

A Case of Baclofen-induced Encephalopathy

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We report a case of acute transient encephalopathy with mental alteration, myoclonic jerks, and periodic triphasic wave electroencephalographic patterns caused by a therapeutic dose of baclofen. The clinical and electroencephalographic abnormalities improved to a normal range shortly after baclofen was discontinued. We discuss the pathogenesis and review the literature about baclofen-induced encephalopathies.

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Baclofen (-4-chlorophenyl-aminobutyric acid), a gamma-aminobutyric acid (GABA) derivative, has become a drug of choice for the treatment of spasticity.¹ This drug is also used with limited success for various neurologic conditions such as trigeminal neuralgia,² stiff-man syndrome,³ Huntington's disease.⁴ When used in therapeutic doses, it acts principally at a spinal level to reduce muscle tone. However, with increasing doses of the drug, other involvement of the central nervous system has been noted, especially with toxic doses.^{5,6} An acute encephalopathy with unusual clinical and electroencephalographic findings caused by low doses of baclofen has rarely been reported,^{7,8} and never in Korean literatures. Here, we report a patient who was treated with relatively low doses of baclofen (20 mg three times per day) and who experienced an acute encephalopathy with unusual electroencephalographic findings.

Case

A 64-year-old male with a long-standing history of atherosclerotic cardiovascular disease developed mental deterioration 5 days after coronary artery bypass surgery. He was found to have chronic renal failure due to underlying

gout and hypertension. Also, he had suffered pulmonary tuberculosis, recurrent gouty arthritis and hypothyroidism. The family history was negative for epilepsy. The operation was well performed without any remarkable complication and he was in very stable post-operational state. During his stay in coronary intensive care unit, no specific problem was noted except for mild, asymptomatic electrolyte imbalance (Na⁺ 129 mEq/l, K⁺ 4.8 mEq/l). He was given anti-anginal drugs (aspirin, isosorbite dinitrate, diltiazem, atenolol), diuretics (furosemide, spironolactone), pain-killers (sulindac, tridol), and antibiotics (cefomandol). Then he was transferred to general ward and at that time, he complained of both leg cramping pain. Baclofen 20 mg tid p.o. was prescribed for pain relief. Twenty-four hours after initiating oral baclofen, he became confused, disoriented, and agitated, with periods of lethargy. There was no focal, lateralizing neurologic deficit except for mental deterioration and myoclonic movement of both lower legs. One day later, his mental status and responsiveness rapidly deteriorated to stupor. Vital signs were normal. Light reflexes gave a slow response with isocoric pupils. Meningeal irritation signs were absent and funduscopy was normal. Doll's eye sign was absent with decreased corneal reflexes. Toe signs were bilaterally extensor. All extremities were flaccid without any resistance to passive movement. Blood chemistries including hepatic and renal panels and computed tomographic (CT) scan of the brain did not disclose evidence of a precipitating cause. An electroencephalogram (EEG) showed prolonged runs of generalized triphasic waves (Fig. 1). Three days

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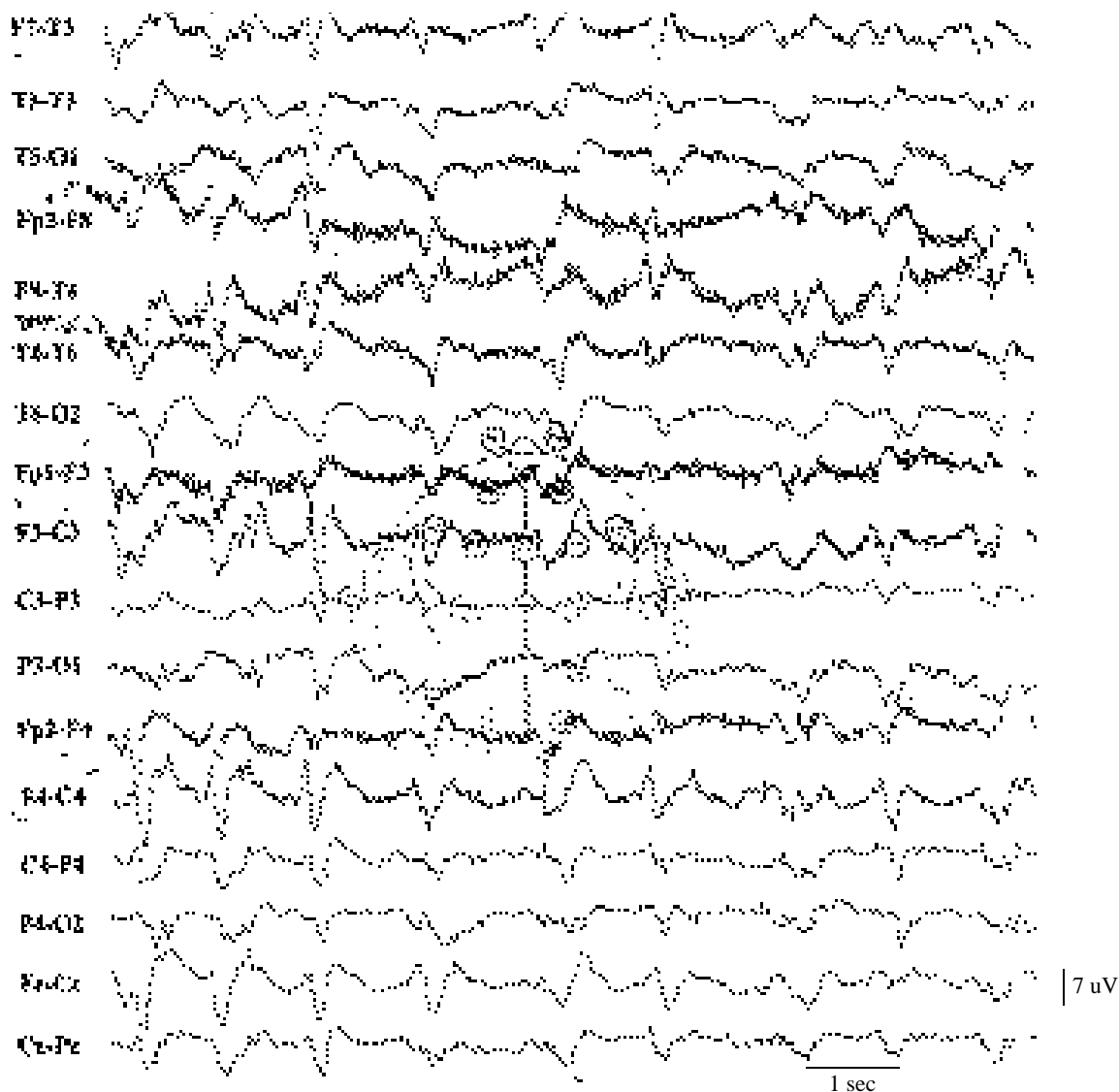


