Endozepine Stupor: Disease or Deception? A Critical Review

Ron Granot1; Samuel F Berkovic, MD2; Scott Patterson; Malcolm Hopwood, MD3; Olaf H. Drummer, PhD4; Rod Mackenzie, MD

1Institute of Neurological Sciences, Prince of Wales Hospital; 2Epilepsy Research Institute, Department of Medicine (Neurology), University of Melbourne; 3Department of Psychiatry, University of Melbourne; 4Victorian Institute of Forensic Medicine, Australia

Abstract: Presentation of patients with recurrent stupor associated with apparently elevated levels of an endogenous benzodiazepine-like agent, endozepine-4, has been reported from several centers, and a new syndrome, endozepine stupor has been proposed. We recently reported a case with typical features of this syndrome, which proved to be an example of surreptitious administration of exogenous benzodiazepine. This and other examples of clandestine drug use, together with uncertainties about the validity of tests used to distinguish exogenous and endogenous benzodiazepines, prompted us to undertake a reappraisal of this clinical syndrome.

Key Words: coma, recurrent stupor, idiopathic stupor, Munchausen syndrome by proxy, benzodiazepine, endozepine.

Citation: Granot R; Berkovic SF; Patterson S et al. Endozepine stupor: disease or deception? A critical review. SLEEP 2004;27(8):1597-9.

INTRODUCTION

RECURRENT STUPOR IS A COMMON NEUROLOGIC PROBLEM AND IS USUALLY DUE TO SEIZURES, INTOXICATIONS, SLEEP DISORDERS, OR METABOLIC ENCEPHALOPATHIES.1 Idiopathic recurrent stupor associated with elevated levels of an endogenous benzodiazepine-like agent was first described by the Balogna group,2-4 and they then published a definitive study of 20 patients with the condition from all parts of Italy.5 The cases comprised 16 men and 4 women; the age range was 24 to 69 (mean 50.6) years. There was no diurnal pattern of presentation, and onset was not related to activities of daily living or to psychological factors. The altered state of consciousness had persisted for 2 to 120 hours. Patients could have fairly frequent episodes (> 6 per year) or rare attacks (1-6 per year). In nine patients, the episodes had disappeared spontaneously 2 to 6 years previously, after 1 to 6 years of recurring episodes. At the time of onset of the stuporous episodes, all patients were in good mental and physical condition, and none were receiving medical treatment. No patient had a previous history of psychiatric disorder, and there was no family history of sleep disorder. Blood, urine, and cerebrospinal specimens were taken and were unremarkable during all instances of stupor. Blood oxygen always remained normal (O2 saturation > 90%), even in those patients with some evidence of respiratory disease. Brain structural studies were normal during and between attacks. Urine immunoassays and blood gas-chromatography mass spectrometry (GCMS) were negative for benzodiazepines, barbiturates, tricyclic antidepressants, ethanol, opiates, and cocaine. The electroencephalogram (EEG) was normal between attacks but, during altered consciousness, was characterized by diffuse low-amplitude unreactive activity with a peak at 13 to 16 Hz. Intravenous administration of 0.5 to 2.0 mg flumazenil, a benzodiazepine antagonist, under EEG monitoring, led to a transient reappearance of 8- to 12-Hz EEG alpha activity associated with behavioral awakening or arousal; however, this reversal lasted only 10 to 15 minutes. Intercital polygraphy showed normal sleep patterns. Daytime somnolence, measured by the Multiple Sleep Latency Test, was normal in 17 and borderline in 3 cases. The investigators reported that high-performance liquid chromatography (HPLC) showed an elevation of serum and cerebrospinal fluid levels of endozepine-4, an endogenous ligand for the benzodiazepine recognition site of the γ-aminobutyric acid (GABA)-A receptor.6,7 Between attacks, serum (9 subjects) and cerebrospinal fluid (4 subjects) HPLC endozepine-4 levels were no different from controls, but they rose to more than 4000 times normal (cerebrospinal fluid ) and 20,000 times normal (serum) during episodes of stupor. The investigators thought that such cases, which they had originally termed idiopathic recurrent stupor, constituted a novel though not so rare syndrome that they now prefer to call endozepine stupor. The condition has also been reported in the elderly8 and in children.9 There have been 2 cases reported outside Italy,10,11

COVERT BENZODIAZEPINE ADMINISTRATION

In late 1998, the same Balogna group12 reported 9 patients presenting with recurrent stupor, which proved to be due to exogenous benzodiazepine administration. The patients had all presented over a short period of time to hospitals in a restricted rural area of Tuscany. Except for the extraordinary clustering in time and space, these patients were similar to the sporadic cases. They had the same clinical picture and EEG pattern during stupor and a reversal of these states after flumazenil administration. Again, toxicologic immunoenzymatic tests failed to detect even traces of synthetic benzodiazepines. However, since the original report, a newer more specific toxicologic assay, liquid-chromatography mass spectroscopy (LCMS) had become available, and this test detected lorazepam in the blood of all the Tuscan patients. The investigators diagnosed fraudulent lorazepam intoxication in these patients and excluded an endogenous benzodiazepine (endozepine) origin of the stupor. It was conceded that the chemical tests used to exclude exogenous benzodiazepines in the orig-
inal cases had been imperfect and “the endozepine origin of the stuporose episodes in previously reported patients...should be considered as still unproven.”

