
Clomipramine and fluoxetine effects in the treatment of panic disorder

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Abstract

Panic disorder (PD) is an acute psychobiologic reaction manifested by intense anxiety and panic attacks, that occur unpredictably with subjective sense of intense apprehension or terror, accompanied by temporary loss of the ability to plan, think, or reason and the intense desire to escape or flee the situation. Panic attacks may last from a few seconds to an hour or longer. Symptoms typically include, among others, palpitations, tachycardia, hypertension, chest pain, dyspnoea, and fear of losing control or going crazy and vague feeling of imminent doom or death. Since pharmacotherapy of PD includes the administration of selective serotonin reuptake inhibitors and tricyclic antidepressants, the objective of this study was to perform a pilot double blind clinical trial designed to compare the effects of two studied drugs in the treatment of PD.

A total number of 40 patients with a history of panic disorder were randomly assigned into two groups of 20 patients each. Hamilton anxiety rating scale and Standard Psychiatric Interview were methods for PD assessment. One group was treated with clomipramine hydrochloride (ANAFRANIL®) 75 mg/day and the other with fluoxetine (OXETIN®) 60 mg/day. Both drugs were administered by mouth (PO) two times-a-day in equally divided doses for 6 weeks.

Both studied agents produced similar antipanic effectiveness. Favourable response was achieved in 95% of patients treated with fluoxetine and 90% of patients treated with clomipramine. The onset of antipanic effects was quicker in all clomipramine treated patients, while fluoxetine produced more-favourable response in male patients. The duration of treatment with both antidepressants studied should be at least 10 weeks, instead of 6 weeks.

Key words: panic disorder, clomipramine hydrochloride, fluoxetine hydrochloride, antipanic effectiveness.

Introduction

Panic disorder is a psychiatric disorder characterized by recurrent and unpredictable panic attacks involving a feeling of terrifying fear and extreme discomfort with an impending sense of doom (BENNETT et al., 1998). It

may be accompanied by temporary loss of the ability to plan, think, or reason and the intense desire to escape or flee the situation. This disorder affects approximately 2% to 4% of the population (BALLENGER et al., 1998). It usually begins in the late adolescence or early adulthood and affects women two to three times more often than men.

Panic attacks are the main feature of panic disorder, but other problems may also include anticipatory anxiety, panic-related phobias, poor overall well-being, and disability (BALLENGER et al., 1998). Whilst panic disorder is uncommon, affecting less than 1% of the population in a six month period, panic attack is common, affecting more than 1/3 of the population in a single year. Panic attacks usually last from a few seconds to an hour or longer, vary in frequency from several times a day to once a month and they are accompanied by the strong body reactions or profound physiological effects.

Symptoms of a panic attack typically include chest pain or discomfort, choking, dizziness, unsteady feelings or faintness, fear of dying, fear of becoming insane or of losing control, feelings of unreality, strangeness or detachment from the environment, flushes or chills, nausea or abdominal distress, numbness or tingling sensations, palpitations or accelerated heart rate, shortness of breath or smothering sensation, sweating, and trembling or shaking.

Most persons suffering from panic attacks recover without treatment, and a few develop panic disorder. For these persons, especially without treatment, panic disorder follows a chronic waxing and waning course. Pharmacotherapy and behaviour therapy usually help to control symptoms of panic attacks. There is strong evidence suggesting that selective serotonin reuptake inhibitors and tricyclic antidepressants are effective therapies (BALLENGER et al., 1998). These drugs can prevent or greatly reduce the number and intensity of panic attacks and are usually recommended as first-line agents for the treatment of panic disorder (BENNETT et al., 1998).

Objective

Since pharmacotherapy of panic disorder includes the administration of selective serotonin reuptake inhibitors and tricyclic antidepressants as first-line agents in the

treatment of this disorder, the objective of this study was to perform a pilot double-blind clinical trial designed to compare the effects of the representatives of those two groups of drugs in the treatment of panic disorder.

Patient and trial characteristics

Type of trial

A pilot randomized double-blind trial.

Patient selection

A total number of 40 patients (23 males and 17 females) with a history of panic disorder, between 35-45 years of age and of similar educational background.