Figure 1. Electroencephalogram during the period of encephalopathy. This shows generalized triphasic waves with a repetition rate of 1 to 2 Hz.



Figure 2. Electroencephalogram performed 5 days after discontinuation of baclofen. There are no any abnormal findings.

after discontinuation of baclofen, his neurologic status gradually improved and returned to base-

line state without any neurologic deficit five days later. Serial follow-up electroencephalograms during the recovery period revealed gradual improvement to normal (Fig. 2).

Discussion

Baclofen, an agonist of GABA, is commonly used for the management of spasticity and pain in various neurologic conditions. Acute overdose of baclofen may lead to altered consciousness, seizures, respiratory depression, hypotension, muscular hypotonia, hypothermia, and arrhythmia.⁹ Some authors ascertained that coexisting brain lesions might also have enhanced the risk of developing baclofen toxicity.¹⁰ Various degrees of change in the mental status, often with myoclonus, have been

reported in relation to baclofen overdose.¹¹ As in our patient, when toxicity is severe, decreased mentality, muscle paralysis, unreactive pupils, and even respiratory depression may ensue. These complications are considered to be due to direct depressant action of baclofen on the central nervous system. Baclofen has been shown to cause neuronal hyperpolarization and decrease the release of neurotransmitters such as glutamate, catecholamines, and substance P.¹² This inhibitory effect of baclofen is likely to have an important role, although it is not clear which of these neurotransmitters are important in the pathogenesis of the encephalopathy and the electroencephalographic changes.

The most interesting feature in our patient was the dramatic change in electroencephalogram, which showed prolonged runs of triphasic waves associated with encephalopathy. Although triphasic waves were typical of hepatic encephalopathy, they were also reported in patients with Creutzfeldt-Jacob disease, uremic encephalopathy, advanced Alzheimer's disease, hypercalcemia, Binswanger's leukoencephalopathy, lithium and water intoxication. Agulia et al¹³ demonstrated that triphasic waves may occur in patients with brain tumors (2 malignant glioma, 1 craniopharyngioma) involving subcortical midline structure without any metabolic abnormalities. Some cases in which reversible encephalopathy due to baclofen is associated with characteristic electroencephalogram features showing burst of triphasic waves, have been reported.^{7,11} In the case described above, the absence of pre-existing brain lesion, the normal CT scan, and the absence of any metabolic disturbances, the acute onset and rapid resolution of clinical and EEG abnormalities after discontinuing the drug suggest a direct cerebral toxic effect of baclofen. Rapid resolution of clinical and electroencephalographic abnormalities after discontinuation of the drug further strengthens this assumption. The encephalopathy associated with almost continuous sharp periodic complexes raised the suspicion of spongiform encephalopathy e.g. Creutzfeldt-Jacob disease. However, acute onset and rapid resolution of clinical and electroencephalographic abnormalities make this diagnosis very unlikely.

Although our patient had chronic renal failure, there was no interval change in the level of blood urea nitrogen at that period. Therefore, renal failure in our patient may not contribute to the development of uremic encephalopathy and triphasic waves.

