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Acute Psychosis Associated with Phenibut Ingestion

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INTRODUCTION

β-Phenyl-γ-aminobutyric acid (phenibut) is a glutamic acid analog that acts on the γ-aminobutyric acid receptors ($GABA_A$ and $GABA_B$) and B-phenethylamine receptors.[1] It has been used for anxiety, post-traumatic stress disorder, and insomnia, but it has not been approved by the U.S. Food Drug Administration (FDA) for use. Phenibut is advertised as a supplement and easily purchased from online retailers and has high abuse potential. Common adverse effects occur on abrupt withdrawal and may mimic neuroleptic malignant syndrome or serotonin syndrome.

We present a case of a man who presented with hallucinations and acute psychosis following ingestion of phenibut in combination with his usual prescriptions. This case highlighted the need for clinicians to become aware of potent pharmaceutical substances masquerading as supplements.

CASE REPORT

A 40-year-old man with a past medical history of anxiety, depression, hypertension, and substance abuse presented to the hospital via emergency medical services for agitation, auditory and visual hallucinations, and one episode of seizure-like activity. His mother provided most of the initial history due to the patient's altered mental status. She reported her son had experienced auditory and visual hallucinations for three to five days after taking phenibut, which he had ordered online. The patient also was taking hydroxyzine, gabapentin, and trazodone. Urine drug screen and alcohol level were negative on admission.

The patient became increasingly agitated and paranoid in the days leading up to the presentation. In the emergency department (ED), he became agitated and belligerent to a degree requiring intravenous lorazepam and physical restraints as re-orientation was ineffective. His speech was incoherent. He was shaking, profusely sweating, and tachycardic, with a pulse rate above 140 beats per minute. Due to a decreased Glasgow Coma Scale score, he required intubation in the emergency department for airway protection and sedation. He was placed on multiple sedative medications and was admitted to the intensive care unit (ICU).

Laboratory tests revealed elevated lactic acid of 9.1 mmol/L, creatine phosphokinase at 5,422 U/L, serum creatinine of 2.03 mg/dL, white blood cell count of 15,000/μL, which peaked on day two at 23,700/μL, and mildly elevated transaminase levels. His urinalysis on admission was positive for 3+ ketones and 2+ blood. The patient had no history of diabetes mellitus and did not have hyperglycemia. He was given empiric antibiotics in the emergency department and blood cultures were ordered. The patient was rehydrated, and his renal function was monitored. He remained sedated and on mechanical ventilation for two days in the ICU. He was agitated whenever sedation was weaned for sedation holiday each morning.

The patient was extubated on the third day of hospitalization as he was calm enough to cooperate with spontaneous breathing trials but continued to have intermittent episodes of agitation, which responded to scheduled quetiapine, as needed lorazepam, and dexmedetomidine. His mental status slowly normalized, and he was discharged on day six of hospitalization.

DISCUSSION

The U.S. Centers for Disease Control and Prevention reported a rapid increase in the use of phenibut from 2009 to 2019, and most of this use was driven by unregulated online sales.[1] This case highlighted some of the dangers of co-ingestion of phenibut with other pharmacologically similar drugs that potentially can enhance its effects. Our patient had co-ingestion of gabapentin and phenibut, which have very similar mechanisms of action, potentially enhancing the toxicity of phenibut. Like other reported cases,[2] our patient experienced significant agitation. As in this case, standard urine drug screens do not detect phenibut.

Phenibut was synthesized in St. Petersburg, Russia, in the 1960s.[3] The compound's effects on $GABA_A$, $GABA_B$, dopaminergic, and benzodiazepine receptors were compared to diazepam and a related compound, piracetam. The chemical structure of phenibut results from combining GABA with a phenyl ring with the expectation that this would facilitate blood-brain barrier permeability. Though chemically similar to GABA, phenibut has no activity at the $GABA_A$ receptors and has a lower affinity to $GABA_B$ than the related compound baclofen.

In addition to binding $GABA_B$ receptors, phenibut also has activity on α2δ1 voltage-dependent calcium channels (VDCC), like gabapentin. The R isomer of phenibut acts on $GABA_B$ receptors with a lower affinity than baclofen, while the S isomer has no activity at the $GABA_B$ receptors.[4] Both R and S isomers of phenibut bind with similar affinities to the α2δ1 VDCC. R phenibut binds to the α2δ1 VDCC with a higher affinity than the $GABA_B$ receptor.[5] Though it has a similar mechanism of action as gabapentin, it does not possess anticonvulsant activity. This may be due to gabapentin having activity on α2δ2 VDCC while phenibut does not.[6,7]

