Reprinted from *HEADACHE* Journal, Volume 36, Number 2, February, 1996 Printed in U.S.A.

Case Reports

Severe Barbiturate Withdrawal Syndrome in Migrainous Patients

Michele Raja, MD; Maria Concetta Altavista, MD, PhD; Antonella Azzoni, MD; Alberto Albanese, MD

Three patients who presented with grand mal seizures and an associated behavioral disorder were recognized as suffering from a severe butalbital withdrawal syndrome. All were migraineurs who had become dependent on barbiturates. We propose that the occurrence of seizures, psychotic behavior, or a recent personality change should be considered clues to possible barbiturate abuse in patients with migraine.

Key words: barbiturates, dependence, headache, seizures, withdrawal

Abbreviations: CDH chronic daily headache

(*Headache* 1996;36:119-121)

Migraineurs often have the habit of taking excessive amounts of drugs for immediate headache relief,[1-3] thereby risking the development of rebound headache or interdose withdrawal headache. This allows for many cases of migraine to transform into a chronic daily headache (CDH).[4] The management of patients with headache and medication overuse is difficult. Psychologic, as well as physiologic, dependence is common in migraineurs, who may require inpatient comprehensive and multidisciplinary treatments.[2,5]

Preparations containing short-acting barbiturates, particularly butalbital, are most often taken by those with frequent migrainous attacks.[6-10] Overuse of barbiturates may induce rebound headache, tolerance, and dependence. Most who take at least 500 mg of butalbital a day are bound to develop drug-induced CDH.[11] The chance for a barbiturate withdrawal syndrome to occur depends on the daily dosage and on the duration of drug use. Secobarbital (at least 0.6 g/day for 30 days or 0.4 g/day for 90 days) induces physical dependence.[12,13] No data are available for butalbital.

From the Dipartimento di Salute Mentale, Ospedale Santo Spirito (Drs. Raja and Azzoni); the Dipartimento di Scienze Neurologiche, Ospedale San Filippo Neri (Dr. Altavista); and the Istituto di Neurologia, Universita Cattolica del Sacro Cuore (Dr. Albanese), Roma, Italy.

Address all correspondence to Dr. Michele Raja, Dipartimento di Salute Mentale, Ospedale Santo Spirito, Borgo Santo Spirito, 3, CAP 00193, Roma, Italy.

Accepted for publication July 27, 1995.

Psychiatric comorbidity, that is often associated with migraine, may further increase the risk of addiction and dependence. Possibly due to a common pathogenesis and pathophysiology, migraine is strongly associated with either affective or anxiety disorders.[14-16] The latter have been related to sedative, hypnotic, or anxiolytic abuse. In a large series of patients attending an addiction unit, tranquilizer and barbiturate abusers were most likely to suffer from associated psychiatric disorders, particularly anxiety or mood disorders.[17] Thus, several risk factors consistently can expose migraineurs to high risk of barbiturate misuse.

We observed three cases of severe barbiturate withdrawal syndrome following intense use of suppositories containing propyphenazone, caffeine, and butalbital for treatment of migraine.

CASE HISTORIES

Patient 1.—A 28-year-old woman was brought at night to the psychiatric ward. She complained of having been beaten by her parents. Bruises and scratches were scattered on her skin. She was alert and oriented, although she looked upset, anxious, and depressed, but presented no delusions or hallucinations.

Her medical and psychiatric record was unremarkable, except for headache that she had been controlling with up to four butalbital-containing suppositories per day. During the last few months, she had gradually become anxious, irritable, and violent and had three episodes of loss of consciousness. Her physical examination was normal. A provisional diagnosis of barbiturate withdrawal syndrome was made, and barbiturate plasma levels were measured.

On the following day, she had a grand mal seizure. Phenobarbital in the plasma was 16.7 µg/mL; alcohol and other psychoactive drugs were not detected in the urine. Neurological examination, brain CT scan, and EEG were normal. Phenobarbital (100 mg daily) was prescribed. On her third night in hospital, she vomited, became agitated, fearful,

and presented olfactory, auditory, and visual hallucinations. Poorly systematized persecutory delusions were also present. Haloperidol (4 mg) and phenobarbital (75 mg) provided immediate partial relief.

During the following days, the patient remained quiet and oriented during the day, but became confused, upset, and hallucinated at night; phenobarbital was increased to 200 mg at bedtime. The clinical conditions remarkably improved; a week later, a gradual withdrawal of barbiturate was initiated. The patient was later discharged in good health. She was followed up for 1 1/2 years, during which time she remained in good health and did not use butalbital-containing preparations.

