Dopaminergic Modulation of Working Memory in Schizophrenia: Evidence for D1 receptor Involvement

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Background

Experimental evidence points to a positive modulation of dopamine (DA) D1 receptors agonists on working memory (WM)(1). DA D1 receptor subtypes predominate in mesocortical pathways. There is evidence for disturbed D1 receptors in prefrontal cortex (PFC) of schizophrenic patients. Moreover according to clinical reports functional disturbances related to PFC in schizophrenia improves after administration of DA agonists (2,3). However the selective effect of DA subreceptors on cognitive function associated to PFC in schizophrenia is not well investigated.

Objective:

The aim of the study is to examine whether WM in different stimulus modalities (Auditory; Visual-Matching; Spatial), a function associated with the PFC, improves with dopamine agonists in schizophrenia and whether this is related to D1 modulation. This study is part of a larger trial. Since no D1 agonist is available for human research we used a design comparing a dopamine agonist with mixed D1 and D2 properties (pergolide) to placebo as adjuvant therapy to amisulprid (D2/D3 antagonist). With this design the D2-component of pergolide can be antagonized by amisulprid and a D1 agonistic effect can be isolated, as well as protecting patients against a psychotic re-exacerbation. The clinical relevance of this study is that although cognitive deficits in schizophrenia are believed to be one of the most important factors predicting functional (work and social) outcome in the course of the disease (4), cognitive deficits are resistant to antipsychotic treatment.

Methods:

We used a randomized, placebo controlled, parallel group design.

Inclusion criteria:

inpatients, non-acute, with the diagnosis of schizophrenia at the Psychiatry Hospitals of the Universities of Heidelberg and Hamburg-Eppendorf (Clinical interview to establish diagnosis with DSM-IV - MINI-SCID); age: between 18-45 years; Verbal IQ > 80 (Mehrfachwahl-Wortschatz-Intelligenztest).

Exclusion criteria:

neurological and internistic diseases (like untreated thyroid hyper/hypofunction, liver, cardiovascular or kidney dysfunction, seizures or history of traumatic brain injury); Known allergy to ergolines; Actual history of drug abuse/addiction, concomitant other psychiatric disorder (screened by MINI-SCID; other long term pharmacological treatment which can interact with dopamine agonists and antagonists (e.g. anticoagulants, digitoxine).
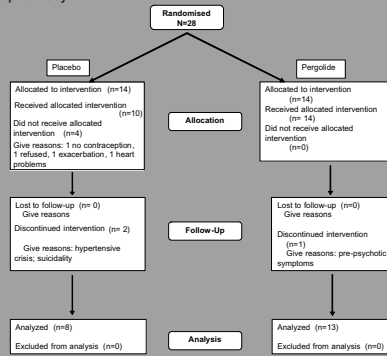
Treatment:

Patients were randomly assigned to a sequence of treatments of either pergolide or placebo p.o. under continuous concomitant antipsychotic therapy (stable at least 2 weeks prior trial begin) with amisulprida, a D2/D3 dopamine antagonist.

1. 0,3 mg pergolide (the first two days begin with 0,05mg, then increase of dose of 0,1mg every 3 days for a maximum of 0,3mg/d, taken orally 3x 0,1mg/day). Then stable dose of 0,3mg for one week.
   Subsequently slow reduction of dosage of 0,1mg every 3 days then 0,05 mg
   every day for the last two days.

Or

2. Identical in appearance and number placebo capsules, in the same starting and maintenance scheme as for pergolide, prepared by the clinic pharmacy.

Flow Chart

Randomised N=28

Placebo — Pergolide

Allocation

Allocated to intervention (n=14)
Received allocated intervention (n=10)
Did not receive allocated intervention (n=4)
Give reasons: 1 no contraception, 1 refused, 1 exacerbation, 1 heart problems

Allocated to intervention (n=14)
Received allocated intervention (n= 14)
Did not receive allocated intervention (n=0)

Follow-Up

Lost to follow-up (n= 0)
Give reasons
Discontinued intervention (n=2)
Give reasons: hypertensive crisis; suicidality

Lost to follow-up (n=0)
Give reasons
Discontinued intervention (n=1)
Give reasons: pre-psychotic symptoms

Analysis

Analyzed (n=8)
Excluded from analysis (n=0)

Analyzed (n=13)
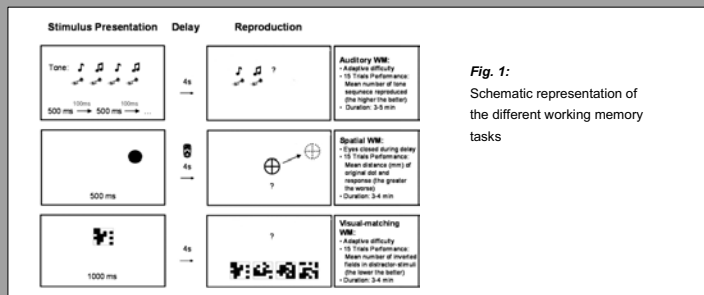Excluded from analysis (n=0)

Experimental Battery:

Fig. 1:
Schematic representation of the different working memory tasks

References

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2) Levi-Minzi, S., P.C. Bermanzohn, and S.G. Siris, Bromocriptine for "Negative Schizophrenia". Comprehensive Psychiatry, 1991. 32: p. 210-216.
3) Davidson, M., P. Harvey, et al. (1990). "Effects of the D1 agonist SKF-39393 combined with haloperidol in schizophrenic patients (letter)." Archives of General Psychiatry 47: 190-1.
4) Green, M. F. (1996). "What are the functional consequences of neurocognitive deficits in schizophrenia?" Am J Psychiatry

Results:

Subjects

Twenty-eight patients were allocated to treatment. 25% of patients (N=7) did not complete the trial. There were 4 patients (14.3% - all allocated to placebo) who did not start receiving medication. 3 patients (10.7%) dropped out while receiving treatment. See Flow Chart. See Table 1 for demographic data and disease variables of the sample. No differences in baseline were found.

