

Benzodiazepine toxicity with profound suppression of the electroencephalogram

JASON P. STABLEY, DO
EDWARD J. FREAR
MARVIS WINE
MILIND J. KOTHARI, DO

The authors report the case of a 60-year-old man with respiratory distress secondary to exacerbation of chronic obstructive pulmonary disease, right lower lobe pneumonia, and severe bronchospasm. High doses of lorazepam were given intravenously after failure to control bronchospasm and agitation with bronchodilators and mucolytic agents; the patient was unresponsive to all stimuli while receiving lorazepam. Electroencephalography revealed a profoundly suppressed pattern without accompanying low-voltage fast activity—this was reversible following withdrawal of the lorazepam.

(Key words: toxicity, benzodiazepines, lorazepam, electroencephalography)

Benzodiazepines are widely used in clinical practice as anxiolytics, anti-convulsants, anesthesia inducers, hypnotic agents, and antispasmodics.¹ As a class, they are well known to cause ventral nervous system depression. Electroencephalographic changes associated with use of benzodiazepines have also been described. The authors report profound reversible suppression of the electroencephalographic record in a patient receiving large doses of lorazepam (Ativan).

At the time this article was written, Dr Stabley was a fellow in neurophysiology in the Division of Neurology, College of Medicine, Pennsylvania State University, Hershey, Pa; Mr Frear is supervisor of the EEG laboratory in the Division of Neurology, College of Medicine, Pennsylvania State University, Hershey, Pa; Ms Wine is an EEG technician in the Division of Neurology, College of Medicine, Pennsylvania State University, Hershey, Pa; Dr Kothari is an associate professor of neurology and director of the neurology residency program, Division of Neurology, College of Medicine, Pennsylvania State University, Hershey, Pa.

Correspondence to Milind J. Kothari, DO, Section of Neurology, Penn State Geisinger Health System, PO Box 850, MC H037, Hershey, PA 17033-0850

Report of case

A 60-year-old Caucasian man was transferred to the Milton S. Hershey Medical Center for respiratory distress secondary to exacerbation of chronic obstructive pulmonary disease, right lower lobe pneumonia, and severe bronchospasm. He was started on intravenous corticosteroid and antibiotic therapy several days before transfer to our facility. One day before transfer, he had acute onset of right upper extremity weakness. On the patient's admission to our facility, computerized tomography revealed two small subcortical hypodensities in the left frontotemporal region that were believed to represent subacute cerebral infarcts.

Past medical history was positive for chronic obstructive pulmonary disease secondary to alpha₁-antitrypsin deficiency, diverticulitis, multiple rectal polyps, and heavy tobacco smoking.

Physical examination initially revealed an intubated man who was mildly drowsy. Vital signs were stable. General physical examination was positive for diminished breath sounds throughout both lung fields, with a moderate amount of inspiratory and expiratory wheezing. Neurologic examination revealed mod-

erate right-sided weakness involving mainly the upper extremity. Findings of the cranial nerve examination were unremarkable. Reflexes were mildly brisk on the right. Plantar responses were extensor on the right and flexor on the left. Sensory, cerebellar, coordination, and gait examinations could not be adequately assessed.

Hospitalization was initially complicated by severe bronchospasm and mucous plugging of the airways. This was treated with aggressive pulmonary toilet, bronchodilators, and mucolytic agents without success. Large doses of lorazepam were administered intravenously via drip infusion (variable doses up to 20 mg/h) after failure to control bronchospasm and agitation with the bronchodilators and mucolytic agents. The patient was unresponsive to all stimuli while receiving lorazepam. Before and during lorazepam administration, there was no evidence of hypoxia, hypercapnia, or significant metabolic disturbances.

Electroencephalography revealed a profoundly suppressed pattern without accompanying low-voltage fast activity (Figure 1). Within 72 hours after withdrawal of lorazepam, the patient began to arouse. Five days after discontinuing lorazepam, electroencephalography revealed significant return of baseline activity with mild focal slowing on the left, believed to be secondary to the recent left hemispheric infarcts (Figure 2).

Discussion

The most common electroencephalographic change noted with the use of benzodiazepines is excessive low-voltage fast activity,²⁻⁴ which is most prominent anteriorly,⁵⁻⁷ but may spread posteriorly.⁸ A decrease in slow activity has also been shown to accompany the increase in low-voltage fast activity.³ Others have noted that in acute benzodiazepine intoxication, prominent fast activity is followed by coma patterns similar to those seen in barbiturate intoxication.⁹ Other reports have described alpha coma, delta slowing with superimposed beta activity, and, rarely, isoelectric coma. Spindle coma associated with benzodiazepine intoxication has also been reported.¹⁰



Figure 1. Electroencephalogram recorded while patient receiving lorazepam; sensitivity of 200 mV peak to peak, high linear filter 70 Hz, low linear filter 1.0 Hz.

