Possible antipsychotic effects of minocycline in patients with schizophrenia

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Abstract

We present two cases of patients with schizophrenia treated with minocycline. Minocycline (a second-generation tetracycline) is an established and safe broad-spectrum antibiotic that crosses the blood–brain barrier, with additional efficacy for diseases such as acne and rheumatoid arthritis. Animal studies have suggested that minocycline may prevent progression of some neurological disorders. Moreover, it has been reported that minocycline might have antidepressant effects. We report two cases of acute schizophrenia with predominant catatonic symptoms that responded to minocycline.

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1. Introduction

Minocycline is a semisynthetic second-generation tetracycline which exerts anti-inflammatory effects that appear to be completely separate and distinct from its anti-microbial action (MacDonald et al., 1973). Minocycline, one of the more brain-penetrable of the tetracyclines, has recently been shown to have neuroprotective effects in models of ischemic injury (Yrianheikki et al., 1999) and the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson’s disease (Du et al., 2001). The neuroprotective properties of minomycine have been shown to be due in part to indirect effects in inhibiting glial (astrocytic/microglial) caspase 1 and iNOS activity, although direct neuroprotective effects have also been observed (Amin et al., 1996; Yong et al., 2004). Furthermore, recent reports have shown that minocycline treatment delays mortality or disease progression in mouse models of Huntington’s disease (Chen et al., 2000; Berger, 2000) and amyotrophic lateral sclerosis (Zhang et al., 2003). In a case report, Levine et al. (1996) reported that minocycline treatment had apparent antidepressant effects. In this report, minocycline was effective in treatment of acute schizophrenia with predominantly catatonic symptoms.

To our knowledge, this is the first published case report of successful treatment of schizophrenia with minocycline, while there are unpublished study plan (http://www.stanleyresearch.org/programs).

2. Case report

2.1. Case 1

The patient was a 23-year-old male. The patient’s birth was uneventful, and he developed normally. After graduating from university, he worked in a company. His level of functioning in society was normal. There was no history of alcohol, drugs or epileptic seizures. Nothing was known regarding psychiatric or developmental disorders in his family. When the patient was 23, he developed insomnia and felt “nervous”. Further, he became agitated and talked incoherently, with persecutory delusions and paranoid ideation. Disturbance of consciousness and convulsions were not observed. He was admitted to Shimane University Hospital. Examination of his mental state showed auditory hallucination and persecutory delusions, psychomotor excitement, catatonic stupor, and deterioration in the level of social functioning. He was diagnosed with “catatonic schizophrenia” according to DSM-IV criteria (APA, 1994). Physical and neurological examinations revealed no marked abnormalities or
anomalies. Laboratory examinations of serum and urine were normal. Electric encephalography (EEG), computed tomography (CT), and magnetic resonance imaging (MRI) of the brain showed no abnormal results. Haloperidol (HPD) (4–20 mg/day) was started. One week later, his psychomotor excitement, auditory and catatonic stupor and persecutory delusions continued. Moreover his symptoms were complicated by severe pneumonia. At this point, NMS was negative since serum CK and renal parameters were normal. A regimen of minocycline, 150 mg/day was initiated, and HPD treatment was continued. Two weeks later, his psychiatric symptoms and pneumonia were recovered, and minocycline treatment was discontinued for a period of 1 week, which was followed by significant worsening of his psychiatric symptoms. Therefore, minocycline (150 mg twice daily) treatment was resumed and, within 3 days, a noticeable clinical improvement was observed. He was maintained on HPD and a dose of 150 mg/day of minocycline. 24 days later, the patient became practically symptom-free. He was maintained on minocycline plus HPD (2 mg/day) treatment, with no need for any additional drugs. His psychiatric symptoms were evaluated by the positive and negative symptom scale (PANSS) (Kay et al., 1987). The clinical course is shown in Fig. 1. Two years after discharge, the clinical improvement is maintained, and there is no worsening of psychiatric symptoms.

2.2. Case 2

The patient was 61-year-old single male. At the age of 20, he experienced insomnia and auditory hallucinations and was diagnosed with schizophrenia. Since then he has had five psychiatric...
hospitalizations. In the last, he had been hospitalized for 4 years when he deteriorated and became autistic state. He was given 10 mg of HPD and 2 mg of risperidone (RIS) per day for his psychosis. Routine laboratory examination data were within the normal limits for blood, urine, and feces. Electric encephalography (EEG), computed tomography (CT), and magnetic resonance imaging (MRI) of the brain showed no abnormal results. At the age of 60, his mental state showed psychomotor excitement, catatonic stupor, and negativism. Moreover, a large decubitus had developed on his left hip. A regimen of minocycline, 150 mg/day was initiated, and HPD and RIS treatment was continued. Two weeks later, his decubitus was recovered, and minocycline treatment was discontinued for a period of 1 week, which was followed by significant worsening of his psychiatric symptoms. Therefore, minocycline (150 mg twice daily) treatment was resumed and, within 3 days, all noticeable clinical improvement was observed. He was maintained on HPD, RIS, and a dose of 150 mg/day of minocycline. 16 days later, the patient became practically symptom-free. He was maintained on minocycline plus HPD (3 mg/day) treatment, with no need for any additional drugs. His psychiatric symptoms were evaluated by the PANSS. The clinical course is shown in Fig. 2. The patient did not have fever and receive benzodiazepines or any other medication. One year after discharge, the clinical improvement is maintained, and there is no worsening of psychiatric symptoms.

