistically significant reduction in panic attacks. The panic rate was 33% for 10mg of L-365,260 and 0% for 50 mg L-365,260. The experiments with CI-988 yielded similar results. **Conclusion**: 1) Stimulation of CCK-B receptors provides a reliable method to provoke panic attacks in a clinical population of PD patients. 2) This panic inducing properties can be reliably and dose-dependently be blocked by pretreatment with selective CCK-B antagonists. Further studies are necessary to evaluate the anxiolytic potential of CCK-B antagonists.

ASSESSMENT OF THE DESINHIBITION PHENOMENON OF THREE DOSES (1,5 - 3 AND 6 MG) OF BROMAZEPAM IN SUBJECTS WITH ANXIETY PERSONALITY TRAITS

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Introduction

In a previous study (1) in young healthy male volunteers (YHV), we demonstrated that the lowest doses (1,5, 3 mg acute oral intake) of bromazepam (B) could decrease the capacity to delay (GO/NO-GO and DRL tests). The conclusion was that inhibition was decreased at low but not at higher dosages of B (6 mg) in YHV. According to cognitive and behavioral theories, anxiety could be precisely characterized by a blockage of action by an excess of inhibitor reactions. It seemed useful to repeat the study in subjects with anxiety personality traits (SAPT).

Aim of the study

Desinhibition induced by B at 3 doses (1,5, 3 and 6 mg) has been studied in SAPT (18-30 u.o.) using a double-blind, randomized, versus placebo, double Greco-Latin square design.

Method

Sixteen (16) male SAPT have been included in the study. Their profile has been determined during computerized preselection tests (SILPSY from DANJOU (2)) in 150 subjects : Cattell's anxiety scale; Eysenck's personality inventory; modified MMPI Inhibition and capacity to delay are assessed through the Logan 's procedure (% of blockades), DRL (time to count); decision test. Vigilance (CFF) and divided attention were simultaneously measured. Subjects were regularly followed-up during 8 hours, in day-time post-dosing.

Results

The results previously obtained in YHV were not reproduced in this population. No statistically significant results were noted on the main assessment criteria : DRL (p=0.4709), GO-NO/GO (p=0.4879), CFF(p=0.4083) and Divided Attention (p=0.2439).

Conclusion

I. First we could discuss the sensibility of the tests used, in our population with anxiety personality traits. 2. Low doses of B(1.5. to 6 mg) are inefficient in individuals with anxiety personality traits to modify the pathophysiological core of this status. 3. The flexibility or reactivity of the biological systems underlying inhibition is reduced in anxiety.

(1) ALLAIN H. et al., 9th World Congress of Psychiatry, Rio, June 1993.
(2) DANJOU Ph. et al, Thérapie 1991 ; 46 : 125-129.

Anxiolytic and antiphobic effects of antidepressants in social phobia

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Social phobia is a serious and incapacitating anxiety disorders which, in contrast to other anxiety disorders, has been little studied in psychopharmacological trial. The disorder often begins in adolescence, affecting 1-2% of the general population. Traditionally, the treatment of social phobia has been the domain of psychotherapy, but recent progress in pharmacotherapy of panic disorder has directed attention of psychopharmacologists also to social phobia. Recently, it was found that phenelzine, a nonselective and irreversible MAO inhibitor, markedly improve symptoms of social phobia. There have also been some case reports on the efficacy of other antidepressants, while β-blockers appear to be of limited therapeutic value. The latter class of compounds may relieve some somatic symptoms, but does not affect general anxiety or phobic avoidance. Apparently, the same therapeutic profile seen previously with panic disorder is now being observed with social phobial.