Patients with renal impairment are known to be particularly vulnerable to toxicity with baclofen. After ingesting a single dose, more than 85% of the drug is excreted unchanged by the kidney, the half-life being approximately 3.5 hours.¹⁴ Because of the pre-existing impaired renal clearance as in our patient, the drug might have accumulated to a toxic level with resultant baclofen-induced encephalopathy.

In view of the rarity of triphasic waves in patients with convulsive disorders found by Bickford and Butt, it could be argued that the epileptogenic nature of triphasic waves is unique to cases of baclofen toxicity.

Epilepsy is not generally listed among the nonmetabolic causes of triphasic waves. However, Rochelle et al¹⁵ reported a patient with a history of spinal multiple sclerosis who developed acute confusional state after administering high dose of baclofen (110 mg/day). EEG revealed continuous generalized sharp waves with a repetition rate of 1-2 Hz similar to our patient. After intravenous diazepam and phenytoin injection the mental status and EEG became normalized. From that point of view, the author believed that his case had generalized nonconvulsive status epilepticus and not metabolic encephalopathy with triphasic waves as previously reported. Actually, there were some reports that seizures including status epilepticus might complicate baclofen administration, especially intrathecal route.¹⁶ Baclofen is one of the GABA agonist at GABA_B receptors. Baclofen acts at presynaptic and postsynaptic sites within the central nervous system and exerts anticonvulsant¹⁷ as well as proconvulsant¹⁶ effects. A possible explanation for the seemingly contradictory effects may be the delicate balance between suppression of recurrent inhibition by a presynaptic effect relative to the activation of receptors mediating postsynaptic inhibition, as demonstrated in an *in vitro* rat model.¹⁸ A proepileptic effect *in vivo* would then result from greater suppression of inhibition

than excitation in a traumatized brain region.

Baclofen-induced encephalopathy with myoclonus and a periodic triphasic wave in electroencephalogram may masquerade as subacute spongiform or other metabolic/toxic encephalopathies. The prognosis of this acute encephalopathy induced by baclofen is excellent after discontinuation of the drug, when it is recognized early.

REFERENCES

1. Sachais BA, Logue JN, Carey MS. Baclofen, a new antispastic drug : A controlled, multicenter trial in patients with multiple sclerosis. *Arch Neurol* 1997;34:422-428.
2. Fromm GH, Terrence CF, Chattha AS. Baclofen in the treatment of trigeminal neuralgia : double blind study and long-term follow-up. *Ann Neurol* 1984;15:240-244.
3. Alberca R, Romeo M, Chaparro J. Jerking stiff-man syndrome. *J Neurol Neurosurg Psychiatr* 1982;45:1159-1160.
4. Barbeau A. GABA and Huntington's chorea. *Lancet* 1973;2:1499-1550.
5. Abarbanel J, Herishanu Y, Frisher S. Encephalopathy associated with baclofen. *Ann Neurol* 1985;17:617-618.
6. Paulson GW. Overdoses of Lioresal. *Neurology* 1976; 26:1105-1106.
7. Hormes JT, Benarroch EE, Rodriguez M, Klass DW. Periodic sharp waves in baclofen-induced encephalopathy. *Arch Neurol* 1988;45:814-815.
8. Joseph TH, Eduardo EB, Moses R, Donald WK. Periodic sharp waves in baclofen-induced encephalopathy. *Arch Neurol* 1988;45:814-815.
9. Holly EP, Robert OW, Michael WS, Alan DW. Baclofen overdose-drug experimentation in a group of adolescents. *Pediatrics* 1998;101(6):1045-1048.
10. White WB. Aggravated CNS depression with urinary retention secondary to baclofen administration. *Arch Intern Med* 1985;145:1717-1718.
11. Abarbanel J, Herishanu Y, Frisher S. Encephalopathy associated with baclofen. *Ann Neurol* 1985; 17:617-618.
12. Bowery NG, Hill DR, Hudson AL. Baclofen decreases neurotransmitter release in the mammalian CNS by an action at a novel GABA receptor. *Nature* 1980;283:92-94.
13. Agulia U, Gambardella A, Oliveri RL, Lavano A, Camerlingo R, Quattrone A. Triphasic waves and cerebral tumors. *European Neurology* 1990;30(1):1-5.
14. Knutsson E, Lindblom U, Martensson A. Plasma and cerebrospinal fluid levels of baclofen(Lioresal) at optimal therapeutic responses in spastic paresis. *J Neurol Sci* 1974;23:473-484.
15. Rochelle Z, Gail S, Frank P, Douglas L. Baclofen-induced generalized nonconvulsive status epilepticus. *Ann Neurol* 1994;36(1):113-114.
16. Saltuari L, Marosi MJ, Kofler M, Bauer G. Status epilepticus complicating intrathecal baclofen overdose. *Lancet* 1992;339(8):373-374.
17. Dralle D, Neuhauser G, Tonn JC. Intrathecal baclofen for cerebral spasticity. *Lancet* 1989;2:916.
18. Mott DD, Bradgon AC, Lewis DV, Wilson WA. Baclofen has a proepileptic effect in rat dentate gyrus. *J Phar Exp Ther* 1989;249:721-725.