Panic disorder assessment

- Hamilton anxiety rating scale (HAMA) (HAMILTON, 1959)
- Standard Psychiatric Interview (SPI)

Inclusion criteria

- Only HAMA diagnostic criteria proven panic disorder
- Only SPI diagnostic criteria proven panic disorder

Exclusion criteria

- History of anxiety-depressive disorder
- History of generalized anxiety
- History of abdominal upset or gastrointestinal complaints (hiatus hernia)

Drug administration

Patients with proven panic disorder were randomly assigned into *two groups*. Each group of 20 patients was treated with one of *two investigated drugs*, which were administered by mouth two times-a-day in equally divided doses for *6 weeks*:

- One group (12 males and 8 females) was treated with *clomipramine hydrochloride* (ANAFRANIL®) 75 mg/day *b.i.d.* Initial dose of 25 mg/day was increased gradually to a maximum of 75 mg/day during the first 2 weeks (depending on patient tolerance).
- The other group (11 males and 9 females) was treated with *fluoxetine hydrochloride* (OXETIN®) 60 mg/day *b.i.d.* Initial dose of 20 mg/day was increased gradually to a maximum of 60 mg/day during the first 2 weeks (depending on patient tolerance).

Results

Favourable response (reduced frequency and severity of panic attacks, prolongation of the period of clinical remission from panic attacks, decrease in anxiety and

phobic avoidance and improved quality of life) was achieved in 19 (95%) patients treated with *fluoxetine hydrochloride* and 18 (90%) patients treated with *clomipramine hydrochloride*.

Clomipramine hydrochloride produced quicker effects (onset after 2 weeks) and complete recovery in almost all treated patients with less (20%) adverse reactions (tremor, nausea) in 4 patients, sex regardless (2 females and 2 males).

Fluoxetine hydrochloride showed a greater but slower efficacy (onset after 3 weeks) in male patients with more (35%) adverse reactions in seven female patients (drowsiness, nausea, vomiting, sweating, hyperhydration, insomnia).

The effectiveness of *clomipramine hydrochloride* and *fluoxetine hydrochloride* treatment with regard to sex is shown in Graphs 1 and 2, respectively.

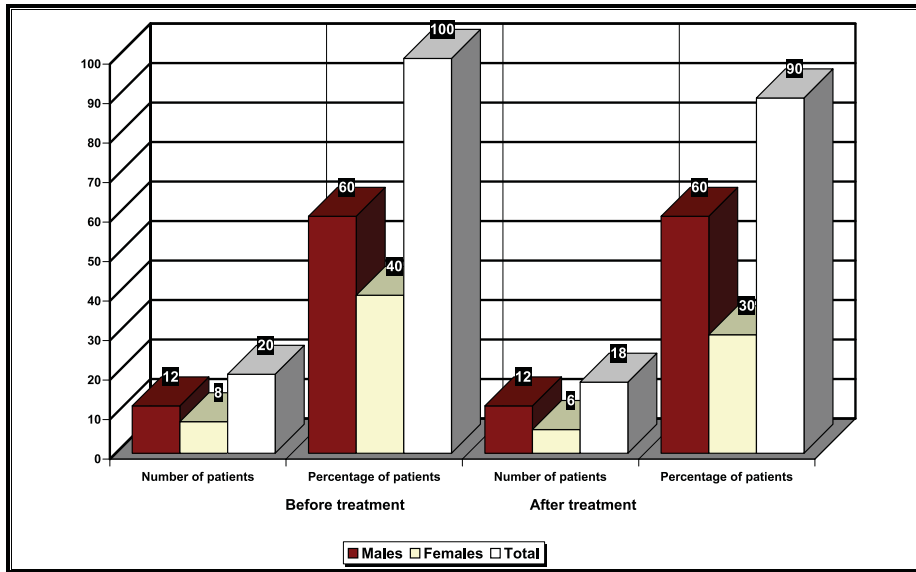
Discussion

Panic induction has three postulated neurochemical pathways: benzodiazepine receptor binding, noradrenergic function, and serotonergic function. Evidence suggests that it is the serotonergic component that modulates the proposed noradrenergic and benzodiazepine receptor binding mechanisms (De VANE, 1997). The relationship between serotonin and anxiety is very complex (NUTT, 1998). There are two opposing theories: one involves an excess of serotonin and the other a serotonin deficit. Multiple regions of the brain appear to be involved along with the serotonin receptors (NUTT, 1998).

