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The Influence of Risperidone on Cognitive Functions in Schizophrenia

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A B S T R A C T

Introduction of the antipsychotics of the second generation (SGA) into the therapy of schizophrenia roused expectations that, finally, the cognitive dysfunction in schizophrenia could be eliminated by psychopharmacological therapy. The purpose of the study was to verify the effect of atypical antipsychotic risperidone on cognitive functions in schizophrenic patients. The study was carried out upon 48 male schizophrenic patients aged 21–47 years who were switched from the antipsychotics of the first generation (FGA) to the antipsychotic risperidone, due to intolerance, during the treatment. Intelligence, abstract and concrete thinking and mental speed, attention, and short-term nonverbal memory prior to the switch, one month after the switch, and three months after the switch to risperidone, were evaluated. One month after the switch the number of subjects with severe impairment of intellectual abilities decreased significantly from 62% to 15% and after three months the number was even lower–8%. The impairement of concrete and abstract thinking and mental speed also showed the same tendencies of decrease. The improvement of the cognitive functioning after the switch from the antipsychotics of the first generation to the antipsychotic risperidone is explained by removal of the antipsychotics of the first generation from the therapy and the consequential disinhibition of secondary cognitive impairments and by decreased average dose of anticholinergic and decreased number of patients who need anticholinergic therapy beside risperidone. The possibility of clear pro-cognitive effect of risperidone is suggested and its verification is proposed with strict control of other factors that improve cognitive functioning of schizophrenic patients during the treatment.

Key words: *schizophrenia, risperidone, cognitine function.*

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Introduction

Schizophrenia is accompanied by a unique group of mental and especially cognitive impairments. Short-term and long-term memory, intelligence, mental speed, attention, precision, perception, social problem solving ability, planning and abstract reasoning are impaired. These impairments were considered a side effect of productive psychotic symptoms for a long time. Only recently they are considered a central phenomenon of schizophrenia and a main cause of poor social and professional adjustment[1,2]. The impairments of cognitive functions in schizophrenia were considered stable and permanent characteristics of the disorder until recently. The introduction of the antipsychotics of the second generation (further in the text SGA) into the therapy of schizophrenia has changed such approach. These new, antipsychotics of the second generation surely cause fewer secondary negative symptoms and cognitive impairments compared to the old antipsychotics of the first generation (further in the text FGA) but there still is not enough convincing evidence to prove their effect on primary negative symptoms[3]. The evidence of their pro-cognitive efficacy from double-blind controlled studies is also modest, especially if the evidence, that is a result of reduction of extrapyramidal side effects, is excluded[4]. Nevertheless, the question remains open, because it is repeatedly pointed out to the beneficial effect of SGA on cognitive functions in schizophrenia[5]. The improvements are not spectacular and do not result in complete normalization, for, in general, residual impairments remain[6]. Results of some studies point to genetic, neurodegenerative determination of neurocognitive impairments in schizophrenia[7], because the same can be found in relatives of those who suffer from schizophrenia, as well as in children and adult with attention-deficit hyperactivity disorder[8]. These findings and a good tolerance of SGA backed up the idea of their application in prodromal phase of schizophrenia, in order to act therapeutically as early as possible upon cognitive dysfunction. Small dosages of risperidone proved to be tolerable and safe for adolescents with prodromes of schizophrenia with significant improvement on the test of verbal learning[9]. Until recently, the switch from FGA to SGA ones was motivated by their better tolerance and safety[10,11], and now, besides these advantages, clinicians more and more emphasize their effect on negative symptoms and cognitive dysfunction as a reason for the switch[12,13]. The purpose of the study was to verify the effect of atypical antipsychotic risperidone on cognitive functions in patients with schizophrenia. Secondary purposes were: a) to evaluate intelligence, abstract and concrete thinking, and mental speed, attention and short-term nonverbal memory in schizophrenic patients prior to treatment, after one month of treatment, and after three months of treatment with risperidone; and b) to compare the evaluations of cognitive functions before and during the treatment and to conclude on the effect of risperidone on particular cognitive functions in schizophrenic patients.

Subjects and Methods

The subjects were male schizophrenic patients aged 21–47 years, who were switched from AFG to risperidone, due to intolerance or the lack of efficacy. Prior to the switch they were taking FGA fluphenazine or haloperidol, and the switch was made by gradual cross-reduction of dosages in three to seven days, until their discontinuance.

