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DOUBLE-BLIND PLACEBO-CONTROLLED RANDOMIZED EFFICACY AND SAFETY TRIAL OF ADD-ON TREATMENT OF DIMEBON PLUS RISPERIDONE IN SCHIZOPHRENIC PATIENTS DURING TRANSITION FROM ACUTE PSYCHOTIC EPISODE TO REMISSION

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SUMMARY

Background*: There is evidence that blockade of 5-HT 6 receptors can improve cognitive dysfunction in schizophrenic patients. A number of antagonists of 5-HT6 receptors are in development as cognitive enhancers. One of the agents with relatively strong 5-HT6 activity is dimebon. We tested the hypothesis that this 5-HT6 antagonist administered in the early stage of stabilization after an acute episode can improve both neurocognitive and clinical symptoms in schizophrenia. A phase II study of dimebon as add-on to risperidone therapy was conducted.*

Subjects and methods*: 56 male subjects with paranoid schizophrenia were included in the study. All the patients demonstrated therapeutic response to risperidone as treatment of the acute psychotic episode. After 4 weeks of stability patients were randomized into two groups with placebo or dimebon add-on treatment in a 1 to 1 ratio for 8 weeks. PANSS, CGI-S, CSDS and NSA-16 were used as clinical measures of symptom severity. Different aspects of memory, psycho-motor coordination and executive functioning were assessed with a battery of cognitive tests. Clinical and cognitive assessment was performed twice: after a patient was randomized and 2 months later.*

Results*: Severity of negative symptoms (by NSA-16) were significantly lower in the dimebon group then in the placebo group (p=0.036). Patients in the dimebon group demonstrated improvement in more cognitive dimensions than patients in the placebo group, including working memory, attention, psycho-motor coordination and planning.*

Conclusion*: Dimebon as add-on therapy to antipsychotic treatment in the period of stabilization after an acute episode can improve some aspects of clinical and cognitive status in schizophrenic patients.*

Key words: *schizophrenia - cognitive dysfunction – dimebon - add-on treatment*

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INTRODUCTION

The existing psychopharmacological agents can improve some but not all manifestations of schizophrenia. They address mostly the less specific of the known biological mechanisms of the disease (Kane & Correll 2010). For example antypsychotics that block dopamine receptors appear to be effective in the treatment of acute psychosis of any genesis but cannot significantly improve the emotional, volition or cognitive deficits which are specific for schizophrenia, especially during the period of stabilization (Ibrahim & Tamminga 2011, Laruelle et al. 1999, Barak & Weiner 2011). In the last decade a lot of research was performed to discover more specific neurochemical targets for schizophrenia (Rubeša et al. 2011). A number of compounds were tested in the hope that they would demonstrate a broadened spectrum of activity. Special interest was dedicated to compounds that could improve cognitive dysfunction as an important, and according to some authors, fundamental feature of schizophrenia (Meltzer & McGurk 1999, Stip 2006, Šoštarić & Zalar 2011). Some antypsychotics showed positive effects on certain aspects of cognition in schizophrenic patients (Keefe et al. 2007, Houfthofd et al. 2008), however there are also contradictory results (Faber et al. 2011).

Anticholinesterase agents as adjunctive treatment were of limited efficacy (Ribeiz et al. 2010). Compounds with novel mechanisms of action, such as an antagonist of the glycine transporter (Nikiforuk et al. 2011) or the agonist of the nicotinic alpha7 acetylcholine receptor (Wallace & Porter 2011) are in the stage of development.

There are indications of possible involvement of 5-HT6 receptors in learning and memory processes (Mitchell & Neumajer 2005, Arnt et al. 2010). It was shown that antagonists of these receptors facilitate cholinergic and glutaminergic neurotransmission, reversing scopolamine and NMDA receptor antagonist-induced memory impairment (Fone 2008). Limited data suggested that 5-HT6 receptors play some role in animal models of psychosis such as emotional learning and prepulse inhibition deficits induced by apomorphine and

scopolamine (Mitchell & Neumaier 2005, Mitchell & Neumaier 2008). A number of atypical antypsychotics with well established antypsychotic and possible procognitive activity such as clozapine, olanzapine and asenapine have high affinity to 5-HT6 receptors and act as antagonists (Dupuis et al. 2008, Meltzer & Massey 2011).