	Pergolide (n=14)		Placebo (n=14)		
	M	SD	M	SD	p
Gender (M/F)	10/4		11/3		
Age (years)	28,43	9,38	29,54	7,58	0,74
Education (school years)	11,29	1,68	11,08	1,93	0,77
Verbal IQ	104,14	12,97	99,80	13,11	0,43
PANSS Global	39,21	15,52	39,58	13,30	0,95
PANSS Negative	18,93	5,14	21,50	7,43	0,31
PANSS Positive	10,57	2,17	12,25	3,52	0,15
PANSS Disorganization	11,93	7,51	11,75	5,86	0,95
Calgary Depression Scale	2,64	3,00	3,71	4,34	0,45
Number of Hospitalizations	2,71	2,37	2,23	1,24	0,52
Duration of Disease (years)	3,71	4,07	4,69	4,68	0,57
Age of onset (years)	24,93	7,27	26,23	6,91	0,64

Table 1: Mean (M) and Standard Deviation (SC) of age, education, verbal IQ and clinical characteristics of patients according to medication (all patients allocated to treatment)

1) Auditory Working Memory

Hypothesis: Patients on pergolide treatment show increased number of recalled tones to baseline in comparison to those on placebo. **Results**: A significant interaction of treatment vs. drug type was found $F_{(1, 19)}=7.8$, p=.012. Post-hoc tests (Newmann-Keusl) showed that patients did not differ at baseline but when treated with pergolide showed increased number of recalled tones (p=.02), while patients treated with placebo did not increase performance. Effect size of treatment effect was d=1.25. There was also a trend towards a time effect p=.09, where patients showed better performance after being treated, independently of drug type. Because of small sample size we confirmed the above findings with non-parametric analyses. See Figure 2.
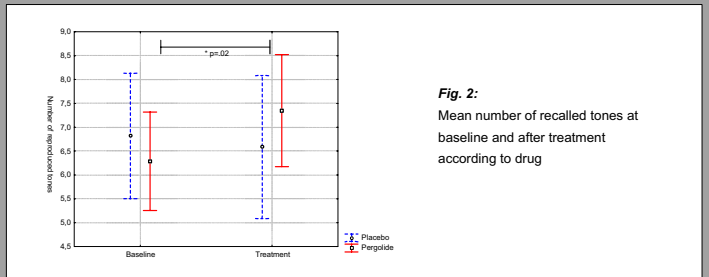

Fig. 2:
Mean number of recalled tones at baseline and after treatment according to drug

2) Visual-matching WM:

Hypothesis: Patients on pergolide treatment present lower number of inverted fields at baseline in comparison to those on placebo. **Results**: No significant interaction was found. A main effect (trend) for time was found, were subjects performed worse after treatment independent of drug type $F_{(1, 19)}=3.79$, p=.07.

3) Spatial WM:

Hypothesis: Patients on pergolide treatment present decreased distance scores to baseline in comparison to those on placebo. **Results**: Because of technical reasons 1 person on placebo was excluded from analyses. No significant interaction or main effects were found.

Effect of Treatment on Psychopathology

Hypothesis: Patients on pergolide show a decrease of negative symptoms (PANSS negative subscale, depression (Calgary Depression Scale) in comparison to those taking placebo in relation to baseline. No differences in positive symptoms between treatments is expected.

Results: Patients did not show differences in negative symptom scores at baseline. There was no significant treatment vs. drug type interaction after two weeks. There was a trend for a time effect: $F_{(1, 19)}$=3.08, p=.095, were patients after two weeks of treatment tended to have lower negative scores independently of drug type. No differences in positive symptoms or depressive symptoms were found between treatments. See Figure 3.
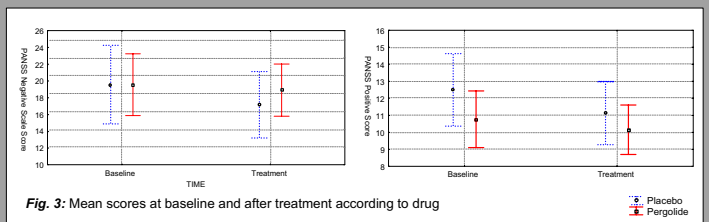

Fig. 3: Mean scores at baseline and after treatment according to drug

Conclusion

Patients on pergolide showed better auditory WM performance as on placebo, but not on the visual-matching nor spatial WM. We could not support the hypothesis of a beneficial effect of pergolide in comparison to placebo on negative nor on depressive symptoms. As expected patients on pergolide treatment did not show higher rates of positive symptoms. There was a trend for a treatment-time effect on negative and positive symptoms, with patients getting better with treatment, independent of drug.

The beneficial effect of pergolide on auditory WM as adjuvant therapy to amisulrpide (D2/D3 antagonist) points to the involvement of D1 receptors in the procesing of WM. Because of the small sample size the results have to be interpreted as preliminary .