Psychiatry Research 175 (2010) 179–180

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Brief report

Varenicline and P50 auditory gating in medicated schizophrenic patients: A pilot study

Merilyne C. Waldo *, Laurie Woodward, Lawrence E. Adler

The Denver VAMC VISN19/MIRECC and UC Denver, School of Medicine, Department of Psychiatry, United States

ARTICLE INFO

Article history:
Received 22 May 2008
Received in revised form 16 January 2009
Accepted 21 January 2009

Keywords:
Schizophrenia
Sensory gating
Varenicline

ABSTRACT

Most schizophrenic patients have a deficit in auditory sensory gating that appears to be mediated by the α-7 nicotinic receptor. This pilot study examines the effects of varenicline, an α-7 agonist, on the P50 auditory evoked potential in six schizophrenic patients. The study was canceled because of concerning side effects consistent with those reported by the FDA. However, in this small group of subjects, varenicline did not consistently enhance P50 auditory gating.

Published by Elsevier Ireland Ltd

1. Introduction

Deficits in auditory sensory gating characterize the majority of patients with chronic schizophrenia (Adler et al., 2004) and are not improved by conventional antipsychotic treatment (Freedman et al., 1987). Gating can be transiently improved by nicotine in schizophrenic patients and their family members, half of whom share the gating deficit (Adler et al., 1992, 1993). Additional studies have confirmed the role of the α-7 nictotinic receptor in sensory gating (Leonard et al., 1998). Previous studies from our laboratory have demonstrated that ondansetron, a $5HT_3$ receptor antagonist, significantly enhanced P50 auditory gating in patients with schizophrenia (Adler et al., 2005) by increasing the release of acetylcholine, which in turn stimulates the α-7 nicotinic receptor (Luntz-Leybman et al., 1992), thus supporting a role for the usefulness of $5HT_3$ receptor blockade in restoring P50 auditory gating.

Varenicline is a partial agonist selective for α4β2 nicotinic acetylcholine receptor subtypes in the brain, as well as a full α-7 agonist (Mihalak et al., 2006). The partial binding of varenicline to the α4β2 receptors blocks the ability of nicotine to activate them and stimulate the mesolimbic dopamine system. This study was designed to examine the effects of varenicline on P50 sensory gating, and to allow us to compare these effects with previous studies of ondansetron in enhancing P50 auditory gating.

2. Methods

2.1. Subjects

Six stable schizophrenic patients (5 men and 1 woman, mean age=48.0 years ± S.D. 5.9) were studied on two occasions, 1 week apart. All were taking atypical antipsychotic medications, including risperidone ($n=2$), aripiprizole ($n=2$), olanzapine ($n=1$), and clozapine ($n=1$). Baseline P50 auditory gating ratios (test amplitude/conditioning amplitude) ranged from 50% to 248%, all in the impaired range compared with a large cohort of previously reported controls (Adler et al., 2004). All gave informed consent prior to participation in the study.

2.2. Experimental procedure

Subjects were given a single dose of varenicline 1 mg or placebo in a double-blind, placebo-controlled, randomized and balanced, crossover design. Serial measurements of the P50 evoked potential were done before dosing (baseline) , and at 1 h and 2 h after placebo or varenicline treatment. Subjects were rated on the Memory Assessment Clinics test battery (Network Neurometrics, 2004) after the second post-treatment evoked potential recordings were completed.

2.3. Electrophysiological recordings

Details of the paired click recording paradigm have been described previously (Adler et al., 2004). Briefly, three sets of 16 artifact-free trials were obtained at each recording time point – prior to treatment with varenicline or placebo, 1 h and 2 h post-ingestion, recorded from electrodes at CZ and EOG leads. These three sets of trials were averaged and are reported as three grand averages (BL, 1 h, 2 h).

The auditory stimulus was set at hearing threshold (as assessed by the method of auditory thresholds prior to the initial recording) +50 DBA. The P50 potential was identified and measured using a previously described computer algorithm (Nagamoto et al., 1989). The amplitude of the P50 test wave was divided by the amplitude of the P50 conditioning wave, expressed as a percentage, the P50 ratio. Subjects were given no special instructions concerning the clicks they were hearing.