Based on these observations we hypothesized that addition of an antagonist of 5-HT6 receptors to antypsychotic therapy can improve the activity profile of the latter in patients with schizophrenia. It turned out that the well-known Russian antihistamine drug dimebon possesses additional anti- 5-HT6 activity with higher affinity compared to the other targets (Shaffhouser et al. 2009, Rossé & Schaffhauser 2010). In animal models it showed efficacy profile relevant to certain aspects of pathophysiology of neurodegenerative diseases such as Alzheimer's disease and Huntington's disease (Bachurin et al. 2009, Bachurin et al. 2001, Vignisse et al. 2011, Wang et al. 2011, Webster et al. 2011, Yamashita et al. 2009). The results of in vitro and in vivo models (Vignisse et al. 2011, Yamashita et al. 2009, Schaffhauser et al. 2009) suggested that the effect of dimebon could also improve overall treatment response.

Although up to this moment all but one clinical trial of dimebon in clinical treatment of neurodegenerative diseases were not successful (Shelkovnikova et al. 2011, Jones 2010), we considered it interesting to explore the effects of this compound as an add-on treatment for functional disorder such as schizophrenia based on the facts mentioned above.

The main objective of this study was to evaluate cognitive and overall clinical benefits of dimebon as an add-on treatment in patients with partial remission after an acute episode of schizophrenia. The rationale for this clinical model was as follows: the primary antipsychotic medication has already demonstrated its efficacy profile but there are remaining positive, negative and cognitive symptoms, which can be reduced by adding dimebon to the therapy.

As primary antipsychotic treatment we have chosen risperidone due to its relatively benign side effect profile, absence of anticholinergic activity (would not cause major additional impact on cognitive dysfunction) and no antagonism to 5-HT6 receptors.

The study was carried out at a single clinical site. The study protocol was approved by the institutional review board. The study drug and placebo were provided by the Institute of Bioactive Substances.

SUBJECTS AND METHODS

Subjects

In order to reduce inter-gender data variability all subjects were male. The subjects were inpatients aged 18 and older, who met the criteria for the diagnosis of schizophrenia, paranoid type (F20.0.1), according to ICD-10 (corresponds to 295.30 by DSM-IV). All patients were in the phase of establishing remission after an acute psychotic episode. To be included in the study, patients were required to have a score 4 or less at the screening visit on PANSS items "Conceptual disorganization" (P2), "Hallucinatory behavior" (P3), "Excitement" (P4), and "Suspiciousness/persecution" (P6). There was no limitation of total PANSS score.

All the participants provided written consent. Patients were informed about the potential benefits, e.g. improvement in cognitive dysfunction, and potential risks, e.g. no information about adverse reactions and tolerability of dimebon for this indication.

The trial lasted for 2 years. The first phase (selection) lasted for 5 months. During the first phase we selected schizophrenic patients with an acute psychotic episode who met the main inclusion criteria for screening, and cross overly transferred them from routine therapy to risperidone monotherapy. When the first clinical signs of pharmacological response were registered by clinicians, the risperidone dosage was fixed and remained stable for 4 weeks prior to randomization and for the rest of the trial. Those patients who did not develop a response to risperidone were excluded and then stabilized with other antipsychotic drugs or their combinations.

If a patient was excluded from the trial prior to randomization another patient was included for screening instead of him. If the patients showed signs of clinical stabilization and good tolerability of risperidone they were randomly assigned by double blind method to add-on placebo or dimebon treatment group in a 1 to 1 ratio for 8 weeks.