According to the protocol, the psychiatrist introduced the subjects that were indicated for the switch from FGA to risperidone, to the plan of examination. The

subjects that agreed to the examination signed an informed consent. The criteria for inclusion, beside intolerance and the lack of efficacy, were: diagnosis of schizophrenia according to DSM-IV[14], minimum score of 4 on CGI (Clinical Global Impression) scale[15], total of 60 points on PANSS scale (Positive and Negative Syndrome Scale)[16], repeated episode of schizophrenia, earlier treatment with typical antipsychotics, and intellectual ability of a patient to comprehend the nature of examination and to conform to protocol. The criteria for exclusion were: primary intellectual subnormality, another attached mental disorder and a heavier physical impairment. 50 subjects were included into the study, in order of their arrival to the psychiatric outpatient clinic and they were examined three times: prior to switch to risperodone (n = 50), after 1 month of treatment with risperidone (n = 48) and after 3 months of treatment with risperodone (n = 48). 48 subjects finished the examination, 2 subjects were excluded from the treatment with risperidone: one because of its insufficient efficacy and the other because of side effect – insomnia. They are not included into statistical analysis. The subjects took the doses of 3.0–4.0 mg of risperidone once a day in the morning. As an additional therapy they were allowed to take only biperiden in case of extrapyramidal side effects and oxazepam to ameliorate anxiety. The doses of biperiden prior to the switch were 4.0–6.0 mg, and after the switch it was 1–3 mg a day. Prior to the switch biperiden took 75%, and after the switch 30% of subjects included into the study. The process of switching from FGA to risperidone was carried out according to recommendations from the literature.

Peroral FGA was gradually excluded from the therapy during 7 days while risperidone dose was gradually raised for 2 mg per day during 3 days. If the subjects were taking biperiden, it had been gradually excluded during 2 weeks. While switching depot form of FGA, we introduce risperidone in the same manner during the first part of the therapeutic cycle and biperiden was left till the end of the therapeutic cycle of depot form in the same dose with gradual reduction during next two weeks[10,12,17].

Concrete and abstract thinking, intelligence, attention and short-term nonverbal memory of subjects were evaluated. Intelligence was evaluated by Army Beta test (revised)[18]; attention was evaluated by the Attention test[19], and short nonverbal memory by the Benton's revised visual retention test[20]. The analysis of subtest results in intelligence test allowed the evaluation of abstract and concrete thinking and mental speed.

The characteristics examined were analyzed by classifying them into three degrees of test achievements – low, medium, and high; except the memory that was classified into two categories – with disturbances, and without disturbances. Definitions of the achievement degrees: 1) intelligence – underaverage IQ < 89, average IQ = 90–109, above average IQ > 110; 2) concrete thinking – pondered points on the subtest of space orientation and perceptive reasoning ranging from 31–50, 51–70, and 71–90; 3) abstract thinking – pondered points on the subtest of noticing connections and relations between situations, on the subtest of perceptive reasoning and, on a subtest of perceptive inadequacy ranging from 21–40, 41–60, and 61–80; 4) mental speed – pondered points on the subtest of perceptive speed and of a simple transformation speed ranging from 21–40, 41–60, and 61–80; 5) attention – underaverage 10^{th}–24^{th} centile, average 25^{th}–74^{th} centile, and above average 75^{th}–90^{th} centile; 6) memory – with disturbances = lower number of exact reproductions and/or higher number of mistakes compared to expected considering the age and IQ, – no distur-

bances = the expected number of exact reproductions equal or higher, and the number of mistakes equal or lower than expected considering the age.

The results obtained were analyzed by appropriate statistical methods (frequency and χ^2 test).

Results

The results of intelligence evaluation in schizophrenic patients prior to the switch from FGa to risperidone show that 62% of subjects had impaired intelligence. After one month of treatment with risperidone their number decreased to 15%, and after 3 months there were 8% of subjects with the impairments of this mental function. At the same time the number of subjects with average and above average intelligence increased. Transformation is significant ($df = 4$; $\chi^2 = 43.86$; $p < 0.01$). In Table 1 other results of the study are presented in the same way. Analysis of subtest results in the intelligence test allowed evaluation of abstract and concrete thinking and mental speed. Prior to the switch from FGA to risperidone 62% of subjects had severe concrete thinking impairment. After one month of treatment their number decreased to 19%, and after three months none of the subjects showed severe impairment. Concrete thinking

TABLE 1
COGNITIVE FUNCTIONS AFTER THE SWITCH FROM THE ANTIPSYCHOTICS OF THE FIRST GENERATION TO RISPERIDONE IN THE TREATMENT OF SCHIZOPHRENIA

