Baclofen-induced Generalized Nonconvulsive Status Epilepticus

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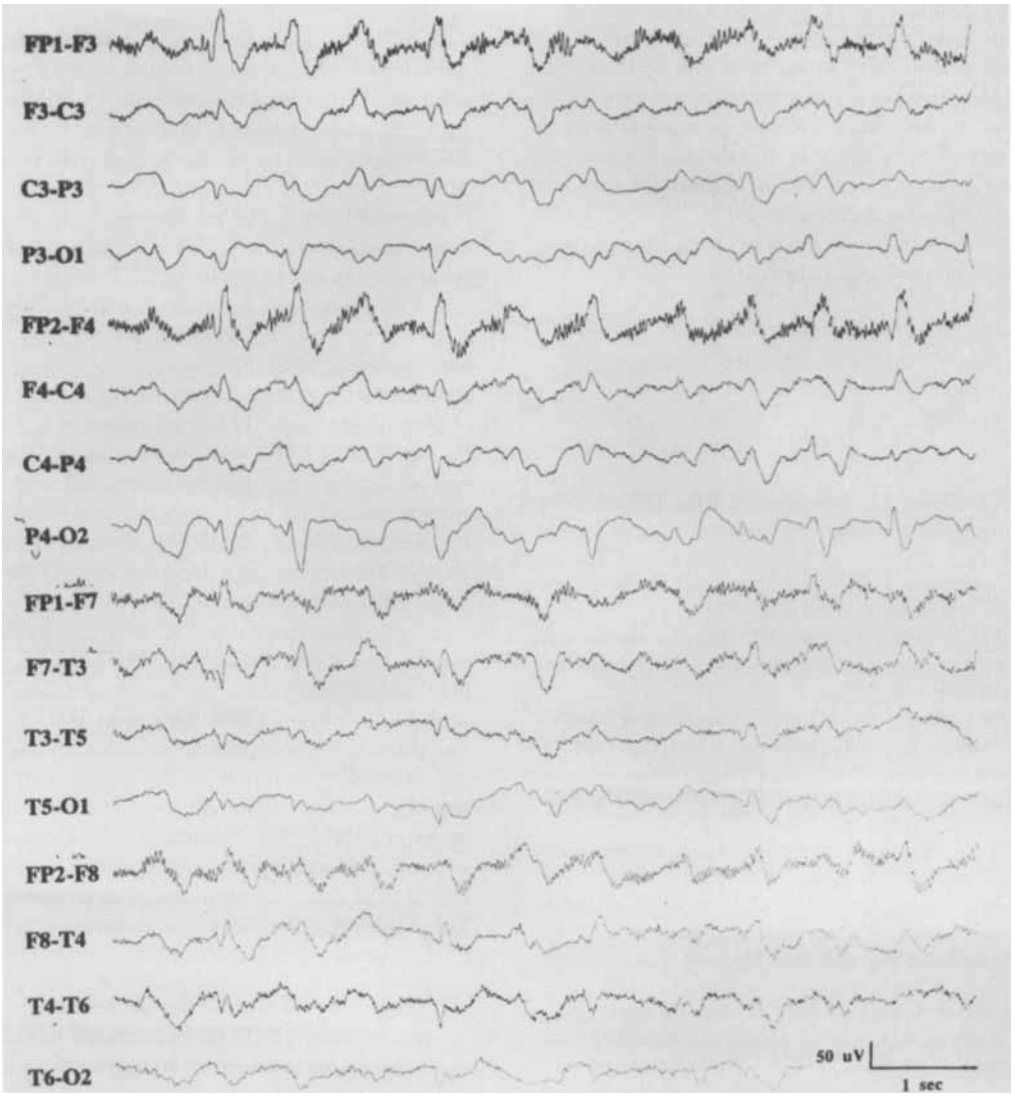
Baclofen has been reported to produce a "metabolic" type encephalopathy with periodic generalized electroencephalographic (EEG) sharp waves in 3 previous cases [1, 2]. We recently cared for a similar patient, whose mental status and EEG normalized after treatment with diazepam and phenytoin. Thus, we believe all 4 cases had generalized nonconvulsive status epilepticus (GNCSE) and not metabolic encephalopathies with EEG triphasic waves as previously believed.

A 50-year-old woman with a long-standing history of predominantly spinal multiple sclerosis (MS) developed an acute confusional state. Video-EEG monitoring revealed continuous generalized sharp waves occurring periodically with a repetition rate of 1 to 2 Hz (Fig). After intravenous administration of 5 mg of diazepam and 1,000 mg of phenytoin, the sharp waves disappeared and the patient's mental status normalized. Thus, with the epileptiform EEG and confusional state that was terminated immediately by antiepileptic drugs we were able to diagnose GNCSE.