A total of 56 patients were included: 29 were in the risperidone plus dimebon and 27 in the risperidone plus placebo group. The risperidone dosage varied from 4 to 6 mg (5.15±0.8 mg). The dimebon dosage was fixed at 20 mg for all the patients. Concomitant medication was allowed excluding antypsychotics other then risperidone. Forty one patients completed the trial: 21 were in the dimebon group and 20 were in the placebo group.

Table 1 presents demographic data of the patients included in the study.

Methods

At screening, medical history was obtained and physical/vital signs examination was performed. Clinical symptoms were assessed at baseline and at the end of the study using the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987), Calgary Depression Rating Scale (CDRS) (Addington et al. 1990), CGI-S, CGI-I, NSA-16, Abnormal Involuntary Rating Scale (AIMS) (Guy 1976), the Simpson-Angus Scale for Extrapyramidal Symptoms (SAS) (Simpson & Angus 1970), the Barnes Akathisia Scale (BAS) (Barnes 1989).

Table 1. The demographic characteristics of the populace under study

	Dimebon group	Placebo group
The number of completed	21	20
Age	34.6+10.5	35.8+14.1
Age at the beginning of the disease	23.0+7.2	24.8+6.3
Duration of the disease	12.1+8.7	8.6+7.5

There were no statistically significant differences between the main demographic characteristics in the groups

The cognitive battery was composed of tests for assessment of memory, attention, psychomotor speed and executive functions.

We selected the tests according to the following criteria: validity; references in relevant studies; the possibility of repeated testing (several sets of the stimuli material available); quantitative interpretation of test results for statistical analysis; availability of standard indices of the data; tolerability for the examinee.

As a result, the battery of tests was compiled of a number of widely-used tests, subtests from well-known batteries and tasks used in Russian pathological psychology:

- Memory – working memory (Wechsler Adult Intelligence Scale, WAIS, subtest V "Number Sequencing") (Filimonenko & Timofeyev 2000), verbal associative memory (Wechsler Memory Scale, WMS, subtest VII "Verbal Paired Associates") (Wechsler 1945), visual-spatial memory (Benton Visual Retention Test) (Sivan 1992), semantic memory (WMS subtest IV "Logical memory") (Wechsler 1945).
- Attention: shifting (Shulte tables, 3 series) (Rubinstein 1970), productivity, stability, and concentration (Proof Assay of Bourdohn) (Soboleva 1999), selectivity and vigilance (Continuous Attention Task, CAT) (Tiplady 1992).
- Psychomotor speed and visual-motor coordination (WAIS, subtest VII, "Digit Simbol-Coding") (Filimonenko & Timofeyev 2000).
- Executive functioning: planning (Tower of London, Drexel University (TOLDX) (Culbertson & Zillmer 1999) and abstract reasoning, the ability to shift cognitive strategies in response to changing environmental demands (Wisconsin Card Sorting Test, WCST, computer version CV3 for Windows) (Heaton et al. 1993).

The clinical assessment procedures were performed by two qualified psychiatrists with sufficient inter-rater reliability throughout the study. The cognitive testing was performed by two trained clinical psychologists. Each patient was rated or tested twice by the same clinician or psychologist respectively.

Statistical analysis

The data were analyzed using statistical software package Statistica, version 6.0 (StatSoft, Inc., Tulsa OK, USA). Endpoint changes in clinical scales and cognitive tests in each group were assessed with the Wilcoxon Matched Pairs Test. The differences between the groups were tested by the Mann-Whitney criterion. The results were estimated as significant at the level of $P<0.05$. We did not use LOCF analysis.

RESULTS

Only those patients who completed the trial were included into the analysis. Therefore in the final analysis 41 patients were included: 21 were in dimebon group and 20 were in placebo one. Fifteen patients discontinued early due to withdrawal of informed consent (7 patients), lost for follow-up (3 patients), exacerbation of psychosis (3 patients), somatic disease (2 patients). There was no significant difference between the groups in the number of discontinued patients.