Patients suffering from panic disorder should be told that their disorder results from both biologic and psychological dysfunction and that pharmacotherapy and behaviour therapy usually help control symptoms. Since pharmacotherapy of panic disorder may include the administration of selective serotonin reuptake inhibitors and tricyclic antidepressants, as effective first-line initial agents for the treatment of this disorder, the objective of this study was to perform a *pilot double-blind clinical trial* designed to compare the effects of the representatives of those two groups of drugs in the treatment of panic disorder. *Clomipramine hydrochloride* (ANAFRANIL®) and *fluoxetine hydrochloride* (OXETIN®) were representatives of tricyclic antidepressants and *selective serotonin reuptake inhibitors*, respectively.

The exact mechanism of action of *clomipramine* is not known. The drug is classified as a tertiary amine tricyclic antidepressant with very potent serotonin uptake blocking activity and moderate blocking activity for noradrenalin (BERTILSSON et al., 1974; ASBERG et al., 1977). On the other hand, its active metabolite, *desmethyl-clomipramine*, is a potent noradrenalin uptake inhibitor

Graph 1. The effectiveness of clomipramine hydrochloride (ANAFRANIL®) (75 mg/day p.o.) treatment by sex

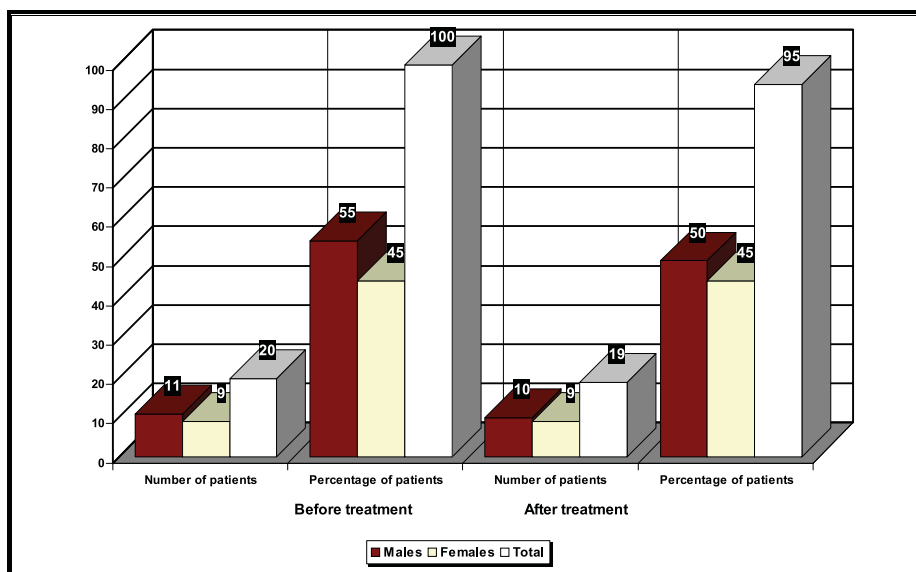


and may retain some serotonin uptake inhibition (BENFIELD et al., 1980). Fluoxetine is a "second-generation" antidepressant agent, which is a specific inhibitor of serotonin reuptake (STARK et al., 1985). Treatment initiation of these agents is recommended at low doses with slow increases (BALLENGER et al, 1998). Outcome of drug therapy has not been associated with baseline frequency of panic attacks (DAVIDSON, 1998). However, level of phobic avoidance at baseline has been an important predictor (DAVIDSON, 1998).

