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Therapeutic Efficacy of *N*-Methyl D-Aspartate Antagonist Amantadine in Febrile Catatonia

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Acute akinetic crisis in Parkinson's disease can be treated successfully with the *N*-methyl D-aspartate (NMDA) antagonist amantadine. Patients with catatonia also show complete akinesia, which, similar to Parkinson's disease, may hypothetically be treated with amantadine as well, implying glutamatergic hyperfunction in both diseases. However, in the case of akinetic catatonia, such an assumption would be rather inconsistent, considering the following observations: (1) catatonia is often associated with either schizophrenic or affective psychosis, in which glutamatergic hypofunction in the prefrontal cortex 1 and the anterior cingulate 2, 3 has been reported; (2) NMDA antagonists, including amantadine, can produce psychosis and should therefore rather lead to deterioration than to amelioration of catatonic syndrome in schizophrenic or affective psychosis; (3) catatonia shows considerable symptomatic similarities (motor and vegetative symptoms) to Parkinson's disease and neuroleptic malignant syndrome in which, on the basis of successful therapeutic intervention with the NMDA antagonist amantadine, glutamatergic hyperfunction is postulated 4, 5; (4) catatonic syndrome can be treated quite well with amobarbital, lorazepam, or electroconvulsive therapy (ECT),6, 7 with all three of these types of therapies modulating the GABA-ergic rather than the glutamatergic system.

We present two cases of akinetic, febrile catatonic patients with nonresponse to lorazepam and/or amobarbital in previous catatonic episodes for which both were treated successfully with the NMDA antagonist amantadine-a finding not previously reported.

Case 1

A 60-year-old married white housewife suffered from bipolar disorder (DSM-IV: 296.54) for 25 years with 12 hospitalizations resulting from recurrent depressive (responsive to imipramine and/or fluvoxamine) and some manic (responsive to haloperidol) phases. She had four acute catatonic episodes previously which were treated successfully only with ECT and not with lorazepam and amobarbital. This time, because of noncompliance (as several times before), she completely discontinued her medication (lithium and fluvoxamine) 6 weeks before, became increasingly depressive and withdrawn, and was finally admitted in an acute akinetic, febrile (40.2°C) catatonic state with motor (rigidity, akinesia, stereotypies, posturing, paratonia ["gegenhalten"]), behavioral (mutism, staring, negativism, autism, accompany ["mitgehen"], echopraxia), and vegetative (hyperpyrexia, tachycardia, high blood pressure) abnormalities (Bush-Francis Catatonia Rating Scale 6 [BFCRS] score = 35). Initially she was treated with amantadine 200 mg intravenously. After 2 to 3 hours, vegetative measures (blood pressure, temperature, pulse rate) returned to normal values, whereas her motor and behavioral abnormalities persisted (BFCRS score = 25). Seven hours after the first application, we therefore treated her with a second infusion of 200 mg of amantadine. Motor and behavioral symptoms gradually diminished within the following 4 hours (BFCRS score = 12). Seven hours after the second application, she received a third infusion of 200 mg of amantadine, which led to the complete resolution of catatonic symptoms within 3 hours. In the following days, she was maintained on amantadine 3 × 100 mg orally, and because of her now apparent depressive symptoms (anxiety, loss of appetite, depressed mood, anhedonia, insomnia, irritability, irritability, poor concentration), she was also given fluvoxamine (2 × 150 mg), on which she was discharged 4 weeks later.

Case 2

A 52-year-old married white woman suffered from schizoaffective psychosis (DSM-IV: 295.70) for 13 years (11 hospitalizations) with 5 catatonic (all nonresponsive to lorazepam but responsive to ECT) and recurrent depressive (responsive to trimipramine) and manic (responsive to haloperidol) episodes with strong schizophrenic features (delusions, acoustic hallucinations). Because of noncompliance, she completely discontinued her medication (lithium) 9 weeks before, became increasingly depressive and withdrawn, and was finally admitted in an acute akinetic, febrile (39.4°C) catatonic state (mutism, posturing, staring, catalepsy, autism; BFCRS = 31). After an initial treatment with 200 mg of intravenous amantadine, catatonic symptoms partially resolved (BFCRS = 18) and disappeared entirely after a second infusion with amantadine 6 hours later, showing no recurrence of catatonic symptoms. After the first infusion of amantadine, hyperpyrexia disappeared completely, showing no recurrence at all. After the resolution of catatonia, she displayed severe depressive symptoms (anxiety, anhedonia, hopelessness, loss of interest, insomnia, somatic complaints, irritability) which were treated successfully with trimipramine (3 × 100 mg), on which she was discharged 5 weeks later.

Discussion

This is the first report of successful therapeutic reversal of acute akinetic states with amantadine, an NMDA antagonist and dopamine agonist, in patients with febrile catatonia. Depending on further studies, amantadine may consecutively be considered as a therapeutic alternative to lorazepam and amobarbital in akinetic catatonia. In addition, catatonic patients with fever and nonresponse to lorazepam/amobarbital should be given a therapeutic trial with amantadine before undergoing ECT.

Application of amantadine may therefore be considered as a therapeutic alternative to immediate treatment with ECT in febrile catatonia and in catatonic nonresponders to lorazepam/amobarbital.

Furthermore, therapeutic efficacy of amantadine raises some interesting questions about regional alterations of NMDA-receptor function in catatonia. Cortical regions such as the prefrontal cortex 1 and the anterior cingulate 2, 3 show glutamatergic hypofunction in schizophrenic and/or affective psychosis, so that one would expect no therapeutic efficacy of NMDA antagonists in these patients. However, amantadine given to both catatonic patients with underlying affective/schizoaffective psychosis showed good therapeutic efficacy with regard to catatonic symptoms. Catatonia may consecutively be characterized not only by prefrontal/cingulate glutamatergic hypofunction (due to underlying psychosis) but by concomitant glutamatergic hyperfunction (due to therapeutic efficacy of an NMDA antagonist) in another cortical region as well. Glutamatergic hypofunction in the prefrontal cortex and the anterior cingulate may lead to decreased excitation of inhibitory (i.e., GABA-ergic) projections from prefrontal cortex/anterior cingulate to premotor (i.e., supplementary motor area) and motor (i.e., motor cortex) cortical areas, resulting in a net effect of frontostriatal glutamatergic hyperfunction. Amantadine may antagonize this frontostriatal glutamatergic hyperfunction and may consecutively lead to successful reversal of akinesia in catatonia, which is similar to results seen in Parkinson's disease.4, 5 In addition, such glutamatergic corticosubcortical interactions may modulate nigrostriatal and tuberoinfundibular dopaminergic systems, thereby resolving akinesia and hyperpyrexia.

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