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Article *in* Turkish Nephrology · September 2013

DOI: 10.5262/tndt.2013.1003.10

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Gabapentin Toxicity in Patients with Chronic Kidney Disease; Series of Our Cases

Kronik Böbrek Yetmezlikli Hastalarda Gabapentin Toksisitesi; Olgu Serimiz

ABSTRACT

Gabapentin is an anticonvulsant with analgesic and anxiolytic effects and also an agent used for treatment of a variety of chronic neuropathic pains. Because gabapentin is eliminated solely through the kidney, kidney failure poses a risk for gabapentin accumulation and toxicity. Gabapentin toxicity in kidney failure hasn't been clearly proved till now. We want to emphasize the gabapentin toxicity on five cases with chronic kidney disease at the present study.

KEY WORDS: Chronic kidney disease, Gabapentin toxicity, Hemodialysis

ÖZ

Gabapentin, kronik nöropatik ağrı tedavisinde kullanılan analjezik ve anksiyolitik etkili bir antikonvülzandır. Gabapentin yalnızca böbrekten atıldığı için, böbrek yetmezliği gabapentin toksisitesi için bir risk faktörüdür. Böbrek yetmezliğinde gabapentin toksisitesi tam olarak gösterilmemiştir. Bu yazımızda, kronik böbrek yetmezlikli (KBY) beş hastada gelişen gabapentin toksisitesini bildireceğiz.

ANAHTAR SÖZCÜKLER: Kronik böbrek yetmezliği, Gabapentin toksisitesi, Hemodiyaliz

INTRODUCTION

Gabapentin is an anticonvulsant with analgesic and also an agent used for treatment of a variety of chronic neuropathic pains (1). This medicine has been frequently prescribed by the doctors since the beginning of its use. In recent years, gabapentin has been also used for the other indications, including restless legs syndrome, postherpetic neuralgia, migraine, cancer-related pain, and spinal cord injury. Furthermore, this agent has been used as an analgesic on the patients with chronic kidney disease, whose incidence has been gradually increasing (2).

Its gastrointestinal absorption is well; it is not protein-bound or metabolized during circulation. Its elimination is predominantly carried out by the kidney. By using that agent which is frequently prescribed, kidney's functions are ignored unfortunately. Therefore it brings comorbidity and even deaths with it (3).

In our present study, we want to point out gabapentin toxicity on five cases with diabetes-related chronic kidney disease.

CASE REPORT

Gabapentin toxicity has been determined in five patients who were admitted to nephrology clinic and emergency room of our hospital complaining of chronic kidney disease. Estimated glomerular filtration rate (eGFR) calculated according to Modification of Diet in Renal Disease equation. Serum gabapentin concentration was determined by high performance liquid chromatography in all patients. The characteristics of these patients are shown in Table I.

Gabapentin was prescribed by neurologists in cases with diabetic neuropathy. Case 1 was admitted to emergency clinic complaint with coma and he had been attending haemodialysis and using gabapentin 600 mg/day. In Cases 2, 3 and 4, patients re-

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Received : 23.02.2012

Accepted : 16.05.2012

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ferred to emergency room with ataxia, lethargy and weakness. The drug dosages have been shown in Table I. In the first four cases, patients had been using for 2-weeks, Case 5 had been taking gabapentin (1800 mg/day) for 3-weeks and he was referred to nephrology department with vertigo, myalgia and fatigue. All of the cases received haemodialysis for consecutive 3 days, except for Case 5. Case 1 recovered rapidly right after the first haemodialysis and unconsciousness of the patient did not relapsed in following period. After three haemodialysis sessions, ataxia, lethargy and weakness complaints of Case 2, 3 and 4 completely resolved. However, Case 5 recovered gradually after giving up the drug use.

DISCUSSION

Gabapentin is an agent used effectively in treatment of neuropathic pains. That agent, which has anticonvulsant effects, is tolerated much more easily. Nowadays the indications of drug uses have been increased gradually. Gabapentin has been increasingly used for lots of cases, including restless legs syndrome, migraine, phantom limb pain, cancer-related pain, spinal cord injury (3).

Gabapentin is competitive inhibitor of transferase enzyme in glutamate transformation of branched chain amino acids. So it decreases glutamate's level in brain. Moreover gabapentin increases the intracellular level of gamma-amino acid. It blocks calcium flow in neuronal synapses by voltage-dependent calcium channels (alpha₂ delta subunit) in presynaptic area, so it inhibits neurotransmitter secretion such as acetyl choline, noradrenalin, and serotonin. Even if the analgesic effect of the drug has not been found out exactly, that it effects cerebral neocortex, hippocampus and spinal cord through calcium channels may be important for those effect (4).

