Comparison of Antidepressant Effects of Azafan, Tianeptine, and Paroxetine

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny,* Vol. 148, No. 7, pp. 65-67, July, 2009
Original article submitted April 15, 2009

Antidepressant activity of Russian product Azafen (pipofezine) and foreign products Paroxetine and Tianepine was compared using behavioral despair test (Porsolt test) and forced swimming test in a container with wheels (Nomura). Azafen significantly shortened the duration of depressive state in both tests. The results suggest that Azafen exhibits pronounced antidepressant activity, superior to that of the reference drugs.

Key Words: *antidepressant activity; Azafen; Paroxetine; Tianeptin*

The search for efficient antidepressants with minimum side effects remains a pressing problem, despite dynamic development of psychopharmacological investigation. New groups of products with improved characteristics and original mechanism of action were obtained; the new drugs produce selective effects on serotonin and norepinephrine transmission and are characterized by minor side effects, better tolerance, but lesser thymoleptic activity, particularly in the treatment of severe depression [5], or dose-dependent effects [6]. Moreover, such pharmaceuticals are very expensive. Original Russian product Azafen (pipofezine) can partially compensate shortage in antidepressant agents on the Russian market. Azafen is a member of the tricyclic antidepressant family and nonselective monoamine reuptake inhibitors; it exhibits thymoanaleptic, sedative, and anxiolytic properties. At the same time, the agent does not practically block muscarinic receptors and does not affect monoamine oxidase activity.

Here we compared antidepressant activity of Russian product Azafen with that of well-known foreign products, including Paroxetine (selective serotonin reuptake inhibitor) and Tianeptine (tricyclic antidepressant and serotonin reuptake stimulator) in accordance with current basic methods for the assessment of antidepressants with different mechanisms of action.

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MATERIAL AND METHODS

Experiments were carried out on 70-90 day-old mongrel albino rats weighing 200-250 g (n=240, Stolbovaya nursery, Russian Academy of Sciences). The animals were kept in a vivarium in accordance with GLP and Russian Ministry of Health order No. 267, dated June 19, 2003, "Establishment of laboratory rules". For evaluation of the effect of antidepressants, modified [4] basic tests were used: Porsolt test of behavioral despair [2,8] and forced swimming test in a container with wheels (Normura) [2,7].

In the model of behavioral despair (Porsolt test), the animals placed in water tried to escape from closed container 40 cm in diameter, 60 cm in depth, filled with water (25°C); they made swimming movements, then floated for some time, and then again attempted to escape from the container. The duration of immobility periods after unsuccessful efforts for escape was used as a characteristic value for the severity of depression. Immobilization episodes were recorded over 10 min. Input and registration of the experimental parameters were carried out using software [3].

In Normura test, attempts to escape from a container with water 64×30×42 cm divided into 4 equal com-

0007-4888/09/1481-0054

partments within free-rotating 11-cm wide wheels were assessed. The container was filled with water (25°C) to a level corresponding to the middle of the wheels. The rat was placed on the wheel, and then wheel turns were counted using a electromechanic counter [4]. The number of wheel turns over 10-min period was used for processing of the results for each group.

Since antidepressants irrespective of the mechanism of their action shorten the duration of immobility in the Porsolt test and stimulate attempts to escape in the forced swimming test, the test agents were administered to the experimental animals via a gastric tube 40 min before the start of the experiment. Azafen and Paroxetine were given in doses of 5, 10, and 20 mg/kg, Tianeptine was administered in doses of 5, 12.5, and 20 mg/ml.

Control animals received distilled water 40 min before the start of the experiment via a special tube. Special animal group were used for each agent.

Statistical analysis included calculation of the means and standard deviations. Significance on differences was assessed using ANOVA at $p<0.05$ [1].

RESULTS

Immobility duration in the Porsolt test varied from 438 to 448 sec over 10 min.

Administration of all doses of Azafen significantly decreased immobility time. Azafen in a dose of 5 mg/kg reduced immobility time by 21.4%. Maximum effect was reached with Azafen dose of 10 mg/kg, when reduction of immobility time reached 30.2%. After increasing Azafen dose to 20 mg/kg, the decrease in immobility time was 16.7%.

Paroxetine in doses of 5, 10, and 200 mg/kg also shortened immobility time by 14.1, 18.2, and 16.2%, respectively.

Significant reduction in immobility time following Tianeptin administration was observed only after the dose of 12.5 mg/kg, while administration of 5 and 20 mg/kg Tianeptin did not affect animal behavior (Table 1).

When Normura test was used for modeling the depression-like state, significant increase in activity was observed after administration of Azafen in doses of 5, 10, and 20 mg/kg (the number of wheel turns increased by 53.2, 64.8, and 37.5%, respectively).

Paroxetin also produced an activating effect, but significant increase in number of wheel turns (40.7%) was observed only after administration of 10 mg/kg Paroxetin. Lower or higher doses (5 and 20 mg/kg), produced less pronounced antidepressant effects; the number of wheel turns was higher by 16.7 and 28.5%, respectively, but these differences were insignificant.

Tianeptine in the studied doses (5, 12.5, and 20 mg/kg) significantly increased the number of wheel turns over 10 min period of registration by 46.9, 57.5, and 34.2%, respectively (Table 2).

Thus, these results demonstrated pronounced antidepressant effects of Azafen. This agent was superior

TABLE 1. Effects of Azafen, Paroxetine, and Tianeptine on Time of Immobility in Porsolt Behavioral Despair Test in Albino Mongrel Rats (*M*±*m*)

Dose, mg/kg	Duration of immobility episodes over 10 min, sec	% of control
Azafen		
5	344.52±51.30*	78.6
10	305.91±33.66*	69.8
20	365.28±30.74*	83.3
Control	438.40±26.94	—
Paroxetine		
5	385.57±28.19*	85.9
10	366.93±35.70*	81.8
20	375.86±24.44*	83.8
Control	448.55±31.52	—
Tianeptine		
5	391.77±19.96	88.7
12.5	379.20±36.78*	85.9
20	387.96±20.16	87.9
Control	441.51±31.96	—

Note. Here and in Table 2: *$p<0.05$ compared to the control.

TABLE 2. Effects of Azafen, Paroxetine, and Tianeptine on Motor Activity in Nomura Forced Swimming Test in Albino Mongrel Rats (*M*±*m*)

Dose, mg/kg	Number of wheel turns over 10 min, sec	% of control
Azafen		
5	108.80±21.30	153.2*
10	117.00±28.31	164.8*
20	97.60±19.54	137.5*
Control	71.00±18.66	—
Paroxetine		
5	81.80±22.09	116.7
10	98.60±26.45	140.7*
20	90.10±17.53	128.5
Control	70.10±15.12	—
Tianeptine		
5	97.90±18.28	146.9*
12.5	104.90±18.60	157.5*
20	89.40±16.37	134.2*
Control	66.60±13.01	—

to the reference compounds by activity and depth of antidepressant effect in both Porsolt test of behavioral despair and Nomura forced swimming test.

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