OTHER CASES

Since 1998, there have been only 2 more case reports relevant to this condition. French investigators13 reported a patient with typical features of endozepine stupor who had been prescribed zolpidem, a nonbenzodiazepine hypnotic for insomnia, prior to presenting with 5 episodes of stupor over a 5-month period. The search for poisons, including benzodiazepines, was negative and HPLC was biologically normal. Although these authors were suspicious that an exogenous poison may have been involved and raised some doubts about the authenticity of endozepine stupor, they ultimately concluded that “an endogenous intoxication” was likely. The episodes ceased spontaneously.

We reported14 the case of a 71-year-old man with a 16-year history of recurrent episodes of stupor and coma. The diagnosis of endozepine stupor was regarded as secure over many years (2 positive toxicologic assays were attributed to prescribed benzodiazepine) until upon further inquiry, the patient’s wife admitted administering lorazepam to her husband, causing his episodes of stupor and coma. This was thus an adult example of Munchhausen syndrome by proxy (MSP).

BENZODIAZEPINE DETECTION

In cases of benzodiazepine intoxication where the subject or other perpetrator denies the use of these drugs, the absence of benzodiazepines on a routine “drug screen” may falsely reassure the clinician. There are a number of benzodiazepines that are very difficult to detect using conventional techniques such as immunoassay screening, GCMS and HPLC. These include triazolam and bromazepam, as well as lorazepam; this last substance is the only 1 known to chromatograph in the vicinity of endozepine-4, although other substances may do so. Nonbenzodiazepines such as zopiclone, zolpidem, and zaleplon are ω1 specific to GABA-A receptor; they will cause sedation in the same way as conventional benzodiazepines, but thin-layer chromatography cannot reliably detect these substances.

The initial and subsequent reports of endozepine stupor all used immunoassay, GCMS, and HPLC. These methods are now known to show false-negative results in the presence of certain benzodiazepines, especially lorazepam, and fail to distinguish lorazepam from endozepine-4.15 The Balagna group12 subsequently used LCMS to identify the surreptitious administration of lorazepam in cases initially suspected of having endozepine stupor. This technique and other more sophisticated GCMS techniques are required to detect low concentrations of benzodiazepines.16

ENDOZEPINES

Studies in a number of vertebrate species have established the presence of a family of peptides, which have become known as endozepines. They are widely distributed, especially in glial cells in the central nervous system—in particular cerebellum, amygdala, hippocampus, hypothalamus, and substantia nigra—and are evenly distributed in the spinal cord.17 They act via the GABA-A receptor.18-21 They are also found in peripheral organs, in particu

ular liver, kidneys, adrenal glands, and testis.17,22 They are thought to have various neuroregulatory functions.22,23 It has been suggested that the high affinity of endozepine-4, like synthetic benzodiazepines, for the GABA-A receptor might explain its apparent ability to induce coma.5 Similarly, its affinity for the hippocampal GABA receptors might explain the prominent disturbances of memory that has been observed in patients with recurrent stupor.

However, experimental work has shown that the effects of the endozepines are mediated not only through central benzodiazepine receptors, but also through peripheral-type receptors and a metabotropic receptor.20,23,24 Furthermore, intracerebroventricular injection of endozepines in rodents promotes opposite physiologic effects to diazepam, including anxiogenic effects,25 proconflict behavior,26 and both anxiety and depression27 in rats or no change in pigs28; it has also been shown to reverse the anti-conflict action of diazepam.29 These behavioral data suggesting endozepines may act as inverse agonists on central-type benzodiazepine receptors are now supported by biochemical animal work.30 It has even been shown that endozepines reduce the hypnotic action of pentobarbital in mice.31 There are no examples in animal or human literature of tumors or other pathologic states causing an alteration in levels of endozepine or any alteration in clinical status. These facts raise uncertainties about the likelihood of elevated endozepine levels causing stupor.

COULD MSP EXPLAIN ENDOZEPINE STUPOR?

MSP involves the deliberate exaggeration, fabrication, or induction of physical or psychological symptoms in others. It usually involves an adult, most commonly the parent, perpetrating the act on a child.32-35 However, MSP involving adult victims does occur, and we have found 5 previous examples in the literature of adult MSP involving conditions other than benzodiazepine administration.36-40 Patients in the original Balagna series were adults from all parts of Italy with no family history of recurring stupor and no history of psychiatric disorders; social and psychiatric factors were not detailed in other case reports of endozepine stupor. The ages and social circumstances of the 9 cases that are known to be fraudulent12 were not given; however, the fact that these presentations occurred in a restricted rural area in Tuscany raises the possibility that they were examples of learned behavior.

Little follow-up has been given in these or other reports. No deaths have been reported, consistent with the benign prognosis of benzodiazepine intoxication.

CONCLUSION

The clinical and biochemical similarities between cases of endozepine stupor and exogenous benzodiazepine administration, the difficulty in conclusively ruling out the involvement of exogenous benzodiazepines, and uncertainties about the pathophysiologic role of the endozepines, all make it more likely that most if not all of these cases are due to exogenous drug administration. This may well include further examples of MSP. In our opinion, the concept of endozepine stupor, on current evidence, cannot be sustained.
REFERENCES