

EFFICACY AND TOLERABILITY OF FLUPENTHIXOL IN THE TREATMENT OF PSYCHIATRIC
ILLNESS*

RUH HASTALIKLARININ TEDAVİSİNDE FLUPENTİKSOL'ÜN ETKİNLİĞİ VE TOLEREBİLİTESİ

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Flupenthixol, a thioxanthene derivative, has been shown to have therapeutic activity in chronic psychotic patients. Also some studies indicate that flupenthixol in a low-dose regimen is effective in treating syndromes with depression, anxiety and psychosomatic disorders. Flupenthixol appears to have a more rapid onset of action than conventional antidepressants. Most studies reported clinical improvement within 2 weeks, and some as early as 2, 3 days. In addition, there is no evidence that flupenthixol is dangerous in combination with other psychotropic medications.

Bir tiyoksanten türevidir olan flupentiksol'un, kronik psikotik hastalarda terapötik aktivite gösterdiği saptanmıştır. Bu maddenin, düşük dozlu uygulamalarda, depresyon, heyecanlanma ve psikosomatik hastalıklar şeklindeki sendromların tedavisinde de etkin olduğunu gösteren bazı çalışmalar mevcuttur. Flupentiksol, konvansiyonel antidepressanlara kıyasla daha hızlı bir etki göstermektedir. Pek çok çalışmada, klinik iyileşmenin 2 hafta içinde gerçekleştiği ve bazı hallerde 2, 3 günde de iyileşme görüldüğü belirtilmiştir. Ayrıca, flupentiksol'un diğer psikotropik ilaçlarla kombinasyonunun tehlikeli olduğuna dair hiçbir açıklamaya da rastlanmamıştır.

Keywords : *Flupenthixol; Schizophrenia; Depression; Clinical effects; Side effects*

Anahtar kelimeler: *Flupentiksol; Şizofreni; Depresyon; Klinik etkiler; Yan etkiler*

Introduction

Flupenthixol, a thioxanthene derivative, has been shown to have therapeutic activity in chronic psychotic patients (1). The drug is metabolized in the liver by sulfoxidation, side chain N-dealkylation and glucuronic acid conjugation. When given orally, the percentage of N-dealkylation is higher secondary to first pass metabolism. The metabolites are not pharmacologically active. The drug is highly tissue-bound with high concentrations in the liver and lungs and lower concentrations in brain, blood and spinal fluid (2). Flupenthixol has a weak dopamine (D₂) blocking action (2,3). Antipsychotic activity started after a two-week period of treatment with flupenthixol. This suggests that flupenthixol could be useful in the attack therapy of chronic schizophrenia. Both "negative" and "positive" symptoms of chronic schizophrenia were favorably affected by flupenthixol (1).

Flupenthixol decanoate may be the most interesting of the long-acting injectable preparations. Flupenthixol is suspected of having

clearer antidepressant properties than the other neuroleptics, and at least one double-blind 6-month study in repeatedly suicidal depressive outpatients demonstrated flupenthixol to be more effective than placebo (4). The studies document a mood-stimulating and anxiety-reducing effect in patients with depressive mood, neurotic and endogenous depression of a mild to moderate level, with psychosomatic disorders and depression in older patients and anxious neurotics. Apathic, inactive patients and those with inhibitions are especially helped by the activating effect of flupenthixol. When compared to classic antidepressants, flupenthixol works quicker, in only two to three days and has less unwanted, vegetative side effects (5).

While the antidepressive and anxiolytic efficacy of oral flupenthixol is very well documented, the depot form, flupenthixol decanoate has been examined only in a few studies (2,5). A significant effect on suicidality compared with placebo has been reported

with flupenthixol although in a very small sample (2,6).

Treatment with flupenthixol in schizophrenia

Recommended dosages of 6-12 mg of flupenthixol daily or 20-40 mg every 2-4 weeks of flupenthixol decanoate for schizophrenia, suggest that they are equivalent in clinical effectiveness (7). No studies have been done documenting that these dosages produce the same serum concentrations and none have drawn a correlation between serum concentration and clinical state or outcome for psychosis (2).

Like other neuroleptics, flupenthixol binds to D₁, D₂, inhibitory D₂, 5HT₂ and α_1 receptors. Its antipsychotic activity is presumed to be a result of postsynaptic D₂ blockade, causing a reduction in dopaminergic activity (2,3).

Previous studies exist on the antidepressant effects of flupenthixol in the maintenance treatment of patients with chronic schizophrenia (2).

Antidepressant effects of flupenthixol

Its antidepressant activity at low doses may be a result of prefrontal binding to autoreceptors at low concentration, increasing dopaminergic activity. In terms of ability to elevate mood, flupenthixol has received more attention than any of the other neuroleptics (2,8).

