

THE INFLUENCE OF RISPERIDONE ON COGNITIVE FUNCTIONS IN SCHIZOPHRENIA

INTRODUCTION

Schizophrenia is accompanied by a unique group of cognitive impairments. Impaired are: short-time and long-time memory, intelligence, mental speed, attention, precision, perception, social problem solving ability, planning and abstract reasoning. 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 novel antipsychotics into the therapy of schizophrenia has changed such a stand. These new, atypical antipsychotics surely cause fewer secondary negative symptoms and cognitive impairments compared to the old, typical antipsychotics 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 atypical antipsychotics 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 atypical antipsychotics backed up the idea of their application in prodromal phase of schizophrenia, in order to act therapeutically as early as possible precisely 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 typical antipsychotics to atypical 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-time 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.

EXAMINEES AND METHODS

The examinees were male schizophrenic patients with a mean age of approximately 38 years (ranging from 21 – 47 years of age), who were switched from typical antipsychotics, due to intolerance, i.e., to various manifestations of extrapyramidal syndrome, to risperidone. Prior to the switch they were taking typical antipsychotics fluphenazine or haloperidol, and the switch was made by gradual cross-reduction of dosages in three to seven days, until their discontinuance.

By a protocol, the psychiatrist introduced the examinees that were indicated for the switch from typical antipsychotics to risperidone to the plan of examination with three visits and a battery of psychological tests on every visit. The examinees that agreed to the examination signed an informed consent. The criteria for inclusion were: diagnosis of schizophrenia according to DSM-IV (14), a 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 examinees were included into the study in order of their arrival to the psychiatric outpatient clinic. 48 of examinees finished the examination. Two examinees backed out from the treatment with risperidone: one because of its insufficient efficacy, and the other because of side effects – insomnia. They are not

included into statistical analysis. The examinees took on average 3,9 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 average dose of biperiden prior to the switch was 4,8 mg for the entire group, and after the switch it was 2,5 mg a day. Prior to the switch biperiden took 78%, and after the switch 31% of examinees included into the study. The process of switching from typical antipsychotics to risperidone was carried out according to recommendations from the literature (10, 12, 17). Concrete and abstract thinking, intelligence, attention and short-time nonverbal memory of examinees 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 orientation to place 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 10th-24th centile, average 25th-74th centile, and above average 75th-90th 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 disturbances = 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 using adequate statistical methods (frequency measures and X2 test).

RESULTS

The results of intelligence evaluation in schizophrenic patients prior to the switch from typical antipsychotics to risperidone show that 62% of examinees had impaired intelligence. After one month of treatment their number decreased to 15%, and after 3 months there were 8% of examinees with the impairments of this mental function. At the same time the number of examinees with aboveaverage intelligence increased. Transformation is significant ($df = 4$; $X^2 = 10.757$; $P < 0.05$). In Table No. 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 typical antipsychotics to risperidone 62% of examinees had heavier concrete thinking impairment. After one month of treatment their number decreased to 20%, and after three months none of the examinees showed heavier impairment. Concrete thinking improved significantly after three months ($df = 4$; $X^2 = 11.447$; $P < 0.05$). Prior to the switch from typical antipsychotics to risperidone 44% of examinees had heavier impairment of abstract thinking. After one month their number decreased to 15%, and after three months there were no patients with heavier impairment of abstract thinking. The number of examinees with medium impairment of abstract thinking did not change significantly. Abstract thinking significantly improved after three months of treatment ($df=4$; $X^2=10,492$; $P < 0.05$). Mental speed also improved significantly in the heavier impairment category. Prior to the switch to risperidone even 50% of examinees had heavier impairment of mental speed, and after one month only 10% of them. After three months of treatment there were no examinees with heavier impairment of mental speed ($df=4$; $X^2=10.492$; $P < 0.05$). Attention and memory did not change significantly during the treatment with risperidone.

TABLE 1

DISCUSSION

Comparing the results of our study with similar study results from the literature there are several possible explanations of why there is an improvement of cognitive functions after the switch from typical antipsychotics to risperidone in the treatment of schizophrenia. First of all, this improvement can be a consequence of discontinuance of typical antipsychotics, and not of introduction of a new antipsychotic risperidone into the therapy. McGurk and associates reported in 1997 that typical antipsychotic haloperidol 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 typical antipsychotics (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. Attention and memory did not improve significantly. Other authors noticed the similar effects that occurred after the switch from typical antipsychotics to risperidone (12, 21). The results of the study by Desai and associates (22) also support such an interpretation. 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 examinees, like in our study), but after 16 to 28 weeks only in 35% of examinees cognitive functioning remains improved. The findings support more the disinhibition of cognitive functions prior to the discontinuance of typical antipsychotics 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 typical antipsychotics 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 typical antipsychotics to risperidone from 4.8 mg to 2.5 mg a day. Other authors also report of the decrease in dose of biperiden when risperidone is used in about 30-50% (26, 27). Further,