The data of the psychometric assessments are presented in Table 2. Percentage of improvement by PANSS was calculated by the following formula: (Start PANSS total – Endpoint PANSS total) / Start PANSS total * 100%.

At the beginning of the study, there was no significant difference between the groups in the severity of symptoms, assessed by the total PANSS score and scores of PANSS subscales, as well as by the scores of NSA-16 scale, CDRS and CGI scales. By the end of the trial intragroup changes on nearly all measures differed significantly. The dimebon group showed statistically significant changes from baseline to the end of the trial in all PANSS subscales and total scale scores, CGI-S, CDRS, and NSA-16 scores. There were no changes of scores in PANSS negative subscale and CDRS in the placebo group. By the end of the study the standard deviations practically for all scores in the dimebon group was much larger than that for the placebo group. The standard deviation for the score of improvement by PANSS scores was three-fold more in dimebon than in placebo group.

By the end of the study the groups demonstrated differences on the following measures.

The group of patients that received risperidone in combination with placebo tended to have more severe psychotic symptoms ($p=0.068$). The reduction of symptoms in the responders (improvement of PANSS score more than 20 per cent) was also more prominent in the study group than in the control group (tendency, $p=0.07$). The dimebon group demonstrated a significant decrease in the total score (sum of all scores) of the NSA-16 in comparison to the placebo group ($p=0.036$).

Table 2. Efficacy assessment by psychometric clinical scales

	Dimebon group			Placebo group		
	start	end	P	start	end	P
PANSS total	78.5±14.1	61.9±22.2	P=0.008	71.8±17.99	67.75±16	P=0.00054
PANSS positive	16.9±4.6	12.0±5.9	P=0.0049	14.75±4.87	13.75±3.85	P=0.0029
PANSS negative	22.5±5.15	18.48±7.01	P=0.03	21.3±6.1	21±6.1	ns
PANSS general psychopathology	39.1±8.1	31.4±11.1	P=0.024	35.8±9.04	33±7.97	P=0.0009
Percentage of improvement by PANSS		8.14±49.4			14.4±14.05	
CGI I		2.7±1.0			2.7±0.7	
CGI-S	4.3±1	3.9±1.2	P=0.02	4.75±0.9	4.15±0.67	P=0.003
CDRS	11.6±11.6	8.1±9.97	P=0.034	10.78±14.4	9.0±10.98	ns
NSA-16	64.65±22.8	48.5±22.7	P=0.008	68.0±13.0	61.95±13.7	P=0.003

Analyzing the scores of the individual items of NSA-16, we found an advantage of the dimebon group on speech items (sum of the items "Prolonged time to respond", "Restricted speech quantity", "Impoverished speech content", "Inarticulate speech") (p=0.047) over placebo group at the beginning of the study, and this advantage was present at the endpoint (p=0.01). The analysis of endpoint differences on separate points revealed a statistically significant advantage of the dimebon group on the following items: "Prolonged time to respond" (p=0.00017), "Restricted speech quantity" (p=0.039) "Impoverished speech content" (0.018), "Slowed movements" (0.0004).

Besides, by the time of the final visit the dimebon group tended to have better scores on the items concerning emotions (sum of points "Reduced range", "Reduced modulation of intensity") (p=0.07) was registered in the dimebon compared to the placebo group.

The global negative symptoms rating was better in the dimebon group to the end of the study (p=0.001) without any difference at the beginning.

No endpoint differences between the groups were found in CGI-S, CGI-I and CDRS scores.

We found no differences between the groups on the SARS, BARS and AIMS scores at the beginning as well as at the end of the study. In the course of the trial neither of the groups showed clinically relevant side effects. Tolerability of treatment in both groups was similar.

We did not find significant endpoint differences between the groups (Mann-Whitney U-test) on the cognitive measures with exception of the placebo group's advantage in the Benton test errors' score (p=0.02). However, the groups differed on this parameter at the baseline as well.

Initially there was also a difference in the Benton test correct reproduction score (p=0.01) in favour of the placebo group. At the end of the study we found no difference, which means that dimebon patients improved their results to a greater degree than control group.