Gabapentin is easily absorbed by gastrointestinal tractus and also its bioavailability is about 50% or 60%. It is neither protein-bound nor metabolized during the circulation. Furthermore it is

not affected by the changes happening in cytochrome system. It is eliminated by the way of the kidneys mainly. It is an agent easily passed through blood brain barrier. The serum level of gabapentin serum on healthy people reaches the peak after 2 hours following its being taken by orally and quickly decreases (3-5). Gabapentin's half-life is approximately 5 or 7 hours on the people have healthy kidneys. For the patients with kidney dysfunction (except dialysis patients), that period of time may extend to 132 hours (2, 6). In other words, in patients with impairment of the renal functions will result in especially some neuropsychiatric symptoms and findings due to gabapentin toxicity.

Most doctors practically pay attention to serum creatinine level by evaluating renal functions. But today estimation of creatinine clearance is more preferable and significant. Before the use of the drugs like gabapentin, it is important to adjust the doses of drugs according to renal functions (7). Ignoring those functions will result in morbidity and mortality. Our patients were taking gabapentin because of their neuropathic pains. In addition, our fourth patient in table 1 was also taking pregabalin as 150 mg/day dose.

In gabapentin toxicity, neurotoxicity findings can be often occurred such as dizziness, ataxia, nystagmus, tremor, myoclonus, somnolence, confusion and coma. It may cause psycho-agitation complex, which hallucination and ideas of reference prominently ensue. Furthermore the symptoms can be also sighted such as sickness, nausea, vomiting, tiredness (3, 8). Comatose was observed on our first case in table 1. Other patients were sufferers by ataxia, lethargy, weakness and fatigue. Liver failure, kidney failure and advanced age are risk factors for gabapentin toxicity. Age-related changes of central nervous system and some preexisting central nervous system defects may have contributed to the occasioning of overt toxicity (3). Diabetes mellitus and chronic kidney disease were found in all of our five patients. Except the first one, neither of four patients – in geriatric age group – did have any CNS diseases.

Table I: The general characteristics of our patients.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age	49	65	82	66	74
Gender	Male	Female	Male	Female	Male
Diagnosis	DM, HT	DM, HT, Hypotiroidi	DM, HT	DM, HT	DM, HT
eGFR, ml/min	<10	19.9	23.46	12.2	36
Gabapentin dosage, mg/day	600	800	1600	1200	1800
Serum gabapentin, µg/ml (RL: 2-12)	21.60	20.50	23.00	18.00	12.7
Indication of drug uses	Neuropathic pain	Neuropathic pain	Neuropathic pain	Neuropathic pain	Neuropathic pain

DM: diabetes mellitus, **HT:** hypertension, **eGFR:** estimated glomerular filtration rate, **RL:** reference level.

Hypoglycaemia attack or neutropenia which are the side effects of gabapentin were not monitored on any of the patients. In addition, the side effects of gabapentin vary from person to person. If symptoms such as dizziness, ataxia, emotional lability, tremor, weakness, blurred vision occur, with the use of this drug, gabapentin toxicity should be suspected. The relationship between the serum level of gabapentin and clinical findings was almost noted in our cases. But, an exact relationship between eGFR of the cases and the serum level of the drug was exactly not observed, in contrast to previous studies. However, toxic manifestations of gabapentin more severe in patients with reduced eGFR, especially receiving dialysis, in agreement with previous studies (3, 9).

So far, most case reports on toxicity of gabapentin have been reported by nephrologists (3, 5, 9-11). Therefore, the adverse effects of gabapentin well known among nephrologists, however it is not known exactly by other doctors. When gabapentin toxicity is suspected, the drug usage must be stopped immediately. If haemodialysis is applied urgently, it can be possible to remove that drug from circulation. Neurologic toxicity can be completely resolved (7, 12). Except for the fifth patient in Table I, intermittent hemodialysis was applied to the other four patients and while we were observing, we saw that their somnolence and ataxia had been recovered completely. In patients with kidney failure, especially those advanced age and multiple comorbidity, dose adjustment should be done according to creatinine clearance. The recommended maximum daily dose in patients with creatinine clearance <15 ml/min, 15 ml/min, <30 ml/min, and 30-60 ml/min is 150 mg, 300 mg, 700 mg and 1400 mg/day, respectively.

Consequently, as is found out, we want to underline that dose adjustment is significant in the patients with kidney failure and advanced age and also the patients dramatically respond to haemodialysis especially in the gabapentin toxicity.

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