2.4. Statistical analysis

Both parametric and nonparametric methods were used to evaluate the data. Repeated measures analysis of variance (ANOVA) was used to test the primary

* Corresponding author. VISN19/MIRECC, VA Eastern Colorado Healthcare System, 1055 Clermont St., Denver CO 80220, United States. Tel.: +1 303 399 8020x2404; fax: +1 303 370 7519.
E-mail address: merilyne.waldo@va.gov (M.C. Waldo).

0165-1781/$ – see front matter. Published by Elsevier Ireland Ltd
doi:10.1016/j.psychres.2009.01.025

hypothesis that varenicline would improve P50 sensory gating. The Mann–Whitney *U* test was used to evaluate differences on memory tests.

3. Results

Varenicline did not significantly change P50 sensory gating when compared with placebo (repeated measures ANOVA, $F=0.567$, $df=2,9$, $P=0.59$). There were no significant differences between varenicline and placebo at the 1 h or 2 h time point (Fig. 1), or when each individual's best (lowest ratio) trials were compared. There were also no significant differences between the percent change in gating from baseline recordings to the individual's best C/T gating.

Amplitudes of the conditioning and test waves and latency of the conditioning wave were not affected by treatment with varenicline. S1–S2 calculations were computed for both the conditioning and test waves, and these were also not statistically significant ($P<0.10$). There were no significant effects on scores of any of the memory tests or on the composite memory score (Table 1).

4. Discussion

P50 sensory gating was not significantly changed by a single dose treatment with varenicline as compared with placebo. One possibility is that because varenicline is a full agonist at the α-7 nicotinic receptor, receptor desensitization occurred by the time measurements were taken. In previous nicotine experiments, the major effect was over by 20–30 min (Adler et al., 1992). Because varenicline has been successfully used in smoking cessation with significantly fewer doses than are needed with nicotine, we had allowed a longer experimental duration to observe effects than in previous experiments. The time to the first P50 recording post-ingestion of the drug was exactly the same as in the previous ondansetron study (Adler et al., 2005). In that study, only one of eight subjects failed to demonstrate improved P50 gating, whereas in this study, not only was there no consistent improvement, but three of the six subjects had brief negative psychological effects after a single dose. Although it is possible that further extending the duration of study may have demonstrated improvements in sensory gating, the discomfort of the subjects made it impossible to continue.

Another possibility is that there was incomplete absorption of a single dose of varenicline, leading to insufficient levels of the drug in the CNS. This appears to be less likely because of the significant central nervous side effects that occurred with the active drug but not the placebo. Oral administration of varenicline has been shown to lead to almost complete absorption and high systemic availability, with maximum plasma concentrations occurring within 3 to 4 h and a half-life of 17 h (Obach et al., 2006). In addition, the presence of obvious central side effects in half of our subjects suggests that significant absorption was accomplished. There was no relationship between sensory gating changes and side effects in these subjects.

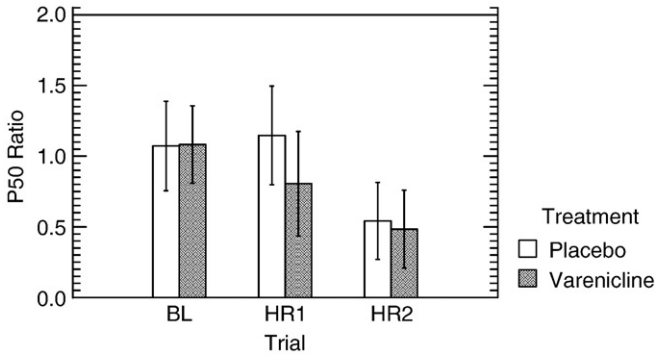

Fig. 1. P50 sensory gating C/T ratio (Tamp/Camp), from baseline before either varenicline or placebo (BL) to 1 h (HR1) and 2 h (HR2) after taking either placebo or varenicline (hour by hour). All of the subjects were clinically stable on antipsychotic medications. Smaller ratios indicate better sensory gating. Repeated measure ANOVA ($F=0.15$, $df=1,10$, $P=0.662$) was not statistically significant for treatment effects.

Table 1
Auditory evoked response data and memory tests.

