Zopiclone Intoxication: Value of Electroencephalography in the Emergency Room

Clemens Bloetzer^a Antonio Carota^a Marc Augsburger^b Paul-André Despland^a
Andrea O. Rossetti^a

^aService de Neurologie, ^bInstitut Universitaire de Médecine Légale, Centre Hospitalier Universitaire Vaudois, Lausanne, Suisse

Dear Sir,

Patients with new-onset stupor represent a common challenge in the emergency room. When etiology remains undetermined on the basis of clinical examination, neuroimaging, blood and urine workup, further investigations are mandatory. The following observation illustrates how electroencephalography (EEG) may point to the diagnosis of drug toxicity, even when results of standard toxicological urine immunoassays are negative.

Case Report

A 26-year-old man, known for personality disorder and previous depression, was admitted to the emergency department because of unusual profound sleepiness in the morning (arousal only for few seconds following intense stimulation). Although he was known to take zopiclone occasionally for insomnia, his girlfriend categorically denied illicit drug or medication ingestion in the last 48 h. Apart from stupor, neurological examination did not reveal any pathological findings; his pupils were slightly mydriatic and reactive. Hematology, blood electrolytes, renal and hepatic tests, glucose, C-reactive protein, thyroid function, blood ammonium and CSF analysis were unremarkable; thiamine administration was uneventful.

Standard urine toxicological immunoassays for benzodiazepines, barbiturates, cannabinoids, opiates, methadone, cocaine, buprenorphine, propoxyphene, LSD and amphetamines were negative; serum ethanol level was undetectable. There were no abnormal findings on brain CT with perfusion and venous angiography. EEG on admission showed essentially normal-structured sleep stage II, with symmetrical spindles and K complexes; following nociceptive stimulation, a poorly sustained α -rhythm appeared; during the whole recording, abundant, diffuse superimposed β (fast)-activity was noted (fig. 1a). A flumazenil test was not performed to avoid provoked seizures.

Stupor recovered spontaneously within 24 h, and a second EEG 6 days later was normal, with minimal superimposed fast activity (fig. 1b). Considering these EEG findings, we performed a serum gas chromatography/mass spectrometry and liquid chromatography UV on the serum sample drawn on admission; this revealed a toxic level of zopiclone (250 $\mu\text{g/l}$; norm <100 $\mu\text{g/l}$ [1]).

Discussion

This report highlights the value of EEG performed emergently in diagnosing drug

toxicity when the routine workup is inconclusive. In fact, prominent EEG β -activity suggested the presence of a GABA-ergic drug and prompted further diagnostic procedures.

Abundant fast EEG activity entails a broad differential diagnosis: commonly, it results from GABA-ergic agents (benzodiazepines, barbiturates, low-dosed propofol and isoflurane) or other drugs (ethanol, cocaine, opiates, tricyclic antidepressants, high-dosed chloral hydrate). However, it may be also rarely observed with fever, hyperthyreosis, brain stem lesions or migraine [2, 3]. In exceptional circumstances, diffuse β -EEG activity might be compatible with recurrent idiopathic stupor, a rare disorder characterized by sleep periods lasting hours to days. Etiologically, acute accumulation of endogenous ligands (endozepines) to the brain benzodiazepine GABA receptor is postulated [4–7].

Zopiclone is a nonbenzodiazepine hypnotic acting through GABA_A receptor modulation, whose effects on human EEG have been described only following therapeutic administration to healthy volunteers. Two studies showed an increment of slow-wave sleep that was more consistent than with benzodiazepines [8, 9], whereas

Fig. 1. a EEG during brief wakefulness on admission, with diffuse 16- to 18-Hz β superimposed on poorly sustained 10- to 12-Hz posterior α . Stage II sleep disclosed abundant spindles and persistent β -rhythms. (Longitudinal bipolar 'long distance' montage, 70 μ V/cm, 30 mm/s, HFF 70 Hz, LFF 0.5 Hz.) **b** EEG during wakefulness 6 days after admission, showing a well-developed, low-voltage 12-Hz α -activity, but almost no superimposed β . (Longitudinal bipolar 'long distance' montage, 70 μ V/cm, 30 mm/s, HFF 70 Hz, LFF 0.5 Hz.)

wakefulness EEG displayed α -activity decrease and β -activity increase [9]. Our report shows that diffuse β -EEG activity represents a prominent feature of zopiclone intoxication, in analogy with benzodiazepines.

As prescription of atypical GABA-ergic agents is gaining in popularity, the diagnosis of related toxicity may challenge emergency physicians. In fact, standard urine immunoassays, which are commonly available in emergency rooms, are not sensitive to these drugs (zopiclone, zolpidem), as well as lorazepam and bromazepam [10]. This observation shows that in these circumstances EEG represents a useful, noninvasive tool to orient early diagnostic procedures.

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