



CASE REPORT

Beneficial effects of *N*-acetylcysteine in treatment resistant schizophrenia

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Abstract

Poor response to antipsychotics is still an important problem in the treatment of many schizophrenia patients. *N*-Acetylcysteine (NAC) is a compound that exerts anti-oxidant and scavenging actions against reactive oxygen species. This paper reports a case of poorly responsive schizophrenia patient who improved considerably with add-on NAC 600 mg/day. The NAC might work through activating cysteine-glutamate antiporters or reducing in nitric oxide (NO) metabolites, free radicals and cytokines or through both of these mechanisms.

Key words: *N*-Acetylcysteine, schizophrenia, drug therapy, combination, treatment resistant

Introduction

Poor response to antipsychotics is still an important problem in the treatment of many schizophrenia patients. Augmentation strategies as suggested in schizophrenia treatment guidelines such as with lithium (Schulz et al. 1999) and anticonvulsants (Basan et al. 2004), fail to produce adequate benefits in significant number of patients. Therefore, it is necessary to look for alternative or additional drug treatment possibilities.

The growing evidence of increased oxidative stress and diminished enzymatic antioxidants may be relevant to the pathophysiology of schizophrenia. These findings may suggest some clues for the new treatment strategies with antioxidants in schizophrenia (Akyol et al. 2002; Zoroglu et al. 2002).

N-Acetylcysteine (NAC) has long been used clinically as a mucolytic agent for chronic bronchitis and for patients with acute lung injury or acute respiratory distress syndrome (ARDS). *N*-Acetylcysteine is a compound that exerts anti-oxidant and scavenging actions against reactive oxygen species. In patients with ARDS, NAC has been shown to reduce the symptoms and to shorten the duration of ARDS, presumably acting as an anti-oxidant and

restoring the decrease in glutathione in cases of lung injury (Kao et al. 2006).

This paper reports a case of treatment-resistant schizophrenia patient who improved considerably with add-on NAC 600 mg/day.

Case

Mrs H.D. was a 24-year-old single, unemployed woman living with her parents. She was brought into Psychotic Disorders Unit of Psychiatry Clinics at the Gaziantep University School of Medicine Hospital by her parents for excitation and worsening psychosis. She claimed that “her parents had wanted to poison her, and they were talking negatively and despised her”. She was irritable, aggressive and guarded. She had depressed mood, decreased of sleep, poor appetite, auditory hallucinations, and persecutory delusions. She has been followed at our clinic for 7 years prior to this presentation. After psychiatric evaluation she was hospitalized for exacerbation of schizophrenia, paranoid type based on DSM-IV-TR criteria. Results of neurological and physical examinations and laboratory tests were within normal limits. She did not have any other medical illnesses. Her vital signs were normal.

She did not have any history of substance abuse or dependence. There were no history of psychiatric disorders in her relatives and extended family.

The symptoms had worsened 5 weeks earlier while she was on ziprasidone 160 mg/day and zuclopentixole decaonate 200 mg intramuscular (i.m.) every 15 days. A week after worsening of her symptoms she was admitted to psychiatric unit at another hospital. Ziprasidone and zuclopentixole decaonate had been discontinued and risperidone 8 mg/day had been initiated. Because of acute dystonia biperiden HCl 4 mg/day and because of akathisia clonazepam 2 mg/day had been added to risperidone. She had been discharged after 4 weeks of inpatient psychiatric treatment and she was brought to our clinic one day after her discharge from other hospital. There was no significant improvement in her psychiatric symptoms.

In history; the patient's age of illness onset was 17. Over 7 years she was continuously treated with several typical and atypical antipsychotics at full therapeutic doses for adequate periods. Overall she demonstrated slight clinical improvement. Her persecutory delusions, auditory hallucinations, social withdrawal and cognitive impairment continued. This current episode was diagnosed as exacerbation of schizophrenia. Delirium, probable organic causes, and substance abuse were ruled out.