It has been shown that both agents used produced similar antipanic effectiveness, but more- favourable response

was achieved with *fluoxetine hydrochloride* (95%) than with *clomipramine hydrochloride* (90%). *Clomipramine hydrochloride* (ANAFRANIL®) produced quicker effects (onset after 2 weeks) and complete recovery in almost all treated patients, sex regardless. Fluoxetine hydrochloride (OXETIN®) showed a greater but slower efficacy (onset after 3 weeks) in males, than in females. These results are in agreement with other data sources. Clomipramine has been studied with favourable results (den BOER, 1998) and it has been found to be effective in the treatment of panic attacks during four clinical trials using this drug. It has been reported (CAILLARD et al., 1999) that low-dose clomipramine (60 mg/kg) was as

Graph 2. The effectiveness of fluoxetine hydrochloride (OXETIN®) (60 mg/day p.o.) treatment by sex



effective as high-dose clomipramine (150 mg/kg) in the treatment of panic attacks (the number of DSM-III-R symptoms of panic attacks was decreased) in a multi-centre clinical trial which lasted 8 weeks. BROOCKS et al. (1998) have reported that in a randomized, placebo-controlled, 10-week study, clomipramine (increasing doses over three weeks up to 112.5 mg/day) was found to be more effective for the treatment of panic disorder, and that significant ($p < 0.001$) improvement was seen after only 4 weeks. It has been shown (PAPP et al., 1997) that clomipramine (initial dose of 10 mg/day was increased slowly to the mean daily dosage of 96.9 mg after 13 weeks of treatment) produced marked or moderate improvements in 84% of patients with panic disorder. PERNA et al. (1997) have conducted double-blind, randomized, placebo-controlled clinical study using clomipramine (10 mg for 3 days and 20 mg for 4 days) and have published that this drug was effective in decreasing panic attacks of patients with panic disorder. Fluoxetine has been found to be effective for treating panic disorder and to be useful, when administered in weekly doses, for preventing recurrence of panic disorder during two clinical trials using this drug. It has been reported (MICHELSON et al, 1998) that fluoxetine (10 or 20 mg/day) was effective (significant reduction in the Clinical Global Impression improvement scores and significant reduction in total panic attack frequency) and tolerated well in patients with confirmed panic disorder in a 10-week, double-blind, randomized, placebo-controlled clinical trial. EMMANUEL et al. (1999) have published that fluoxetine (10-60 mg/week) prevented recurrence of panic attacks in patients with panic disorder for periods of 1 to 26 months.

Patients with panic disorder are particularly sensitive to the adverse effects of medicines. These patients often misinterpret them as anxiety symptoms and thus start the vicious cycle of escalating anxiety that leads to further panic attacks (BALDWIN and BIRTWISTLE, 1998). *Clomipramine hydrochloride* (ANAFRANIL®) produced less (20%) adverse reactions (tremor, nausea) in four patients, sex regardless (2 females and 2 males). *Fluoxetine hydrochloride* (OXETIN®) showed more

(35%) adverse reactions in seven female patients (drowsiness, nausea, vomiting, sweating, hyperhydration, insomnia).

Conclusions

A pilot clinical trial, designed to compare the effects of the representatives of *tricyclic antidepressants and selective serotonin reuptake inhibitors* in the treatment of panic disorder, was performed.

Two agents used were: clomipramine hydrochloride (ANAFRANIL®) as a representative of tricyclic antidepressants and fluoxetine hydrochloride (OXETIN®) as a representative of selective serotonin reuptake inhibitors.

Both agents used produced similar antipanic effectiveness, but *more-favourable* response was achieved with *fluoxetine hydrochloride* (95%) than with *clomipramine hydrochloride* (90%).

The onset of antipanic effects was quicker (two weeks) in clomipramine hydrochloride treated patients, than in fluoxetine hydrochloride treated patients (three weeks).

The effectiveness of clomipramine hydrochloride and fluoxetine hydrochloride treatment with regard to sex was assessed.

Fluoxetine hydrochloride produced favourable response sex regardless (10 males and 9 females), while clomipramine hydrochloride produced more favourable response in male patients (12 males and 6 females).

Adverse effects were less pronounced in all clomipramine hydrochloride treated patients (20%) sex regardless and more noticeable in female patients (35%) treated with fluoxetine hydrochloride.

The *duration of treatment* with representatives of *both groups* studied should be *at least 10 weeks* instead of 6 weeks.

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