among atypical antipsychotics, 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 typical antipsychotics 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 atypical antipsychotics towards 5-HT₂ 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-HT₂ receptor antagonists (30) and 5-HT_{1A} receptor agonists (31) to the antipsychotic therapy. For specific atypical antipsychotic profile of particular antipsychotics the ratio between 5-HT₂/D₂ blockade is essential. Beside the 5-HT₂/D₂ ratios, faster dissociation of atypical antipsychotics from D₂ receptor, which is different for every one of them (33), also influences the specific atypical profile. It seems that combination of 5-HT₂/D₂ ratios, with low affinity for cholinergic receptors and dissociation from D₂ receptors positioned between olanzapine and typical antipsychotics, 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 typical antipsychotics, 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 are needed that will control the effect of these factors and secondary cognitive deficits of another etiology on the assessment of pro-cognitive efficacy of risperidone.

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 typical antipsychotics. After the switch from typical antipsychotics, due to intolerance, to risperidone, 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 typical antipsychotics to risperidone. The improvement of cognitive functioning can be explained by the removal of typical antipsychotics from the therapy, decreased average dose of anticholinergics necessary to control extrapyramidal side effects and decreased number of patients who need such additional anticholinergic therapy, and 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 risperidone and to distinguish the contribution of other factors that improve cognitive functioning of schizophrenic patients during the treatment.

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J. Barkic

Psychiatric clinic, Clinical hospital Osijek, Huttlerova 4, 31000 Osijek, Croatia

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SUMMARY

Schizophrenia is characterized by a unique group of cognitive impairments that were considered for a long time permanent and stable characteristics that follow episodic or permanent productive psychotic symptoms and are the main cause of a poor social and professional adjustment. Introduction of novel, atypical antipsychotics 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 with the mean age of approximately 38 years who were during the treatment switched from typical antipsychotics, due to intolerance, to atypical antipsychotic risperidone. Evaluated were: intelligence, abstract and concrete thinking and mental speed, attention, and short-time nonverbal memory prior to the switch, one month after the switch, and three months after the switch to risperidone. One month after the switch the number of examinees with heavier impairment of intellectual abilities, concrete and abstract thinking and mental speed decreased significantly, and after three months the number was even lower. There was no significant improvement of attention and memory functions. The improvement of cognitive functioning after the switch from typical antipsychotics to atypical antipsychotic risperidone is explained by removal of typical antipsychotics 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.

TABLE 1

NUMBER OF PATIENTS WITH CHANGED COGNITIVE FUNCTIONS AFTER
THE SWITCH FROM TYPICAL ANTIPSYCHOTICS TO RISPERIDONE IN THE
TREATMENT OF SCHIZOPHRENIA

Cognitive function examined	Ability level	Prior to switch N=48	After 1 month N=48	After 3 months N=48	df	X ²	P
Intelligence	Underaverage	30 (62,50%)	7 (14,58%)	4 (8,34%)	4	10,757	<0.05
	Average	18 (37,50%)	36 (75,00%)	32 (66,66%)			
	Above average	0 (0,00%)	5 (10,42%)	12 (25,00%)			
Concrete thinking	31-50 points	30 (62,50%)	10 (20,83%)	0 (0,00%)	4	11,447	<0.05
	51-70 points	18 (37,50%)	33 (68,75%)	36 (75,00%)			
	71-90 points	0 (0,00%)	5 (10,42%)	12 (25,00%)			
Abstract thinking	21-40 points	21 (43,75%)	7 (14,58%)	0 (0,00%)	4	9,729	<0.05
	41-60 points	27 (56,25%)	34 (70,84%)	28 (58,33%)			
	61-80 points	0 (0,00%)	7 (14,58%)	20 (41,67%)			
Mental speed	21-40 points	24 (50,00%)	5 (10,42%)	0 (0,00%)	4	10,492	<0.05
	41-60 points	21 (43,75%)	24 (50,00%)	24 (50,00%)			
	61-80 points	3 (6,25%)	19 (39,58%)	24 (50,00%)			
Attention	Underaverage	30 (62,50%)	19 (39,58%)	8 (16,67%)	4	3,923	>0,05
	Average	18 (37,50%)	24 (50,00%)	32 (66,66%)			
	Above average	0 (0,00%)	5 (10,42%)	8 (16,67%)			
Memory	Disturbances	36 (75,00%)	38 (79,17%)	24 (50,00%)	2	2,052	>0,05
	No disturbances	12 (25,00%)	10 (20,83%)	24 (50,00%)			