The available literature on the antidepressant effects of flupenthixol consists of 7 open uncontrolled studies; 3 placebo-controlled, double-blind trials and 10 trials comparing the agent with traditional antidepressants. The dosages used in all but three of the studies were between 0.5 and 3 mg daily via peroral route which are much lower than those required for an antipsychotic effect. It is unclear from the papers why a low dosage was suspected to have an antidepressant effect. Unfortunately, no systematic studies have investigated the dose-response relationship. Two groups compared the effect of flupenthixol 1 versus 2 mg/day perorally and found no difference in antidepressant effect. According to Gruber and Cole (1991) 1-1.5 mg/day was effective and higher dosages were found to be counterproductive as a result of the comparative studies with flupenthixol 1-2 mg/day and

fluvoxamine 100-200 mg/day over a period of 4 weeks in 72 subjects. Assessment tools were the Hamilton and CGI. The reduction in Hamilton scores was greater in the flupenthixol group ($p < 0.05$). As measured by the CGI after 4 weeks, 78% of the flupenthixol group were rated as normal or borderline compared with only 42% of the fluvoxamine group ($p < 0.01$). Side effects as measured by new symptom development were twice as common with fluvoxamine and four patients in this group had to be withdrawn due to adverse effects, whereas none in the flupenthixol group was observed (2).

Flupenthixol combined with other antidepressants

The literature contains three open, uncontrolled trials of flupenthixol used with other antidepressants in patients with treatment-resistant depression. In one of these, 90 patients received flupenthixol 0.5-2 mg/day, many of whom continued taking their TCAs or MAOIs. The author concluded that 64% improved with the addition of flupenthixol, many within 2-3 days after starting treatment and that no dangerous side effects were encountered due to the interaction between the drugs (9).

In 45 patients who had responded poorly to TCAs, flupenthixol was an effective antidepressant, either added to a tricyclic regimen (36 patients) or by itself (9 patients). According to the author's clinical impression, 93% showed improvement within 2 weeks and the side effects were mild (2).

Twenty-six patients who did not respond adequately to flupenthixol or amitriptyline alone were treated with a combination of both drugs for four weeks. The author did not report how many of them responded to the combination but did note that 15 developed additional symptoms of the same type were observed with monotherapy. Also symptom development was more common when amitriptyline was added to flupenthixol than when flupenthixol was added to amitriptyline (2).

Mood stabilization

An open study of 30 patients with periodic

or cyclic depression was conducted over 2-3 years. The patients failed treatment with lithium because of unresponsiveness, inability to tolerate the side effects or noncompliance. Those who received flupenthixol decanoate 20 mg every 3 weeks obtained a mood stabilizing effect, that is a decrease in the number of manic and depressive episodes comparable to that produced by lithium. Hospitalizations decreased from 0.92 to 0.26 patient/year (10).

Similar results were seen in 93 patients with bipolar illness who had failed lithium treatment. Long-term treatment with flupenthixol decanoate 20 mg every 2-3 weeks produced a decrease in the number of manic episodes from 0.47 ± 0.07 to 0.26 ± 0.07 patient/year. However the frequency of depression increased from 0.47 ± 0.07 to 0.72 ± 0.09 patient/year. The authors believe that this increase was due to withdrawal of lithium which can cause depression. Their data supported this hypothesis. Only the patients who were withdrawn from lithium before the start of the study showed an increase in depressive episodes.

Eleven patients with bipolar disorder relapsed despite prophylactic treatment with lithium. They continued to take lithium and were given either placebo injections or flupenthixol decanoate 20 mg every 4 weeks. The trial had a double-blind cross-over design, so each patient received the active drug for one year and placebo for one year (11). In contrast to the above studies, no prophylactic effect of flupenthixol was observed (2).

Even now, flupenthixol may be an option for small subset. Moreover compliance is a major issue in some patients with bipolar disorder. Thus ensuring compliance with depot administration may be advantageous.

Prevention of suicidal gestures

Among 30 patents who met the DSM-III (Diagnostic and Statistical Manual, 3rd ed.) criteria for personality disorders and who had committed at least three suicidal gestures, 14 were treated with flupenthixol decanoate 20 mg every 4 weeks and the other 16 received

Table. Side effects of flupenthixol in 4772 patients (12-14)

Symptom	Number of reports	Percentage
EPS	94	1.9
Akathisia	11	0.2
Drowsiness	97	2.0
Gastroenteropathy	74	1.6
Vertigo	50	1.0
Dry mouth	41	0.9
Restlessness	32	0.7
Weight gain	31	0.6
Cardiovascular disorder	21	0.4
Nausea	14	0.3
Urinary retention	7	0.1
Sleep disorders	13	0.3
Local reactions	11	0.2
Headache	13	0.3
Sweating	7	0.1
Blurred vision	6	0.1

a placebo. During a treatment period of 6 months, 3 of 11 patients in the flupenthixol group attempted suicide compared to 12 of 16 in the placebo group. This suggests that flupenthixol may be useful in patients with personality disorders involving high risk for suicidal attempts (2,6).

Treatment of cocaine addiction

In a preliminary study, 10 patients addicted to crack cocaine were given an on-time dose of flupenthixol decanoate 10 or 20 mg. Reports showed a decrease in cocaine craving and dysphoric symptoms such as anhedonia. In addition 77% were reported with an increase in energy by the third day and a decrease in craving caused by environmental cues. Eighty-eight percent stopped using cocaine during the first week and the remainder did so during the second week. Because flupenthixol may have a more rapid onset of action than desipramine, it can be the major alternative in pharmacotherapy for cocaine withdrawal. On the other hand compliance can be verified by depot administration and its use as a treatment for cocaine withdrawal warrants investigation (2).

In conclusion, flupenthixol is efficient in patients with anxiety, depression and schizophrenia with good tolerability.

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