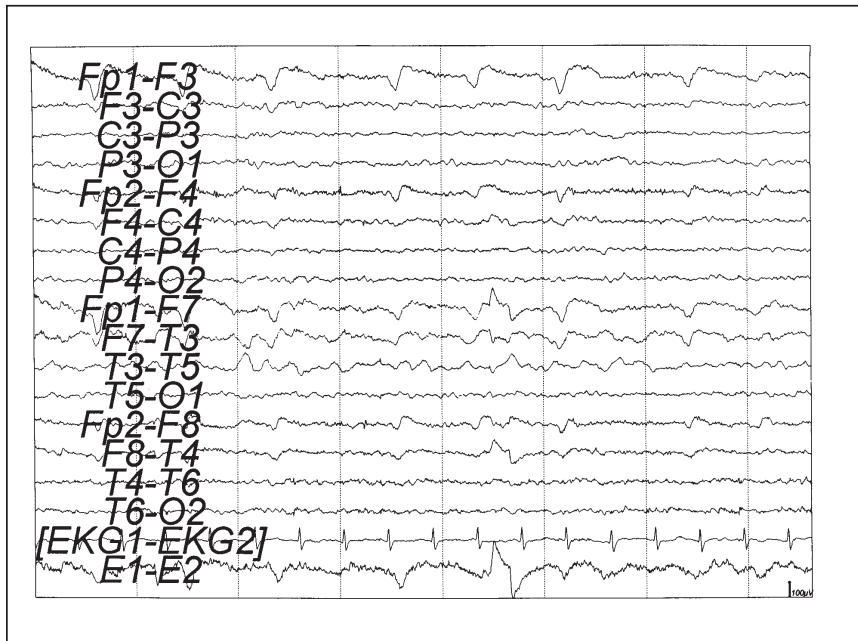


Figure 2. Electroencephalogram 5 days after discontinuation of lorazepam; sensitivity of 200 mV peak to peak, high linear filter 70 Hz, low linear filter 1.0 Hz.

This particular patient was receiving large doses of lorazepam to control agitation and bronchospasm. The electroencephalogram showed significantly suppressed background activity similar to that seen with other causes of severe dif-

fuse brain injury. After withdrawal of the lorazepam, there was a gradual return to a baseline encephalographic record with evident focal slowing of the left hemisphere, believed to be related to the recent ischemic insult.

References

1. Ameer B, Greenblatt DJ. Lorazepam: a review of its clinical pharmacological properties and therapeutic uses. *Drugs* 1981;21:161-200.
2. Matthes A. 1,3-Dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-on als Schafmittel im Kindesalter. *Arzneimittelforschung* 1965;15:1157-1158.
3. Itil et al. Quantitative EEG studies of chlor-diazepoxide, chlorpromazine, and imipramine in volunteer and schizophrenic subjects. In: Evans WO, Kline NS, ed. *The Psychopharmacology of the Normal Human*. Springfield, Ill: Charles C Thomas; 1969:219-237.
4. Hooshmand H. Trial of a new anticonvulsant for uncontrollable minor motor seizures. Paper presented at the annual meeting of the American Epilepsy Society, New York, NY, 1970.
5. Towler ML. The clinical use of diazepam in anxiety states and depressions. *J Neurol Psychiatry* 1962 (Suppl 1):68-72.
6. Kameda H, Hidaka Y, Furukawa T. Changes in human electroencephalogram following administration of chlordiazepoxide. *Folia Psychiatr Neurol Jap* 1962;16:15-24.
7. Metcalf D, Whitley DJ. Experience with diazepam in electroencephalography laboratory controlled evaluation. *Am J Psychiatry* 1964;120:1114-1115.
8. Towler ML, Beall BD, King JB. Drug effects on the electroencephalographic pattern with specific consideration of diazepam. *South Med J* 1962;55:832-838.
9. Bauer G. EEG, drug effects and central nervous system poisoning. In: Niedermeyer E, Lopes da Silva FH, ed. *Electroencephalography: Basic Principles, Clinical Applications and Related Fields*. Baltimore, Md: Urban and Schwarzenberg; 1982:479-489.
10. Mouradian MD, Penovich PE. Spindle coma in benzodiazepine toxicity: case report. *Clin Electroencephalogr* 1985;16:213-218.