

Over Sedation After Mirtazapine Ingestion and a Workup in a Comatose Patient: A Case Report

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Received: September 25, 2019; **Published:** October 17, 2019

Abstract

Background: Altered mental state represents 5% and coma represents 1% of all admissions to the emergency department. The management starting from history till to the cranial CT or magnetic resonance imaging (MRI) basically depends on the identification of the reason and the group of the coma at the first step. Mirtazapine, as a new generation anti-depression agent, is claimed to be more tolerable than other antidepressant agents with less incidence of neurological, cardiac and anticholinergic side effects. In this case report, we presented a challenging case of deteriorating consciousness from stupor to coma without any documentable reason except mirtazapine overdose.

Case Report: A 67-year-old man was admitted to the ED with altered consciousness. The history and physical examination were nonspecific while laboratory and radiologic examinations could not specify any abnormality. His GCS was 6 at admission and he was intubated and admitted to ICU. He was monitored and supported in the ICU and by day 4 of hospitalization, he recuperated consciousness and became alert with GCS 9E.

Discussion: One of the main reasons of coma is poisoning or drug intoxications while the in-hospital mortality rate was lower than the other causes. The management algorithm is nearly identical in most centers and ICU's starting from oxygenation and ending with specific antidotes. Mirtazapine which is a tetracycline antidepressant is considered as an alternative treatment for the resistant cases and it was found safer than older antidepressants with 3.1 deaths/million prescriptions with lower fatal toxicity index. Although in higher doses insomnia-noradrenergic effect becomes more dominant than antihistaminergic effect- is the expected adverse effect, in our patient's case it causes over sedation. We did manage our patient in a stepwise manner and in line with algorithms described by Plum and Posner. A full recovery was managed after supportive care and close hemodynamic monitoring.

Keywords: Mirtazapine; Coma; Overdose; Over Sedation

Abbreviations

ED: Emergency Department; ICU: Intensive Care Unit; GCS: Glasgow Coma Score; CT: Computer Tomography; 5-HT: 5-hydroxytryptamine

Introduction

Structural and nonstructural brain disorders like intracerebral hemorrhage, anoxic brain injury, metabolic encephalopathy, encephalitis, and drug or ethanol intoxications may cause neuronal dysfunction leading deterioration in alertness and consciousness [1]. Altered consciousness is a critical entity which requires urgent judgment making upon admission at the emergency department (ED) or intensive care unit (ICU). It is challenging for intensivists due to etiological variety and a high rate of morbidity and mortality unless

managed effectively. The altered mental state represents 5% and coma represents 1% of all admissions to the emergency department [2]. Mainly Glasgow Coma Score (GCS) is utilized to determine the level of consciousness and point 8 is generally accepted as cut-off point to refer as coma. According to the etiology, the clinical entity of coma is divided mainly two groups; traumatic coma and non-traumatic coma [3]. Another classification is done according to the cranial computer tomography (CT) findings and the groups are structural and non-structural causes. The management starting from history till to the cranial CT or magnetic resonance imaging basically depends on the identification of the reason and the group of the coma at the first step. Cerebral infarction, encephalitis, and intracranial hemorrhage are main structural coma reasons while non-structural coma is including anoxic or metabolic encephalopathy, poisoning and extracranial infections [4].

Mirtazapine, as a new generation anti-depression agent, blocks central alpha 2 adrenergic receptors and this obstruction increases serotonergic and noradrenergic neurotransmission which is the mechanism for the antidepressant effect [5]. Approximately 3 hours after single oral doses of 15-75 mg the plasma concentration peaks and the mean elimination half-life is 22 hours. The increment of serotonin levels (5-hydroxytryptamine; 5-HT) only stimulates 5-HT-1 receptors while 5-HT-2 and 5-HT-3 are blocked by mirtazapine [4]. It also blocks peripheral and central histamine receptors and this blockade is accused of sedation effect as well as serotonergic activity [6]. The clinical efficacy of mirtazapine is like those of other currently available antidepressants like amitriptyline and clomipramine. It is claimed to be more tolerable than other antidepressant agents with less incidence of neurological, cardiac and anticholinergic side effects [7]. The main adverse effects of mirtazapine are sedation beyond measure, drowsiness and dry mouth and the less frequent ones are increased appetite and body weight gain. Overdose with mirtazapine was related to excessive sedation but this was reported as a transient effect [8,9].

Case Report

A 67-year-old man was admitted to the ED with altered consciousness. He was found lying unconscious on the ground by his relatives and the last time they saw him was 16 hours earlier. They witnessed that he took only one glass of alcohol and later went to sleep. No tablet found close to the patient but he had been medicated mirtazapine 30 mg for depression and sleep disorder-insomnia for 5 days and his relatives claimed that half of the box- total 28 tablets- was full one day before and empty when they found him (total 420 mg). But they were not sure if he ingested the remaining ones. No empty drug boxes other than mirtazapine was found but he had been treated with alprazolam before. His medical history was noteworthy for congestive heart failure and atrial fibrillation which was managed with metoprolol 50 mg, acetylsalicylic acid 100 mg and implantable cardioverter-defibrillator, diabetes mellitus, treated with metformin 1000 mg, and hyperlipidemia, treated with atorvastatin 20 mg.