The cognitive measures at the beginning and at the end of the study for each group (Wilcoxon rank-sum test for dependent samples) are displayed in Table 3.

Positive dynamics of logical memory, as well as of certain characteristics of executive functioning (aspect of control) were common for both groups. After two months of treatment all the patients began to demonstrate better results in memorizing a story. They reproduced its semantic units more clearly and logically, though their results were still below the normal. Besides, they made considerably fewer errors while developing, maintaining and shifting cognitive strategies (WCST). However, there was a difference between the groups in the type of WCST errors. While the placebo group showed lower indices of general inattentiveness (total number of errors, non-perseverative errors, failure to maintain set), the dimebon group showed a decrease in perseverative errors. This dissimilarity is important as perseverative errors are considered a sign of "hypofrontality" in schizophrenia (Pratt et al. 2008).

Overall, the dimebon group improved in a greater number of cognitive measures than the placebo group. Only working memory index changed significantly in the placebo group. Associative and visual-spatial memory, different features of attention (concentration, productivity, stability), psychomotor coordination and planning were improved significantly in the dimebon group. Planning improvement is noteworthy because it involves an ability to work out a purposeful program in an "inner plan" and carry it out optimally.

Analyzing standard deviations of cognitive measures we found that in the dimebon but not in the placebo group there was a decrease in dispersion in a significant number of neurocognitive tests.

There was no negative impact on cognition or clinical symptoms due to the study treatment in both groups.

Table 3. Cognitive measures at the beginning and at the end of the study

	Dimebon group			Placebo group		
	start	end	p	start	end	p
Wechsler memory scale, subtest V: sum (T-score)	9±2.3	8±2.3	0.42	9±3.1	9.5±2.7	0.0185*
Wechsler memory scale, subtest VII: simple pairs	14±4	17±2.9	0.02*	15±2.3	16±5.3	0.52
Wechsler memory scale, subtest VII: complex pairs	3±2.7	4.5±3.34	0.06	4.5±3.28	5±4.24	0.98
WAIS, subtest VII: Symbol coding (T-score)	5.34±1.9	6±1.47	0.026*	6±2.2	7±2.8	0.36
Wechsler memory scale, subtest IV. Text 1, quantity of semantic units	5±2.3	7±2.6	0.007*	6±3.3	7.5 ±4.49	0.0004*
Wechsler memory scale, subtest IV. Text 2, quantity of semantic units	7±2.7	9±3.0	0.009*	8±3.2	11.5±3.8	0.0002*
Benton test: reconstruction	5±1.7	6±2.21	0.038*	6±2.3	6.5 ± 2.26	0.9
Benton test: errors	8±3.8	6.5±4.4	0.21	6±4	5±4	0.9
Shulte tables: total time in sec. (for 3 tables)	160±105	166±64	0.89	169±61.4	132±108	0.297
CAT: total correct responses (max 40)	35±8.5	37±8.2	0.47	36±8.3	38±12	0.6
CAT: reaction time, msec	732.6±296.9	619.7±195.55	0.136	801.1±273.77	740.3±195.3	0.198
Bourdohn test: attention concenration	0.961±0.036	0.983±0.013	0.006*	0.986±0.002	0.989±0.025	0.550
Bourdohn test: attention stability	0.01±0.01	0.009±0.006	0.002*	0.01±0.009	0.01±0.01	0.06
Bourdohn test: attention productivity	399±123	497±170	0.014*	454±167	515±224	0.055
Tower of London: total correct score	2±1.1	3.26	0.04*	3±2.2	3±2.9	0.148
Tower of London: moves score	46±25	34±19	0.01*	38±20	35±31	0.43
Tower of London: sum total time > 60 sec	1.5±3	0±1.5	0.007*	1±2.4	1±3	0.838
Tower of London: execution time, sec	298±227	234±115	0.02*	251±207	234±229	0.058
Wisconsin CS test: categories completed	4.23±1.7	4.28±1.99	0.919	4.76±3.16	4.47±2.03	0.87
Wisconsin CS test: total error (T score)	41.04±6.7	42.89±7.92	0.28	40.43±9.5	45.77±9.4	0.028*
Wisconsin CS test: perseverative responses (T score)	42.68±8.24	45.3±5.59	0.13	44.7±6.02	45.62±9.4	0.83
Wisconsin CS test: perseverative errors (T score)	42.5±8.06	45.26±5.6	0.047*	44.57±6.04	45.46±9.95	0.9
Wisconsin CS test: nonperseverative errors (T score)	41.7±7.8	40.95±9.38	0.87	38.65±10.43	46.85±8.74	0.01*
Wisconsin CS test: conceptual level responses (T score)	42.12±5.79	44±6.62	0.27	42±8.97	47.9±12.8	0.037*