In this paper we will review the results of recent clinical studies on the pharmacotherapy of social phobia. We will focus primarily on controlled studies with antidepressants. In general, these studies converge to suggest that antidepressants are efficacious in social phobia. Thus, placebo controlled clinical trials with brofaromine and moclobemide, two selective MAO-A inhibitors, and a recent study with fluvoxamine, a serotonin reuptake inhibitor, indicate that these compounds are highly effective in treating symptoms of social phobia. Social anxiety is reduced gradually following chronic treatment, whereas social avoidance will mitigate also when treatment is ensued for more than 12 weeks.

These findings suggest that antidepressants, in particular those with an effect on serotonin, are effective treatments for a number of syndromes (depression, panic disorder and social phobia) with overlapping symptom clusters of which general anxiety seems to be a common denominator.

PLACEBO-CONTROLLED STUDY OF THE ANXIOLYTIC ACTIVITY OF SINGLE DOSES OF ZACOPRIDE AMONG INPATIENTS WITH GENERALIZED ANXIETY DISORDER

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5-HT3 antagonists such as ondansetron, zacopride, and tropisetron exhibit anxiolytic potential in several animal models. The purpose of the present study was to test if single doses of zacopride possessed acute anxiolytic activity. After a complete drug-free period of at least 1 week, 14 inpatients with DSM-III-R generalized anxiety disorder (13 F, 1 M; mean age = 40.7 years) and a Hamilton anxiety score of at least 15 (mean = 31.7 ± 5.7) received every other day single oral dose of zacopride 10 μg, 200 μg, diazepam 5 mg, and placebo in a double-blind and crossover design. Assessments included Hamilton anxiety scale performed at baseline and 2 and 6 h later and Norris visual analogue scales completed hourly during 6 h. Two patients did not complete the trial due to spontaneous improvement and were replaced. Statistical analysis used 3-way ANOVA (subjects, drug, sequence) with repeated measures. Results showed better anxiolytic activity of zacopride 10 μg ($p = 0.05$) and diazepam 5 mg ($p = 0.02$) compared to placebo on the Hamilton anxiety scale as well as a superiority of zacopride 10 μg over placebo on 3 items of the Norris scales : troubled/tranquil, proficient/incompetent, happy/sad; a superiority of zacopride 10 μg over diazepam on the item proficient/incompetent; and a superiority of diazepam over zacopride 200 μg on the items attentive/dreamy and proficient/incompetent. These findings support an acute anxiolytic activity for low dose of zacopride.

TREATMENT OF REFRACTORY OBSESSIVE COMPULSIVE DISORDER

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Most patients with OCD can be effectively treated with specific pharmacologic and behavioral approaches. Nevertheless, some patients remain refractory to standard treatments.

Comorbid Axis II disorders, such as cluster A (odd) or B (impulsive) personality disorders, social phobia, tics, neurological illness, or delusional severity may also impede treatment efficacy. Insufficient dosage, slow onset of response (12 weeks are often needed), inadequate duration of treatment (12 months is often necessary for an initial treatment length), and symptom relapse after discontinuation also need consideration.

Augmentation strategies include adding various agents to fluoxetine or SSRIs: fenfluramine (20 - 60 mg/day) or desipramine (10 - 30 mg/day) for depressed OCD patients; buspirone (30 - 60 mg/day) or clonazepam (2 - 8 mg/day) for anxious patients; carbamazepine (400 - 1200 mg/day) or lithium for bipolar or depressed OCD patients. When adding fluoxetine to clomipramine, follow the combined CMI and DMCMI blood levels to avoid increased risk of seizures. Intensive behavior therapy may be thought of as the first augmentation strategy for refractory OCD.

For other target symptom clusters, neurological damage or abnormal EEG suggest the use of an anticonvulsant; comorbid social phobia suggests an MAOI; tics, Tourette's, psychotic symptoms or comorbid Axis II disorders suggest low dose high potency neuroleptic. Alternative treatments for refractory OCD include MAOIs, intravenous clomipramine, antiandrogens, and neurosurgery (including capsulotomy or cingulotomy).

https://doi.org/10.1017/S0924933800004788 Published online by Cambridge University Press