His blood pressure was normal (110/62 mmHg) with heart rate 110 beats per minute while his GCS was 6 (E2, M3, V1) at admission. Pupils were equal and myotic and there was no evidence of myoclonus, muscle rigidity, infection or trauma. At the same time, he was intubated and underwent mechanical ventilation support with 40% FiO₂ and 5 cm H₂O positive end-expiratory pressure (PEEP) as his clinic was deteriorated in the emergency department. The GCS declined to 2E (E1M1VE) 6 hours after admission and pupils were anisocoric. The cranial CT examination revealed no pathology and the electroencephalographic examination was normal. To rule out central nervous system infections and increased intracranial pressure lumbar puncture was performed and the pressure was detected as normal. The cerebrospinal fluid was assessed in the laboratory and no abnormality was detected. The complete blood count and serum chemistry values were normal including the electrolyte levels. We strongly suspected the ingestion of that amount of mirtazapine while both the urine toxicology and serum screening of drug intoxications were negative including alcohol level.

In the aspect of management of our comatose patient Thiamine (100 mg I.V.) was administered following 5% dextrose solution. The other possibility was benzodiazepine overdose and we gave Flumazenil I.V. (with 3 sequential bolus injections and total 1 mg) to rule out this but no positive reaction was seen the patient at all. The patient's medical history was including congestive heart failure treated with implantable cardioverter-defibrillator besides medical therapy. After cardiology consultation the charts and the events were analyzed from the data of implantable cardioverter-defibrillator device and no pulseless ventricular tachycardia or ventricular fibrillation was detected. There was no abnormality or hypoxic change in the control cranial CT 24 hours after admission. No sedation was given in the

ICU process, but his consciousness was not ameliorating. By day 4 of hospitalization in the ICU he recuperated consciousness and became alert with GCS: 9E (E4M5VE). He was weaned from mechanical ventilator support the next day and transferred to the ward for further observation.

Discussion

In this case report, we presented a challenging case of deteriorating consciousness from stupor to coma without any documentable reason except mirtazapine overdose. As far as we investigated, there were a few clinical papers reporting mirtazapine usage and altered consciousness. The altered states of consciousness are defined differently by diverse authors with different terms while stupor and coma are the most used and the most agreed terms in definition. Simply awakens with painful stimuli is defined as stupor and if no reaction is observed it is defined as coma. In terms of scoring systems, GCS less than 9 is defined as coma and GCS between 9 and 12 is defined as stupor [1]. Horsting, et al. [2] claimed that stroke (ranging from 6 to 54%), post-anoxic coma (ranging from 3 to 42%), poisoning (ranging from 1 to 39%) and metabolic reasons (ranging from 1 to 29%) are the most common reasons for non-traumatic coma while there was a wide range of the prevalence in different studies. One of the main reasons of coma is poisoning or drug intoxications and besides its high prevalence in some studies (up to 39%), the in-hospital mortality rate was lower than the other causes [10]. Not only the underlying disorder that leads to coma but also the coma itself is fatal since comatose patients could not protect the airway patency and aspiration pneumonia is frequent. The management algorithm is nearly identical in most centers and ICU's starting from oxygenation and ending with specific antidotes [11].

Mirtazapine which is a tetracycline antidepressant is considered as an alternative treatment for the resistant or intolerant cases to the other classes of antidepressants. The main adverse effects of mirtazapine are the increase of appetite and sedation and they are even requested by the patients [12]. Mirtazapine was found safer than older antidepressants with 3.1 deaths/million prescriptions with lower fatal toxicity index [13]. Over sedation and loss of consciousness were reported in lower doses- 7.5 mg- of mirtazapine and especially in the beginning period of treatment. It eventually subsides with time - 10 days after initiation- and accumulating doses [14] whereas in our case we suspected that higher dose cause somnolence and stupor. This relation was verified in a study and negative correlations between mirtazapine dose and prolonged sleep time was demonstrated [15]. Although in higher doses insomnia-noradrenergic effect becomes more dominant than antihistaminergic effect- is the expected adverse effect [12], in our patient's case it causes over sedation. Unfortunately, we could not prove this estimation due to lack of the knowledge of exact serum level of mirtazapine at admission. There were also reports presenting the relation between mirtazapine overdose and somnolence and even death, but they were few [16,17].

The management of mirtazapine overdose includes mainly supportive care and hemodynamic monitoring [8]. Since in our case the latent period from ingestion to admission was unclear and probably longer than 120 minutes, gastric lavage was not advised by the poison control center and not performed. We did manage our patient in a stepwise manner and in line with algorithms described by Plum and Posner [11]. A full recovery was managed after supportive care and close hemodynamic monitoring.

Conflict of Interest

There is no financial interest or conflict of interest to declare.

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Volume 3 Issue 11 November 2019

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