Severe Reversible Neurological Complications following Amantadine Treatment in Three Elderly Patients with Renal Insufficiency

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Dear Sir,

Amantadine hydrochloride is widely used to treat Parkinson's disease. In Japan, amantadine is also commonly used to treat post-stroke depressive states and influenza A virus infection. There are a few reports describing amantadine toxicity in aged patients with renal dysfunction, but the neurological features of amantadine toxicity are not well recognized and thus might be misdiagnosed. Here, we present 3 patients with amantadine toxicity.

Case Reports (table 1)

Patient 1: A 70-year-old woman with a 9-year history of Parkinson's disease received daily oral treatments of 150 mg amantadine hydrochloride and 200 mg levodopa. She developed progressive renal dysfunction due to chronic glomerulonephritis in 1998, and hemodialysis was introduced in January 2002. Around this period, she developed poor communication, visual hallucinations, gait disturbance, and general myoclonic jerks in her limbs and trunk, without daily fluctuations. She became unable to stand up in March 2002, and she was then admitted to our hospital.

On admission, she was febrile and somnolent. She complained of restlessness, disturbed concentration, memory decline, and concrete visual hallucinations. Myoclonic jerks were present in her limbs and trunk at rest, and were exaggerated during motion. There was no apparent motor paresis or cerebellar ataxia. She was always grasping objects, suggesting marked grasp

reflexes in both hands. Parkinsonism symptoms, such as rigidity, were mild, but she could not stand or walk.

Brain computed tomography showed no apparent ischemic changes, and electroencephalography showed no obvious paroxysmal discharges or triphasic waves. Her plasma amantadine hydrochloride level was high (4,900 ng/ml), and she was eventually diagnosed with amantadine toxicity. After cessation of oral amantadine hydrochloride, all of her symptoms and signs gradually improved; about 3 weeks later she was able to walk without aid.

Patient 2: A 74-year-old woman had a right cerebellar hemorrhage in 1991. She subsequently developed apathy, depression, and gait disturbance, and was treated with 200 mg amantadine hydrochloride and 200 mg droxidopa per day. In March 2005, she began to have visual disturbances, e.g., 'the floor looks crooked'. In April 2005, she developed fever, vomiting, and myoclonic jerks in her limbs, and became unable to stand independently.

On May 18, 2005, she was referred to our hospital. She did not speak voluntarily and was bound to her wheelchair. Neurological examinations revealed myoclonic jerks in limbs and marked grasp reflexes in both hands. There was no apparent motor paresis or cerebellar ataxia. Assessment of muscular tone was difficult because of declined auditory comprehension. Electroencephalography showed no obvious paroxysmal discharges or triphasic waves.

Blood examinations revealed mild renal dysfunction and/or dehydration (blood urea nitrogen: 42.5 mg/dl, creatinine: 1.3 mg/dl). Although her serum amantadine hydrochloride level was not evaluated, these clinical and laboratory features suggested a diagnosis of amantadine toxicity, and oral administration of amantadine hydrochloride was stopped. Her symptoms and signs gradually improved, and after about 3 weeks, she was able to walk without aid.

Patient 3: A 73-year-old woman with a 3-year history of Parkinson's disease had suffered from diabetic nephropathy since 1999, and was admitted to a hospital for dialysis treatment in January 2002. On February 17, 2005, she began treatment with oral 300 mg amantadine hydrochloride per day for parkinsonism. She gradually developed somnolence and gait disturbance, and was bedridden about 1 week after onset. On March 6, 2005, amantadine toxicity was strongly suspected and her amantadine hydrochloride regimen was discontinued. General myoclonic jerks appeared. On March 12, 2005, she had an acute onset of high-grade fever, coma, and status epilepticus. A malignant syndrome was suspected, and treatment with dantrolene sodium was introduced. The treatment alleviated her fever within several days, but somnolence and dementia remained and she became bedridden. She was referred to our hospital and was admitted on August 11, 2005.

Table 1. Clinical features of 3 patients with amantadine toxicity

	Patient 1	Patient 2	Patient 3
Age, years	70	74	73
Gender	Female	Female	Female
Neurological background	PD	Post-stroke depression	PD
Renal dysfunction	Severe (on hemodialysis due to CGN)	Mild	Severe (on hemodialysis due to DN)
Amantadine hydrochloride			
Indication	For PD	For depression	For PD
Dose, mg/day	150	200	300
Medication period			
Until onset	>1 year	>1 year	A few days
From onset	2 months	2 months	3 weeks
Outcome of toxicity	Full recovery	Full recovery	Poor recovery
Features of toxicity			
Disturbed consciousness	+	+	+
Hallucination	+	+	–
Grasp reflexes	+	+	+
Myoclonus	+	+	+
Gait disturbance	+	+	+
Extrapyramidal sign	+ ¹	ND	+ ¹
Pyramidal sign	–	–	+ ²
Cerebellar sign	–	–	–

CGN = Chronic glomerulonephritis; DN = diabetic nephropathy; PD = Parkinson's disease; ND = not determined.

