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Expert Opinion

Why Do Migraineurs Abuse Butalbital-Containing Combination Analgesics?

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About 50 years ago, the neurologist and headache specialist, Arnold P. Friedman, MD, co-founder of the first specialized headache clinic in the world, helped to develop a new combination medication. He named it as an amalgamation of the name of his hospital (Montefiore in the Bronx, New York) and butalbital, thus Fiorinal (Seymour Solomon, MD, personal communication) containing 50 mg butalbital, 40 mg caffeine, and 325 mg aspirin. Butalbital-containing combination (BCC) analgesics may be effective for acute migraine relief,[1] although placebo controlled studies have not been performed.[2] However, the risk for physical and psychological dependency and medication overuse headaches is such a concern that some specialists have called for a ban on butalbital combinations in the USA.[3]

CLINICAL HISTORY

This 39-year-old woman has a history of severe migraine without aura that could last 2-3 days since the age of 17. Two and a half years ago, during the second trimester of her last pregnancy, she was placed on a butalbital, acetaminophen, and caffeine combination (BAC) for symptomatic treatment and propranolol for prevention when the headaches increased to 2 per week compared to about one per month antepartum. Postpartum, she was placed on topiramate for prevention. She tried various triptans with inconsistent results and recurrence. BAC was prescribed as rescue medication if the triptan did not work.

Although I advised her to limit the BAC to no more than 15 to 20 per month using the medication no more than 1 to 2 days per week, she would frequently call during or after office hours for refills of BAC citing various types of stress including her job, children, and later a divorce causing more headaches and not responding to triptans. When the BAC prescriptions were restricted, she would become verbally abusive with office personnel on the telephone and sometimes threaten legal action if her medication was not refilled earlier than recommended. The dose of topiramate was titrated upward to 200 mg a day without benefit and then venlafaxine extended release was started titrating to 150 mg a day.

When last seen several months ago, the headaches were daily. During the previous 2-week period, she had taken 30 BAC, 9 rizatriptan, and 40 aspirin, acetaminophen, and caffeine combination tablets. She was also seeing a psychologist on a regular basis. I

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advised her that she was probably suffering from medication overuse headaches and offered to hospitalize her for an intravenous regimen. She declined but agreed to try an outpatient dihydroergotamine subcutaneous regimen.

She called saying she was unimproved asking for more BAC. I had my secretary call the pharmacies we had previously called prescriptions in to (4 different ones) and were told that, in the prior month, she had received BAC with codeine prescriptions from 3 other physicians. I advised her that she had a habituation problem and offered to arrange urgent psychiatric consultation. She declined and I have not heard from her since.

Question.—How often are BCC used for migraine? Is their use a risk for medication overuse headache? What is known about the psychopathology of migraine patients who abuse butalbital?

EXPERT COMMENTARY

In a US survey of 9694 episodic migraineurs conducted in 2006, yearly usage and average days per month were as follows: BCC, 6%, 7.3; opioids, 11%, 9.7; and triptans, 18.7%, 5.8.[4] Among the 503 persons with chronic migraine surveyed, yearly usage and average days per month were as follows: BCC, 13.5%, 15.9; opioids, 21%, 18; and triptans, 21.9%, 9.8. In a tertiary headache clinic, 24% of patients with probable medication overuse headaches were taking BCC in 2005.[5]

About 2% of the American population suffers from chronic migraine, and about one-third overuse symptomatic medications.[6] The significant percentage of episodic migraineurs using BCC may be at risk for medication overuse as BCC are associated with migraine progression with a critical dose of exposure of around 5 days per month with the effect more pronounced in women.[7] As opiates are also associated with migraine progression, BCC containing codeine add to the risk.[8] The critical dose of exposure for opiates is around 8 days per month, and the effect is more pronounced in men.[7] BCC also contain caffeine and aspirin or acetaminophen with a possible association with medication overuse.[5]