Phenibut has a half-life of approximately 5.3 hours, is not metabolized, and is excreted unchanged in the urine.[2] Clinical trials in Russia have reported phenibut activates intellectual functions, improves physical strength, motivates activity, and reduces asthenia and tiredness. Phenibut is an anxiolytic and a nootropic agent and is used to treat neurologic and psychiatric disorders.[3,8]

Phenibut is a widely available pharmaceutical that has generated other case reports due to its toxidrome.[9,10] The U.S. FDA does not regulate phenibut, and its abuse appears to be rising. Cases reported to poison control centers became significant around 2015 and peaked in 2018. There are 56 reported exposures in the U.S., 48 of which occurred in the last five years.[11]

Commonly reported adverse effects include lethargy, agitation, tachycardia, confusion, and coma, and several phenibut-related deaths

have been reported.[1] Acute intoxication results in central nervous system depression, decreased muscle tone, and stupor. Paradoxically, this may present as hallucinations, seizures, and agitation.[2] Chronic use of phenibut causes downregulation of $GABA_B$ receptors, and discontinuation would explain the toxidrome noted in our patient case. Acute withdrawal may be difficult to differentiate from serotonin or neuroleptic malignant syndrome, however, hyperreflexia has not been reported to be a symptom of phenibut intoxication or withdrawal. There are cases where a baclofen taper was used to treat withdrawal in those who develop a substance abuse disorder.[12] Phenibut is excreted in the urine, thus it may be possible to treat intoxication with hemodialysis. However, studies would have to be done to prove efficacy.

CONCLUSIONS

Though clinical trials reported benefits of phenibut, therapeutic doses are unknown. Toxicity from phenibut is treated with supportive care or a baclofen taper until symptoms resolve. The patient was safely discharged home after six days of hospitalization without any sequelae. With an increase in cases in recent years, ingestion of unregulated psychotropic agents needs to be high in the differential diagnosis in cases of psychosis or other psychiatric concerns. Phenibut is advertised as a supplement and easily purchased from online retailers. This case highlighted the need for clinicians to become aware of pharmaceuticals masquerading as supplements.

REFERENCES

[1] Graves JM, Dilley J, Kubsad S, Liebelt E. Notes from the field: Phenibut exposures reported to poison centers - United States, 2009-2019. MMWR Morb Mortal Wkly Rep 2020; 69(35):1227-1228. PMID: 32881852.
[2] Hardman MI, Sprung J, Weingarten TN. Acute phenibut withdrawal: A comprehensive literature review and illustrative case report. Bosn J Basic Med Sci 2019; 19(2):125-129. PMID: 30501608.
[3] Lapin I. Phenibut (beta-phenyl-GABA): A tranquilizer and nootropic drug. CNS Drug Rev 2001; 7(4):471-481. PMID: 11830761.
[4] Blackburn T. (Ed.) GABAb Receptor Pharmacology: A Tribute to Norman Bowery. San Diego: Academic Press, 2010. ISBN: 9780123786470.
[5] Zvejniece L, Vavers E, Svalbe B, et al. R-phenibut binds to the α2-δ subunit of voltage-dependent calcium channels and exerts gabapentin-like antinociceptive effects. Pharmacol Biochem Behav 2015; 137:23-29. PMID: 26234470.
[6] Sills GJ. The mechanisms of action of gabapentin and pregabalin. Curr Opin Pharmacol 2006; 6(1):108-113. PMID: 16376147.
[7] Taylor CP. The biology and pharmacology of calcium channel alpha2-delta proteins Pfizer Satellite Symposium to the 2003 Society for Neuroscience Meeting. Sheraton New Orleans Hotel, New Orleans, LA November 10, 2003. CNS Drug Rev 2004; 10(2):183-188. PMID: 15317151.
[8] Gol'dblat IuV, Lapin IP. [Phenibut potentiation of the therapeutic action of antiparkinson agents.] [Russian] Zh Nevropatol Psikhiatr Im S S Korsakova 1986; 86(8):1146-1148. PMID: 3776387.
[9] Sankary S, Canino P, Jackson J. Phenibut overdose. Am J Emerg Med. 2017; 35(3):516.e1-516.e2. PMID: 27666756.
[10] Downes MA, Berling IL, Mostafa A, Grice J, Roberts MS, Isbister GK. Acute behavioural disturbance associated with phenibut purchased via an internet supplier. Clin Toxicol (Phila) 2015; 53(7):636-638. PMID: 26114346.
[11] McCabe DJ, Bangh SA, Arens AM, Cole JB. Phenibut exposures and clinical effects reported to a regional poison center. Am J Emerg Med 2019; 37(11):2066-2071. PMID: 30878413.
[12] Ahuja T, Mgbako O, Katzman C, Grossman A. Phenibut (β-phenyl-γ-aminobutyric acid) dependence and management of withdrawal: Emerging nootropics of abuse. Case Rep Psychiatry 2018; 2018:9864285. PMID: 2985431.

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