Cognitive function examined	Ability level	Prior to switch (N = 50)	After 1 month (N = 48)	After 3 months (N = 48)	df	χ^2	p
Intelligence	Under average	31 (62%)	7 (15%)	4 (8%)			
	Average	19 (38%)	36 (75%)	32 (67%)	4	43.86	< 0.01
	Above average	0 (0%)	5 (10%)	12 (25%)			
Concrete thinking	31–50 points	31 (62%)	9 (19%)	0 (0%)			
	51–70 points	19 (38%)	34 (71%)	36 (75%)	4	50.80	< 0.01
	71–90 points	0 (0%)	5 (10%)	12 (25%)			
Abstract thinking	21–40 points	22 (44%)	6 (13%)	0 (0%)			
	41–60 points	28 (56%)	35 (73%)	28 (58%)	4	46.01	< 0.01
	61–80 points	0 (0%)	7 (14%)	20 (42%)			
Mental speed	21–40 points	25 (50%)	5 (10%)	0 (0%)			
	41–60 points	22 (44%)	24 (50%)	32 (67%)	4	43.15	< 0.01
	61–80 points	3 (6%)	19 (40%)	16 (33%)			
Attention	Under average	32 (64%)	26 (54%)	20 (42%)			
	Average	14 (28%)	16 (33%)	21 (44%)	4	3.68	> 0.05
	Above average	4 (8%)	6 (13%)	7 (14%)			
Memory	Disturbances	36 (72%)	38 (79%)	28 (58%)	2	5.11	> 0.05
	No disturbances	14 (28%)	10 (21%)	20 (42%)			

improved significantly after three months ($df = 4$; $\chi^2 = 50.80$; $p < 0.01$). Prior to the switch from AFG to risperidone 44% of subjects had severe impairment of abstract thinking. After one month their number decreased to 13%, and after three months there were no patients with severe impairment of abstract thinking. The number of subjects with moderate impairment of abstract thinking did not change significantly. Abstract thinking significantly improved after three months of treatment ($df = 4$; $\chi^2 = 46.01$; $p < 0.01$). Mental speed also improved significantly. Prior to the switch to risperidone even 50% of subjects had severe impairment of mental speed, and after one month only 10% of them. After three months of treatment there were no subjects with severe impairment of mental speed ($df = 4$; $\chi^2 = 43.15$; $p < 0.01$). Attention and memory did not change significantly during the treatment with risperidone.

Discussion

Comparing the results of our study with similar study results from the literature there are several possible explanations why there is an improvement of cognitive functions after the switch from FGA to risperidone in the treatment of schizophrenia. First of all, this improvement can be a consequence of discontinuance of FGA, and not of introduction of a SGA risperidone into the therapy. McGurk and associates reported in 1997 that haloperidol – FGA causes disturbances of verbal fluency, damages executive functioning, reduces the reaction time, concentration, and achievements of the frontal lobe functioning tests, such as verbal working memory and spatial working memory[21]. All our patients were switched from FGA (fluphenazine or haloperidol) by cross reduction of dosages, in three to seven days, to risperidone. During next few weeks, together with amelioration of extrapyramidal symptoms and pharmacogenic depression, the gradual improvement of intellectual functioning, concrete and abstract thinking, and mental speed occurred. The results obtained by inteligence test represented the intelectual achievement at the moment of the application of the test. Very often the intelectual achievemnt is affected by anxiety, depressive inhibition or attention defict while intelectual potential is higher. Reduction od anxiety, depressive desinhibition and better attention results in better intelectual achievement. Attention and memory did not improve significantly. Other authors noticed the similar effects that occurred after the switch from FGA to risperidone[12,21]. The results of the study by Desai and associates also support such an interpretation[22]. It is interesting that, according to the results of Desai and associates, dramatic improvement of cognitive functions occurs in the period of 4 to 16 weeks after the switch (the improvement occurred in 60% of subjects, like in our study), but after 16 to 28 weeks only in 35% of subjects cognitive functioning remains improved. The findings support more the disinhibition of cognitive functions prior to the discontinuance of FGA than pro-cognitive effect of risperidone. Another reason for the improvement in cognitive functions in the therapy with risperidone might be a significant decrease of the dose of anticholinergic after the switch from AFG to this drug[13,23,24]. Namely, anticholinergics have a significantly negative effect on cognitive functioning[23], and the decrease in dose may be sufficient reason for the improvement. In our study an average dose of Biperiden was decreased after the switch from FGA to risperidone (4–6 mg a day prior and 1–3 mg a day after the switch). Other authors also report of the decrease in dose of biperiden when risperidone is used in about 30–50%[26,27]. Further, among SGA, risperidone has the