Some of our patients like BCC a lot and may get prescriptions from multiple prescribers as in our case or through internet prescriptions.[9] (One internet site offers 90 tablets for $99.36 including the online physician consultation so a prior prescription is not needed.) Another common problem is "fiorinal fugax" where BCC "have an unusual propensity to fleeing or becoming lost in the manner of checks that are in the mail but never received . . . Many of these disappearances are dutifully reported to the physician on Friday night or during the weekend when a new prescription is requested." Interestingly, this rarely occurs with other medications. How often do you receive calls from patients that their antiepileptics, antihypertensives, or triptans were stolen or misplaced? Perhaps we should alert our patients to the risk of "Fiorinal fugax."[10]

Other than migraine pain relief, why do some migraineurs like BCC so much and do they have psychopathology? The short answer is that there is surprisingly little in the literature to answer this question, even though BCC have been prescribed for many years. An early National Institute on Drug Abuse monograph on sedative-hypnotic drugs has no mention of butalbital combination analgesics in their section on barbiturate abuse.[11] Studies of the efficacy and abuse profile of BCC are few and poorly controlled. The intrinsic abuse potential of BCC has not been systematically addressed.[12] One paper suggests that butalbital abusers have histories of multiple substance abuse and dependence as well as personality disorders. "These individuals are typically persistent and remarkably persuasive, often with antisocial personality disorder, who develop convincing stories and feign various illnesses to obtain medications from physicians."[13]

Two studies[14,15] have shown that comorbid psychiatric disorders are prevalent in medication overuse headache, and the onset of the psychiatric condition was likely to precede the onset of the medication overuse. Another study showed that migraine patients with coexisting borderline personality disorder were more likely to have more pervasive headache, more headache-related disability, less likelihood of responding to standard pharmacological therapies, and were more prone to medication overuse.[11,16]

In 1903, barbital was synthesized and found to have hypnotic potency. Under the trade name

Veronal, it became a popular sleep aid and also facilitated relaxation during the daytime. Some claim that its name derived from the peacefulness of the Italian town of Verona. Barbital had low lipid solubility and slow elimination and was followed by drugs with a shorter duration of action. It has been demonstrated that barbiturates having rapid onset of effect and shorter half-lives induce euphoria, reduce anxiety, and have a high abuse potential.[17] Butalbital has a rapid onset of action, duration of action of 3-6 hours, and a plasma half-life ranging from 19 to 88 hours, which may be shorter in drug abusing populations.[18] The pharmacokinetic profile is similar to the historically abused, secorbarbital and pentobarbital. One of the few headache studies showed that BCC provided significantly more relief of emotional tension and anxiety underlying tension headache than either acetaminophen/codeine or placebo.[19] It seems to relieve one dimension of headache impact, termed by some affective distress.[20]

The patient in this case cited a variety of stressors to justify her increased usage of BCC. Diary studies have shown significant correlations between daily stress and migraine.[21] Numerous epidemiologic and clinical research has confirmed elevated risk of anxiety and mood disorders in migraine as well as chronic daily headache.[22,23] Butalbital appears to be an anxiety reducer for this patient in the context of a headache disorder and numerous life stressors, which complicate the issue of drug overuse. BCC may decrease affective distress in patients who have acute or chronic problems with self-regulating negative emotional states. This self-calming deficiency often exists in dual psychiatric diagnosis patients where they have an Axis I mood and/or anxiety disorder as well as an Axis II personality disorder. However, these substances reduce anxiety in many patients without evidence of psychiatric disorder. These individuals often treat anticipatory anxiety related to feared stressors that could trigger migraine or physical sensations perceived as migraine prodromes.[24] The BCC reduces anxiety and "prevents" the migraine, a powerful conditioning process. They tend to escalate use somewhat compulsively, develop medication overuse daily headaches[25] and may develop tolerance and show symptoms of withdrawal including anger, when they need a refill. They often seek multiple prescribers as dependency progresses.

The BCC decrease affective distress in susceptible individuals, some with comorbid psychiatric issues and others with increased levels of life stress. In this population, they pose a high risk for drug dependence and abuse.

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