* statistical significance at level $p < 0.05$

DISCUSSION

The most important result of the trial was the effect of add-on dimebon treatment on negative symptoms. The difference between the groups in regard to the influence on residual positive symptoms was achieved only at the level of tendency. We found that dimebon has a positive impact on most of tested domains of cognitive activity.

Especially interesting is the fact that add-on dimebon treatment contributed to reduction of perseveration errors. We found positive changes in the dimebon group despite the short therapeutic period (2 months) both in some cognitive and psychopathological symptoms. However, these phenomena were revealed only by intragroup analysis. It can be accounted for the small size of the groups which might have made them insufficient for statistical validity. Besides, as was mentioned above, initial individual variability in cognitive abilities can impact the final results. For the time being, it is impossible to overcome the factor of cognitive heterogeneity. In our view there is an objective difficulty in selecting of the most relevant cognitive sign for group homogenization. This in turn relates to lack of knowledge regarding the patho-genetically-oriented key signs of the disease

The high rate of standard deviations for nearly all clinical scales' scores at the end of the study revealed a great variety of individual response in the dimebon group. At the same time, we saw endpoint consolidation of this group in respect of the majority of neurocogni-tive measures – the standard deviations were consider-ably lower than in the placebo group. Thus, we found greater dispersion in clinical scales scores and much less significant dispersion in neurocognitive indices in the dimebon group than in the placebo group. This suggests that dimebon has a relatively similar effect on cognitive dysfunction in all patients, whereas its impact on clinical manifestation is individually variable. This assumption is confirmed by the fact that the clinical dynamics of patients with a clear therapeutic response were significantly greater in the dimebon group. Thus, the main result of our study is the fact that short-term add-on dimebon therapy can improve negative symp-toms and certain components of cognitive dysfunction.

Restrictions in interpretation of the results

This was a pilot study and therefore it has a number of restrictions. The first one relates to the patients' contingent: males only took part in the study due to group homogenization. Only those patients who were sensitive to risperidone and gave a clear therapeutic response in a relatively short period of time were included. We used a standard dosage of the study drug and a universal dosage regime for all the patients, without taking into account individual variability of pharmacokinetic indices. Secondly, the combined treatment lasted for two months, whereas there are no exact data about the optimal period for the effects of a cognitive-enhancing agent in schizophrenia. Thirdly, cognitive testing was carried out at a unified time point with a standard battery of tests without taking into account each patient's personality and his actual mental status at the moment of the testing (such as anxiety fluctuation, affective disturbances, stress reactions etc). And finally, our statistics are vulnerable for type II error due to the very high quantity of the outcome measures. There is evidence to believe that the obtained data reflect a potentially beneficial trend in the therapy of schizophrenia, which enables us to consider further research in this field reasonable.

CONCLUSION

The results of our study demonstrated benefits of dimebon as an add-on therapy during the transition period from acute psychosis to remission after the acute episode in schizophrenic patients. It ameliorates the antipsychotic effect of risperidone and improves effectiveness of treatment for negative symptoms, such as emotional impoverishment and alogia. Despite certain restrictions, we consider these data a good reason for further research in this field.

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