Patient 2.—A 45-year-old woman presented with a confusional state following head trauma. Her appearance suggested poor self-care, insufficient hygiene, and under-nourishment. She was alert, disoriented, logorrheic, and fatuous, with loose associations, excitement, and slurred speech. Her breath was not alcoholic. She was homeless but cared for by a social center, whose staff members provided the information that she used to take suppositories containing a mixture of butalbital, caffeine, and analgesics for migraine. Her psychiatric history was consistent with a diagnosis of mood disorder. She had lost consciousness more than once. The patient's father was an alcoholic, and her mother suffered from migraine. Her family history was, otherwise, unremarkable. Haloperidol (3 mg PO) and diazepam (10 mg PO) were then prescribed. The phenobarbital plasma level was 2.4 µg/mL. A toxin screen of urine did not detect alcohol or other psychoactive substances. On the day following admission, the patient was fully alert and oriented, but irritable and dysphoric. Her speech was loud, voluble, and difficult to interrupt. Her mood was predominantly euphoric; the content of her thought reflected inflated self-esteem and suspiciousness. She first denied but later acknowledged having used suppositories for "throbbing headache and vomit." She claimed to be a sufferer of "toothache" and demanded analgesics. Neurological examination was normal. An EEG and brain CT scan were unremarkable. Therapy with phenobarbital (100 mg daily) rapidly improved the clinical conditions. On her fourth day in hospital, the patient was fully oriented, quiet, and cooperative. Her mood became stable. When phenobarbital was gradually reduced, headache relapsed; propranolol (100 mg daily) was then prescribed and proved effective in preventing further recurrences. After discharge, the patient was lost to follow-up.

Patient 3.—A 48-year-old woman was brought to the emergency department due to the occurrence of grand mal seizures. A brain CT scan was normal. Because of psychomotor agitation, she was admitted to the intensive care unit and was sedated with propofol. Urine samples revealed traces of barbiturates and benzodiazepines. Propofol was discontinued; 3 days after admission, the patient was transferred to the neurologic ward. Her EEG was diffusely slow. She suffered from insomnia, irritability, and postural tremor of the upper limbs.

The patient's medical record revealed hypothyroidism treated with thyroid hormones. Her history was remarkable for panic attacks with agoraphobia and for periodic migraine, recurring monthly since she was 15 years old. Family history was remarkable for migraine in her female relatives. Based on suggestions provided by her mother (a migraine sufferer), she had started ergotamine tablets and butalbital-containing suppositories. Twenty-five years before admission, when she took three to four suppositories per day, she presented with intense sedation and facial jerks on one occasion. She subsequently reduced the medication to one half suppository a day for approximately 10 years. She gradually increased the daily dosage again up to three to four suppositories. Two days before admission, she had presented with intense sedation and facial jerks.

The patient was discharged without treatment for headache. A month after discharge, she presented with insomnia, irritability, and headache. Lorazepam (3 mg per day), amitriptyline (30 mg per day), and propranolol (20 mg tid) provided relief.

COMMENTS

All our patients abused suppositories containing propyphenazone, caffeine, and butalbital. Tablets and suppositories require medical prescription; the tablets contain 50 mg of butalbital, while the suppositories contain 150 mg. Rectal drug administration provides fast and effective absorption for patients with migraine-associated symptoms (eg, delayed gastric emptying, nausea, and vomiting). However, the use of suppositories with the higher concentration of butalbital has a greater chance of priming a state of dependence.

These observations are in keeping with the notion that butalbital may produce strong physical dependence. All the observed patients were medication abusers, who became addicted following a legitimate, although unfavorable, treatment for migraine. The patients developed different strategies to overcome prescription limits. Patient 1 convinced her relatives to obtain prescriptions in

their names, patient 2 was in contact with several social centers and managed to obtain prescriptions from the attending physicians, patient 3 consulted several physicians in different towns. In summary, all the patients developed typical behavior designed to obtain increasing amounts of butalbital. However, they did not have personality traits or behavioral patterns typical of the usual street abuser and did not abuse any other drug.

All the patients reported here suffered from a severe barbiturate withdrawal syndrome featuring epileptic seizures.

Patients 2 and 3 had a concomitant psychiatric disorder. Comorbidity of migraine and psychiatric disorders may have reinforced their drug dependence. Antidepressants by virtue of their antimigrainous and antidepressant action helped patient 3 discontinue the use of butalbital suppositories. Interestingly, all the patients were women. This is consistent with the observation of a higher prevalence of migraine in women.