	P50 amplitude (mean ± S.D.)[a]			P50 latency (mean ± S.D.)[b]			Composite memory score (mean ± S.D.)[c]
	Baseline	Hour 1	Hour 2	Baseline	Hour 1	Hour 2	
Placebo	2.3 ± 1.7	1.8 ± 1.1	2.3 ± 1.2	60.5 ± 6.6	62.7 ± 6.3	58.3 ± 2.1	89.6 ± 33.6
Varenicline	1.7 ± 0.7	2.6 ± 2.0	2.6 ± 1.2	61.7 ± 7.6	57.7 ± 5.5	56.7 ± 3.7	78.8 ± 21.7

Repeated Measures ANOVA.
[a] Amplitude by Treatment $F=0.890$; $df=2,9$; $P=0.444$.
[b] Latency by Treatment $F=0.444$; $df=2,9$; $P=0.406$.
[c] Paired samples t test $=0.715$, $df=5$, $P=0.506$.

This study is limited by the small sample size. However, because of side effects in half of our subjects which were similar to those now being reported by the FDA and the Institute of Safe Medication Practices (2008) as potentially related to varenicline (including suicidal thoughts and aggressive and erratic behavior), we felt that it was prudent to stop the study. Three of our subjects experienced brief but reasonably intense symptoms similar to those now being related to longer term treatment with varenicline, including affective changes. All symptoms resolved within 5 h.

Acknowledgements

This work was supported by VISN19/MIRECC and RO1 MH50787-08.

References

Adler, L.E., Hoffer, L.J., Griffith, J., Waldo, M.C., Freedman, R., 1992. Normalization by nicotine of deficient auditory sensory gating in the relatives of schizophrenics. Biological Psychiatry 32, 607–616.
Adler, L.E., Hoffer, L.D., Wiser, A., Freedman, R., 1993. Normalization of auditory physiology by cigarette smoking in schizophrenic patients. American Journal of Psychiatry 150, 1856–1861.
Adler, L.E., Olincy, A., Cawthra, E.M., McRae, K.A., Harris, J.G., Nagamoto, H.T., Waldo, M.C., Hall, M.H., Bowles, A., Woodward, L., Ross, R.G., Freedman, R., 2004. Varied effects of atypical neuroleptics on P50 auditory gating in schizophrenia patients. American Journal of Psychiatry 161, 1822–1828.
Adler, L.E., Cawthra, E.M., Donovan, K.A., Harris, J.G., Nagamoto, H.T., Olincy, A., Waldo, M.C., 2005. Improved p50 auditory gating with ondansetron in medicated schizophrenia patients. American Journal of Psychiatry 162, 386–388.
Freedman, R., Adler, L.E., Gerhardt, G.A., Waldo, M.C., Baker, N., Rose, G.M., Drebing, C., Nagamoto, H., Bickford-Wimer, P., Franks, R., 1987. Neurobiological studies of sensory gating in schizophrenia. Schizophrenia Bulletin 13, 669–678.
Institute of Safe Medication Practices, 2008. October ISMP's Second QuarterWatch Report Shows Sharp Increase in Reports of Serious Adverse Drug Events. ISMP, Horsham, PA.
Leonard, S., Adler, L.E., Olincy, A., Breese, C.R., Gault, J., Ross, R.G., Lee, M., Cawthra, E., Nagamoto, H., Freedman, R., 1998. The role of nicotine and nicotine receptors in psychopathology. Neuronal Nicotinic Receptors: Pharmacology and Therapeutic Opportunities, pp. 307–322.
Luntz-Leybman, V., Bickford, P.C., Freedman, R., 1992. Cholinergic gating of response to auditory stimuli in rat hippocampus. Brain Research 587, 130–136.
Mihalak, K.B., Carroll, F.I., Luetje, C.W., 2006. Varenicline is a partial agonist at the α4β2 and a full agonist at the α-7 neuronal nicotinic receptors. Molecular Pharmacotherapy 70, 801–805.
Nagamoto, H.T., Adler, L.E., Waldo, M.C., Freedman, R., 1989. Sensory gating in schizophrenics and normal controls: effects of changing stimulation interval. Biological Psychiatry 25, 549–561.
Network Neurometrics, 2004. The Netmet Computerized Test Battery. Targacept, Inc.
Obach, R.S., Reed-Hagen, A.E., Krueger, S.S., Obach, B.J., O'Connell, T.N., Zandi, K.S., Miller, S., Coe, J.W., 2006. Metabolism and disposition of varenicline, a selective 4-2: acetylcholine receptor partial agonist, in vivo and in vitro. Drug Metabolism and Disposition 34, 121–130.