lowest affinity for cholinergic muscarinic receptors[28,29], and the risk of causing the anticholinergic side effects, including inhibition of cognitive functions, is very low. It remains to consider the possibility of pro-cognitive therapeutic effect of risperidone alone, independent of disinhibition effects of the discontinuance of FGA and of decreased dose of biperiden. There is evidence that the possible pro-cognitive effect is related to relatively high affinity of risperidone and other SGA towards 5-HT_2 receptors by whose blockade the atypical antipsychotic effect is achieved. Based on this, cognitive functions in schizophrenic patients are tried to be improved by adding various 5-HT_2 receptor antagonists[30] and 5-HT_{1A} receptor agonists[31] to the antipsychotic therapy. For specific FGA profile of particular antipsychotics the ratio between 5-HT_2/D_2 blockade is essential[32]. Beside the 5-HT_2/D_2 ratios, faster dissociation of SGA from D_2 receptor, which is different for every one of them[33], also influences the specific SGA profile. It seems that combination of 5-HT_2/D_2 ratios, with low affinity for cholinergic receptors and dissociation from D_2 receptors positioned between olanzapine and FGA, is regulated in support of pro-cognitive efficiency of risperidone[33,34]. There are evidence that risperidone really improves the brain activity in prefrontal cortex, which includes thinking processes[35]. Since mild cognitive impairments are already present in prodromal phase of schizophrenia and since cognitive deficits deteriorate with the progression of the illness, it is well-founded to give antipsychotics with pro-cognitive efficacy as early as in prodromes of the illness, although it opens numerous ethical questions[36,37]. The improvement of cognitive functioning in schizophrenic patients that has been noticed in our study appears to be a consequence of all the three factors: removal of AFG, decrease in the average dose of biperiden, and pro-cognitive efficacy of risperidone. Our study was not designed to resolve these factors, or to answer the questions about a clear pro-cognitive efficacy of risperidone. Double-blind studies that will control the effect of these factors and secondary cognitive deficits of another etiology on the assessment of pro-cognitive efficacy of risperidone are needed.

Conclusion

Cognitive dysfunction in schizophrenia is a central phenomenon of this disorder and the main cause of poor social and professional adjustment. It occurs in over 60% of patients treated with FGA. After the switch from FGA to risperidone due to intolerance, after only one month the intellectual functioning, concrete and abstract thinking, and mental speed are significantly improved. The improvement is even more conspicuous three months after the switch from FGA to Risperidone. The improvement of cognitive functioning can be explained by the removal of FGA from the therapy, by the decreased average dose of anticholinergics necessary to control extrapyramidal side effects and by the decreased number of patients who need such additional anticholinergic therapy, and or by pro-cognitive efficacy of risperidone. Double-blind studies, controlled by adequate psychopharmacological standards without pro-cognitive effect, are needed in order to verify pro-cognitive efficacy of isperidone and to distinguish the contribution of other factors that improve cognitive functioning of schizophrenic patients during the treatment.

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UTJECAJ RISPERIDONA NA KOGNITIVNE FUNKCIJE U SHIZOFRENIJI

S A Ž E T A K

Uvođenje novih antipsihotika druge generacije u terapiju shizofrenije probudilo je očekivanja da će se konačno i kognitivna disfunkcija u shizofreniji moći ukloniti psihofarmakološkom terapijom. Cilj istraživanja bio je provjeriti učinak risperidona, antipsihotika druge generacije na kognitivne funkcije u oboljelih od shizofrenije. Istraživanje je izvršeno na 48 muškaraca oboljelih od shizofrenije, u dobi od 21 do 47 godina, kod kojih su u tijeku liječenja antipsihotici prve generacije, zbog teže podnošljivosti zamijenjeni novim antipsihotikom risperidonom. Procjenjivani su: inteligencija, apstraktno i konkretno mišljenje te mentalna brzina, pažnja i kratkoročno neverbalno pamćenje, prije zamjene te jedan mjesec i tri mjeseca poslije zamjene risperidonom. Mjesec dana nakon zamjene značajno je smanjen broj ispitanika s težim oštećenjima intelektualnih sposobnosti, konkretnog i apstratnog mišljenja te mentalne brzine, a nakon tri mjeseca taj broj je postao još manji. Poboljšanje kognitivnog funkcioniranja poslije zamjene antipsihotika prve generacije antipsihotikom druge generacije risperidonom tumači se povlačenjem iz terapije antipsihotika prve generacije i posljedičnom dezinhibicijom sekundarnih kognitivnih oštećenja te smanjenjem potrebne prosječne doze antikolinergika i smanjenjem broja bolesnika koji zahtijevaju antikolinergičku terapiju uz risperidon. Sugerira se mogućnost čistog pro-kognitivnog učinka risperidona te predlaže njegova provjera uz strogu kontrolu drugih faktora koji tijekom liječenja poboljšavaju kognitivno funkcioniranje oboljelih od shizofrenije.