¹ The degree of parkinsonism did not change after toxicity.

² Left hemiparesis due to lacunar infarction.

On admission, she had severe dementia and moderate parkinsonism, such as bradykinesia and limb rigidity with left predominance, without involuntary movement. Grasp reflexes were recognized on both sides, but palmo-mental reflexes were not elicited. She also had mild left hemiparesis due to lacunar infarction in the right corona radiata, which was revealed by brain magnetic resonance imaging scans. There were also multiple cerebral infarctions in the right fronto-parietal and occipital lobes as well as multiple and confluent white matter changes. Electroencephalography demonstrated diffuse θ waves without triphasic waves. Her serum amantadine hydrochloride level was not detectable, suggesting that it had already washed out over the previous 5 months. Oral administration of 450 mg levodopa and 0.25 mg pramipexole per day improved her parkinsonism, but her daily living skills did not improve.

Discussion

The clinical symptoms and signs of amantadine toxicity in patients 1 and 2 were reversible after cessation of amantadine administration, whereas those in patient 3 partially improved, but ultimately persisted. The duration between the initiation and cessation of oral amantadine was 2 months in patients 1 and 2, and 3 weeks in patient 3. Renal dysfunction was relatively mild in patient 2, whereas patients 1 and 3 had chronic renal failure and regularly underwent hemodialysis. The doses of amantadine were 150, 200, and 300 mg/day in patients 1, 2, and 3, respectively. Cerebral ischemic changes were apparent in patient 3, but not in patient 1. The above-mentioned differences among the three patients suggest that the irreversibility of toxicity in patient 3 was due to both high dose exposure combined with severe renal dysfunction and coexisting cerebral ischemic damage.

Somnolence, inability to stand and walk, myoclonic jerks in limbs, and frontal lobe signs, such as grasp reflexes, were common neurological features in all 3 patients. With regard to disturbed consciousness, somnolence was common in all 3 patients. Inability to stand and walk was caused by factors other than motor paresis, cerebellar ataxia, or parkinsonism. Myoclonic jerks were present in all patients, and were exaggerated during motion. A previous study indicated that myoclonic jerks in a patient with amantadine toxicity originated from the cerebral cortex [1]. The above-mentioned features of amantadine toxicity, such as somnolence and myoclonus, resemble those of Creutzfeldt-Jakob disease. The same clinical features have been also reported as drug-induced Creutzfeldt-Jakob-like syndrome in patients with toxicity from lithium, lithium with levodopa, antidepressants, and bismuth [2–6]. It is important to differentiate

the consciousness disturbance in drug toxicity from the dementia in Creutzfeldt-Jakob disease, but this differentiation is not very easy in patients with severe dysfunction, such as patient 3.

Amantadine hydrochloride is only available orally and is well absorbed by the intestine. It is widely distributed and stored in many organs such as the lungs and kidneys; there is a small component in the blood circulation [7, 8]. Because approximately 90% of the drug is excreted unchanged in the urine, it accumulates in various organs in patients with renal dysfunction [7, 8]. The half-life of drug elimination is 11.8 ± 2.1 h (range: 9.7–14.5 h) in subjects with normal renal function, and 8.3 days (range: 7.0–10.3 days) in patients on hemodialysis [9]. Furthermore, the half-life in patients whose creatinine clearance is reduced to 50, 30, and 10 ml/min, has been reported to be 23 h, 40 h, and 7.4 days, respectively [9]. Because the serum creatinine level does not become elevated before creatinine clearance is reduced to <50 ml/min, amantadine excretion might be extended even in patients with a normal serum creatinine level, such as patient 2 in the present report. It is remarkable that only 2–5% of the drug in the body is removed with a single hemodialysis treatment [9].

There are no substantive experimental data regarding the relationship between plasma amantadine levels and the occurrence of amantadine toxic effects. Previ-

ous clinical reports suggested that plasma amantadine concentrations >1,000 ng/ml in humans were associated with toxic manifestations such as hallucinations, depression, confusion, dizziness, disinhibition, seizures, and cortical myoclonus [8]. The plasma amantadine hydrochloride level in patient 1 was very high at 4,900 ng/ml. Striking features such as an inability to walk and frontal lobe signs, which were recognized in our patients, however, have not been described before. Amantadine toxicity from large doses might be fatal because of its cardiovascular effects, e.g., 2 deaths have occurred in patients attempting suicide with doses of 2 g/day [10–12].

In conclusion, practitioners should not use amantadine hydrochloride to medicate patients with renal failure, and extreme caution should be used when medicating older patients with possible occult renal dysfunction. The neurological features of amantadine toxicity vary, but somnolence, myoclonic jerks, and an inability to walk are considered early and important features.

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