3. Discussion

In these patients, minocycline was effective in the treatment of acute schizophrenia with predominantly catatonic symptoms. At the remission of psychiatric symptoms, these patients did not suffer any infection for which minocycline was indicated, and the use of minocycline is exclusive for psychosis. To our knowledge, this is the first published case report of successful treatment of schizophrenia with minocycline.

Minocycline is a semisynthetic tetracycline that has been in use for over 30 years (MacDonald et al., 1973). It is a small (495 kDa), highly lipophilic molecule capable of crossing the blood–brain barrier of human beings better than other tetracycline (Yong et al., 2004). Minocycline is readily absorbed from the intestine gut after oral ingestion; because of its low propensity to produce antibiotic resistance, it is commonly used in the management of chronic conditions such as acne, rheumatoid arthritis, and rosacea. Overall, a good safety record for long-term clinical use has been established for minocycline (Thomas et al., 2003). In 1999, Yrianheikki et al., showed that minocycline was neuroprotective in an animal model of ischemia. Since then, there have been numerous reports of the efficacy and neuroprotective effects of minocycline in various models of neurological disease, including haemorrhagic and ischemic stroke, multiple sclerosis, spinal cord injury, Parkinson’s disease, Huntington’s disease, and amyotrophic lateral sclerosis (ALS) (Chen et al., 2000; Depino et al., 2003; Kriz et al., 2002; Thomas et al., 2003). Reports are emerging of clinical trials of minocycline in several neurological diseases. Some reports suggested that the significant improvement in psychiatric symptoms of these neurological diseases by minocycline (Denovan-Wright et al., 2002). Moreover, Levine et al. (1996) reported a possible antidepressant effect of minocycline, and they mentioned the inhibition of noradrenaline-sensitive adenylate cyclase by minocycline.

Because minocycline has such an impressive effect on many different neuropsychiatric disorders with seemingly diverse causes, several possibilities for the mechanism were considered. First, the possibility of common mechanisms of neurodegeneration in these diseases must be taken into consideration. Microglial activation and the attendant neurotoxic products generated by persistently activated microglia are common features of these diseases (Gehmann et al., 1995). Apoptotic cell death is also a unifying theme. Thus, minocycline is a potent inhibitor of microglial activation and the apoptotic pathway is noteworthy.

Schizophrenia is a devastating illness of unknown etiology. It is characterized by increased brain ventricular volume, suggesting a progressive neurodevelopmental condition (Weinberger, 1987; Waddington, 1993; Arnold et al., 1998; Harrison and Weinberger, 2005). Studies that have examined markers of apoptosis and levels of apoptotic regulatory proteins in postmortem schizophrenia brain tissue indicated a dysfunction of apoptosis in several cortical regions in schizophrenia, including evidence that the apoptotic vulnerability is increased (Arnold et al., 1998; German et al., 2004). Although the exact role of apoptosis in schizophrenia remains uncertain, the potential involvement of non-lethal localized apoptosis is intriguing, especially in earlier stages of the illness (Harrison and Weinberger, 2005).

The continued clinical improvement of schizophrenic patient was surprising in light of their previous deterioration and appears to be at least partly related to treatment with minocycline. Furthermore, minocycline appears to be safe for use in patients with advanced schizophrenia, although the precise mechanism of action of this agent remains unclear. Some patients with stupor improve after a severe infection disease accompanied by fever. However, minocycline treatment was discontinued, which was followed by significant worsening of his psychiatric symptoms without a severe infection disease accompanied by fever. The present results raise the possibility that minocycline may have effects beyond its action as an antiapoptotic agent (Tikka and Koistinaho, 2001; Tikka et al., 2001). The treatment with haloperidol in both cases might have been of disadvantage for the patient. Psychotic patients with catatonic symptoms and even more in patients with catatonic stupor have to be treated with benzodiazepines such as lorazepam and electroconvulsive therapy. In our cases, the patients did not receive at any point the treatment of benzodiazepines.

In our cases, treatment with minocycline was effective in controlling the psychiatric symptoms of schizophrenia. Further research with additional subjects is clearly necessary because the mechanisms of both schizophrenia and the effects of minocycline in CNS are still poorly understood.

References