Barbiturate abuse is, nowadays, almost completely restricted to migrainous patients and is becoming less common in medical practice and may be overlooked. A state of barbiturate dependence may not be considered outside of headache clinics, where early signs of antimigrainous drug abuse (eg, asthenia, nausea, restlessness, irritability, memory problems, poor concentration, depression, and neurotic behavior) are correctly recognized.[4]

In neurologic practice, barbiturate dependence requires a high degree of presumption. Withdrawal signs are sometimes the main clue to the diagnosis. However, if a nonspecific behavioral disorder or an acute psychotic state constitute the main picture, the patient may be misdiagnosed. This may have been the case for patients 1 and 2, who showed symptoms closely resembling "functional" psychiatric disorders, when first visited. The correct diagnosis could have been missed if adequate information had not been available or if seizures had not occurred.

We propose a history of headache should be a clue to possible barbiturate abuse in any adult presenting with a first episode of seizures, psychotic behavior, or with a recent personality change. Absence of barbiturates in plasma or urine is not suffficient to rule out a state of dependence, since short-acting barbiturate levels drop within a few days after withdrawal. Should the use of butalbital-containing preparations be reported, a barbiturate challenge test may allow detection of barbiturate tolerance.[5,18]

Because of the possible occurrence of drug-induced headache or CDH, even the use of simple analgesics, alone or in combination with caffeine, anxiolytics, or codeine, and a nonsteroidal anti-inflammatory must be limited.[19] Butalbital-containing preparations also carry an additional appreciable risk—that of dependence.

The current availability of barbiturates to a population of vulnerable individuals exposes them to an unjustified risk of severe consequences. Remarkably, analgesic preparations with barbiturates as components have been forbidden in Austria since 1992.[20] In our opinion, the use of barbiturates for relief of headache should be definitively discouraged, because of the risk of severe dependence and of the availability of safer drugs.

REFERENCES

1. Greenhouse AH. Headache in the emergency room. *Semin Neurol.* 1983;3:46-56.
2. Saper JR. Drug treatment of headache: changing concepts and treatment strategies. *Semin Neurol.* 1987;7:178-191.
3. Raskin NH. Headache. In: Isselbacher KJ et al, eds. Harrison's Principles of Internal Medicine. 13th ed. New York: McGraw-Hill, Inc; 1994:65-71.
4. Mathew NT. Chronic refractory headache. *Neurology.* 1993;43(suppl 3):S26-S33.
5. Adams RA, Victor M. Principles of Neurology. 5th ed. New York: McGraw-Hill, Inc; 1993:156.
6. Mathew NT, Kurman R, Perez F. Drug-induced refractory headache - clinical features and management. *Headache.* 1990;30:634-638.
7. Rapoport AM. Recurrent migraine: cost-effective care. *Neurology.* 1994;44(suppl 3): S25-S28.
8. Baumel B. Migraine: a pharmacologic review with newer options and delivery modalities. *Neurology.* 1994;44(suppl 3):S13-S17.
9. Markley HG. Chronic headache: appropriate use of opiate analgesics. *Neurology.* 1994;44(suppl 3):S18-S24.
10. Silberstein SD, Lipton RB. Overview of diagnosis and treatment of migraine. *Neurology.* 1994;44(suppl 7):S6-S16.
11. Sholz E, Diener HC, Geiselhart S. Does a critical dosage exist in drug-induced headache? In: Diener HC, Wilkinson M, eds. Drug-Induced Headache. Berlin: Springer-Verlag; 1988:29-43.
12. Richter RW, Stanitis T. The neurologist's approach to alcoholism and drug abuse: outpatient care. *Semin Neurol.* 1987;7:336-343.
13. Sellers EM. Alcohol, barbiturate and benzodiazepine withdrawal syndromes: clinical management. *Can Med Assoc J.* 1988;139:113-120.
14. Merikangas KR, Angst J, Isler H. Migraine and psychopathology. *Arch Gen Psychiatry.* 1990;47:849-853.
15. Breslau N, Merikangas K, Bowden CL. Comorbidity of migraine and major affective disorders. *Neurology.* 1994;44(suppl 7):S17-S22.
16. Stewart W, Breslau N, Keck PE Jr. Comorbidity of migraine and panic disorder. *Neurology.* 1994;44(suppl 7):S23-S27.
17. Ross HE, Glaser FB, Germanson T. The prevalence of psychiatric disorders in patients with alcohol and other drug problems. *Arch Gen Psychiatry.* 1988;45:1023-1031.
18. Sands GH. A protocol for butalbital, aspirin and caffeine (BAC) detoxification in headache patients. *Headache.* 1990;30:491-496.
19. Silberstein SD. Tension-type and chronic daily headache. *Neurology.* 1993;43:1644-1649.
20. Schnider P, Aull S, Feucht M, et al. Use and abuse of analgesics in tension-type headache. *Cephalalgia.* 1994;14:162-167.