Admission to our unit was the tenth psychiatric hospitalization of the patient. She was diagnosed with treatment-resistant schizophrenia according to the NICE criteria (NICE 2002) as evidenced by a lack of satisfactory clinical improvement despite the sequential use of the recommended doses of at least two antipsychotic drugs for 6–8 weeks, at least one of which was a second-generation antipsychotic. At the day of administration initial Positive and Negative Syndrome Scale (PANSS) score was 143, Clinical Global Impression (CGI) severity-of-illness score was 6 and Calgary Depression Scale score was 11. Based on history, the patient benefited most from combination treatment with olanzapine and zuclopentixole decaonate. Thus olanzapine 20 mg/day, zuclopentixole decaonate 200 mg once every 15 days were started. Clonazepam 4 mg/day were continued and risperidone was discontinued. The patient developed oculogyric crisis, which was treated with biperiden HCl 4 mg/day successfully. After 22 days after this treatment regimen PANSS score decreased to 78, CGI score to 4 and Calgary Depression Scale score to 8. Around 37th day of admission her psychotic symptoms worsened. The PANSS score increased to 102 and CGI score increased to 6. Calgary Depression Scale score was still 8. The informed consent was obtained from her

next of kin and NAC 600 mg p.o. daily was added on to the mentioned treatment regimen. Seven days after addition of NAC the PANSS score decreased to 59, CGI score decreased to 4. Calgary Depression Scale remained to 8. She was discharged on the 67th day of the hospitalization. At discharge, PANSS score was 56, CGI score was 4. Calgary depression scale score was 8. The patient and relatives reported marked improvement in spontaneity, social skills and family relations. She was doing routine housework such as cooking and cleaning spontaneously and her self-esteem was normal. One month after discharge from hospital her PANSS, CGI and Calgary depression scale scores were 56, 4 and 8, respectively.

Discussion

A number of studies have indicated that free radical-mediated neuronal damage plays a role in the pathophysiology of psychiatric disorders such as depression, bipolar disorders, and schizophrenia. Oxidative damage may account for deteriorating course and poor outcome in schizophrenia (Akyol et al. 2002; Savas et al. 2002, 2006; Zoroglu et al. 2002; Yanik et al. 2004; Selek et al. 2007). Recently the role of free radicals and nitric oxide (NO) have been studied in schizophrenia (Zoroglu et al. 2002). Increased NO production by nitric oxide synthetases (NOSs) suggests a possible role of NO in the pathophysiology of schizophrenia (Akyol et al. 2002). The generation of NO following *N*-methyl-D-aspartate (NMDA) or norepinephrine receptor activation seems to be important in the context of central nervous system pathology (Moncada et al. 1991). NO is associated to both neurotoxic and neuroprotective effects. NO is responsible for the glutamate-induced activation of guanylate cyclase which is considered its physiological target, but is associated to glutamate neurotoxicity and dopamine-induced cell-death. Oxidative stress plays a role in the cognitive deficits of schizophrenia patients. This may involve reduced glutamatergic neurotransmission since the oxidation of the redox-sensitive site in the NMDA receptor reduces the activation of this receptor (Perez-Neri et al. 2006).

There is growing evidence that the glutamatergic system plays a role in the pathogenesis of schizophrenia (Olney et al. 1995; Heckers et al. 2002). Since glutamate and dopamine interact in a complex way (Farber et al. 1998) the glutamatergic hypothesis of schizophrenia could also integrate dopaminergic abnormalities (Olney et al. 1995; Farber 2003). In a previous study, increased Glu signals in patients with recurrent episodes of schizophrenia

treated with neuroleptics were reported (Tebartz van Elst et al. 2005). In a recent study, significant correlations were found between prefrontal Glu concentrations and rating scores for schizophreniform symptoms, but not with antipsychotic medication in first episode schizophrenia patients. Those Glu findings might reflect factors intimately associated with schizophrenia but not reflect chronic medication effects or factors involved in the progress of illness (Olbrich et al. 2007).

Application of phencyclidine and other glutamate receptor blockers can cause schizophreniform symptoms (Olney et al. 1995). In a previous study, activation of cysteine-glutamate antiporters by using the cysteine prodrug NAC reversed psychomimetic effects in rodent phencyclidine model of schizophrenia (Baker et al. 2007). Mahadik et al. (2006) reported that dietary supplementation of antioxidants and omega-3 fatty acids were found to improve symptoms of schizophrenia. However, in this study, the patients were treated by a combination of antipsychotics and these agents; therefore it is hard to estimate the effect due of antioxidants alone (Mahadik et al. 2006).

In our case we envisaged that the patient might benefit from supplementation of NAC as an antioxidant and a precursor of glutathione. The NAC might work through activating cysteine-glutamate antiporters or reducing in NO metabolites, free radicals and cytokines or through both of these mechanisms.

Finally, with the hypothesized mechanism(s) of action, NAC treatment demonstrated beneficial effects in a treatment-resistant schizophrenia patient and it has been well tolerated. In some cases of schizophrenia, especially in treatment-resistant cases, addition of NAC to the treatment regimen might be a useful intervention.

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Statement of interest

None.