Blood chemistries, spinal fluid, and a magnetic resonance imaging (MRI) scan of the brain did not reveal evidence of a precipitating cause. The only reasonable candidate for triggering the GNCSE was treatment with high-dose baclofen (110 mg/day). The patient subsequently has remained seizure free for 1 year on phenytoin 300 mg/day despite continuing baclofen treatment of 110 mg/day. A repeat EEG



Electroencephalogram showing generalized periodic sharp waves occurring with a repetition rate of 1 to 2 Hz, associated with encephalopathy. Electrode nomenclature and placement followed the International 10–20 System. Silver/silver chloride electrodes were used.

1 month later revealed only mild background slowing, without epileptiform activity.

Encephalopathy with repetitive sharp waves on EEG due to baclofen has been described previously in 3 patients. In those patients, the behavioral and EEG abnormalities resolved in 24 to 48 hours, after discontinuation of baclofen [1, 2]. The dramatic improvement in our patient after antiepileptic drug treatment demonstrates that alteration of consciousness during baclofen treatment may be secondary to GNCSE.

We do not believe our patient's underlying MS caused GNCSE, because there were no changes in the MRI, no inflammatory findings in the spinal fluid, and no change in her clinical condition on neurologic examination. Furthermore, seizures occur only rarely in MS, and GNCSE has not been reported.

On the other hand, generalized convulsive seizures occur with acute baclofen intoxication [3], and generalized convulsive and focal motor seizures have been reported with intrathecal baclofen [4]. Generalized and complex partial seizures occur during withdrawal of baclofen [5, 6]. Intraperitoneal injections of baclofen produce seizures in rats with spontaneous petit mal–like absences [7].

Baclofen is a γ-aminobutyric $acid_B$ ($GABA_B$) (inhibitory neurotransmitter) agonist. At first, it may seem difficult to reconcile baclofen's clinical proconvulsant effects with its biochemical $GABA_B$ inhibitory neurotransmitter properties. However, GABA receptors located presynaptically on GABAergic axonal terminals may functionally "inhibit inhibition," thus providing a potential mechanism for neuronal excitation, in addition to neuronal inhibition, for a $GABA_B$ agonist such as baclofen [8]. We believe baclofen can cause generalized nonconvulsive status epilepticus.

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Expanded Clinical Trials of Treatments for Multiple Sclerosis: Copolymer 1 (COP-1) Treatment Investigational New Drug (IND) Program

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As mentioned by Dr Whitaker (for the Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis of The National Multiple Sclerosis Society. Ann Neurol 1993; 34:755–756.) in his discussion of the possible impact of treatment investigational new drug (IND) protocols on clinical research in multiple sclerosis (MS), our compound, copolymer 1 (COP-1), became the first MS drug to be available through a Treatment IND protocol. This protocol was approved by the Food and Drug Administration (FDA) in January 1993 for patients with the exacerbating–remitting form of MS.

Dr Whitaker raises some valid and important issues regarding the potential impact of treatment IND programs on the conduct of controlled clinical trials. Dr Whitaker also offers some recommendations to minimize the impact of treatment IND programs on controlled clinical trials of new agents for MS.

We at LEMMON/TEVA Pharmaceuticals concur with the committee's concerns. We have worked closely with the MS community in the design of the COP-1 Treatment IND Program. The program's design embodies most, if not all, of the committee's recommendations. Further, we have designed the Treatment IND Program with the input of the clinical investigators involved in our ongoing double-blind study.

When LEMMON/TEVA submitted the Treatment IND to the FDA, COP-1 was already under investigation in a second double-blind placebo-controlled study. All patients were recruited and had completed almost 1 year of the double-blind treatment. Therefore, the implementation of the COP-1 Treatment IND Program was not viewed as being competitive with the double-blind study.

At all times, the controlled trial has remained our first priority and focus. At LEMMON/TEVA, our primary goal is to establish the efficacy and safety of COP-1 through controlled trials. The COP-1 Treatment IND is designed in a way that it will not impair the investigators' ability to conduct the necessary controlled studies required by the FDA and the MS scientific community to determine the efficacy and safety of COP-1. The Treatment IND Program is instituted to provide an alternative to patients not enrolled in the controlled trial and who seek access to a potential treatment. The following controls and procedures are in place for the COP-1 Treatment IND Program:

(1) A limit on the number of patients to be enrolled into the Treatment IND has been established by the sponsor. This is done primarily to remain focused on the double-