References

Akyol O, Herken H, Uz E, Fadillioglu E, Unal S, Sogut S, et al. 2002. The indices of endogenous oxidative and antioxidative processes in plasma from schizophrenic patients: The possible role of oxidant/antioxidant imbalance. *Prog Neuropsychopharmacol Biol Psychiatry* 26:995–1005.

Baker DA, Madayag A, Kristiansen LV, Meador-Woodruff JH, Haroutunian V, Raju I. 2007. Contribution of cystine-gluta-

mate antiporters to the psychotomimetic effects of phencyclidine. *Neuropsychopharmacology* 33:1760–1772.

Basan A, Kissling W, Leucht S. 2004. Valproate as an adjunct to antipsychotics for schizophrenia: A systematic review of randomized trials. *Schizophr Res* 70:33–37.

Farber NB. 2003. The NMDA receptor hypofunction model of psychosis. *Ann NY Acad Sci* 1003:119–130.

Farber NB, Newcomer JW, Olney JW. 1998. The glutamate synapse in neuropsychiatric disorders. Focus on schizophrenia and Alzheimer's disease. *Prog Brain Res* 116:421–437.

Heckers S, Stone D, Walsh J, Shick J, Koul P, Benes FM. 2002. Differential hippocampal expression of glutamic acid decarboxylase 65 and 67 messenger RNA in bipolar disorder and schizophrenia. *Arch Gen Psychiatry* 59:521–529.

Kao SJ, Wang D, Lin IH, Che IH. 2006. N-Acetylcysteine abrogates acute lung injury induced by endotoxin. *Clin Exp Pharmacol Physiol* 33:33–40.

Mahadik SP, Pillai A, Joshi S, Foster A. 2006. Prevention of oxidative stress-mediated neuropathology and improved clinical outcome by adjunctive use of a combination of antioxidants and omega-3 fatty acids in schizophrenia. *Int Rev Psychiatry* 2:119–131.

Moncada S, Palmer RM, Higgs EA. 1991. Nitric oxide: Physiology, pathophysiology and pharmacology. *Pharmacol Rev* 43:109–142.

National Institute for Clinical Excellence (NICE). 2002. Technology appraisal Guidance No. 43, Guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia. London.

Olbrich HM, Valerius G, Rüscher N, Büchert M, Thiel T, Hennig J, et al. 2007. Frontolimbic glutamate alterations in first episode schizophrenia: Evidence from a magnetic resonance spectroscopy study. *World J Biol Psychiatry* 9:59–63.

Olney JW, Farber NB. 1995. Glutamate receptor dysfunction and schizophrenia. *Arch Gen Psychiatry* 52:998–1007.

Perez-Neri I, Ramirez-Bermudez J, Montes S, Rios C. 2006. Possible mechanisms of neurodegeneration in schizophrenia. *Neurochem Res* 31:1279–1294.

Savas HA, Herken H, Yurekli M, Uz E, Tutkun H, Zoroglu SS, et al. 2002. Possible role of nitric oxide and adrenomedullin in bipolar affective disorder. *Neuropsychobiology* 45:57–61.

Savas HA, Gergerlioglu HS, Armutcu F, Herken H, Yilmaz HR, Kocoglu E, et al. 2006. Elevated serum nitric oxide and superoxide dismutase in euthymic bipolar patients: Impact of past episodes. *World J Biol Psychiatry* 7:51–55.

Schulz SC, Thompson PA, Jacobs M, Ninan PT, Robinson D, Weiden PJ, et al. 1999. Lithium augmentation fails to reduce symptoms in poorly responsive schizophrenic outpatients. *J Clin Psychiatry* 60:366–372.

Selek S, Savas HA, Gergerlioglu HS, Bulbul F, Uz E, Yumru M. 2007. The course of nitric oxide and superoxide dismutase during treatment of bipolar depressive episode. *J Affect Disord* 107:89–94.

Tebartz van Elst L, Valerius G, Büchert M, et al. 2005. Increased prefrontal and hippocampal glutamate concentration in schizophrenia. Evidence from a magnetic resonance spectroscopy study. *Biol Psychiatry* 58:724–730.

Yanik M, Vural H, Tutkun H, Zoroglu SS, Savas HA, Herken H, et al. 2004. The role of the arginine-nitric oxide pathway in the pathogenesis of bipolar affective disorder. *Eur Arch Psychiatry Clin Neurosci* 254:43–47.

Zoroglu SS, Herken H, Yurekli M, Uz E, Tutkun H, Savas HA et al. 2002. The possible pathophysiological role of plasma nitric oxide and adrenomedullin in schizophrenia. *J Psychiatr Res* 36:309–315.

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