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Case report on melatonin overdose: Cause and concern

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A B S T R A C T

Melatonin, the primary hormone secreted by the pineal gland, regulates central and peripheral oscillators and adapts the internal environment to the external one through MT1 and MT2 receptors. The authors present a case of 16-year-old male intentionally overdosed on 900mg of melatonin (180 tablets) and 10 tablets of 0.5mg alprazolam. Admitted to the emergency department, he was extremely drowsy and minimally responsive with a Glasgow coma scale score of 8/15. Vital signs were stable, and no renal or liver dysfunction was noted. Elevated total leucocyte count and positive benzodiazepine urine test were observed. Gastric lavage was performed, and toxicology reports showed blood alprazolam levels at 0.15 mg/litre eight hours post-overdose. The patient regained consciousness 32 hours post-ingestion and was transferred to the psychiatry unit. This case underscores the increasing abuse of melatonin due to its easy availability and lack of regulation. Although melatonin has a low toxicity potential, side effects and interactions with other drugs can be severe. Supportive measures and vital sign control are crucial in overdose treatment.

1. Introduction

Melatonin or 5 methoxy-*N*-acetyl tryptamine is the main hormone secreted by the pineal gland. It plays a major role in the regulation and synchronization of central and peripheral oscillators. It also has a role in harmonious internal functioning and adaptation of our internal environment to the external environment through its action on MT1 and MT2 receptors [1]. Melatonin synthesis and secretion are enhanced by darkness. Its synthesis starts soon after sunset, reaches a peak in the middle of the night (between 2 and 4 in the morning), and decreases slowly during the second half of the night [2].

Melatonin is widely used as a nutraceutical. It is primarily recognized for its role as a chronobiotic and for its ability to promote healthy sleep [2]. Exogenous melatonin is used in shift workers, people with jetlag, and delayed sleep-wake phase disorder [3].

It acts on G-protein coupled receptors which are distributed throughout the body. The effect includes alterations in immune response and blood pressure, regulation of the cell cycle, and antioxidant protective properties. Melatonin is metabolized primarily by the liver through the use of cytochrome CYP1A2 [4]. The serum concentrations and bioavailability of melatonin are dependent on concomitant drug use. It is both lipid and water-soluble, so can easily cross lipid membranes such as the blood-brain barrier [5]. A level of 1.4mg/L has been published as lethal for children, however, there is currently no literature that reports a lethal range of melatonin in adults [6].

It is easily available as over-the-counter medication and through online shopping applications without the need for a prescription, thus making it readily accessible to patients. Multiple formulations of melatonin are available, with no clear recommendations for dosing or administration [7]. Limited data exist on the adverse effects and toxicology of melatonin in the literature. The present case discusses melatonin overdose in an adolescent patient.

2. Case description

The patient, a 16-year-old adolescent male, was brought to emergency department by his parents with complaints of intentional overdosing with 900mg of Melatonin (180 tablets of 5mg of melatonin) along with consumption of benzodiazepines (BZD) i.e. 10 tablets of 0.5mg of alprazolam (50mg diazepam equivalent). Attempted suicide was suspected as the medications were brought via an online shopping site without prescription. Parents found him after 6h of overdose, in an abnormally sleepy state. He was rushed to the emergency and had two episodes of vomiting before reaching to hospital.

At the time of admission to emergency department, he exhibited extreme drowsiness and was minimally responsive. His Glasgow coma scale score was 8/15. Pupils were normal and reactive to light. Blood pressure was 110/72 mm Hg, pulse rate 86/minute, respiratory rate 12/min, temperature 95.7F, sPO2 98 % at room air and random blood sugar was 85mg/dl. The patient's weight was 50kg, height 165cm, and BMI 18.5kg/m^2. The patient had no renal or liver dysfunction. Plasma analyses revealed no changes in urea (16.7mg/dl), creatinine (0.55mg/dl), uric acid (4.89mg/dl), total bilirubin (0.83mg/dl), SGOT (28.4mg/dl) and SGPT (29.3mg/dl). Total leucocyte count was elevated (11030/

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microlitre). The arterial blood gas analysis revealed pH of 7.4, PCO2-38.0 mmHg, PO2-98.3 mmHg, serum sodium- 140.2mmol/L, serum potassium-3 mmol/litre and HCO3-24.1mmol/L. Further physical examination revealed no abnormalities. His electrocardiogram showed normal sinus rhythm. Gastric lavage was performed immediately using normal saline. Blood and urine samples were taken for toxicology investigation. The urine cassette test was positive for benzodiazepine. After 8h of overdose, the blood levels of alprazolam were 0.15mg/L 10 Hours after admission the patient was shifted to the pediatrics unit. Patient was kept under observation with 2 hourly vital monitoring. He regained consciousness after 32h of the ingestion of melatonin along with benzodiazepines (alprazolam) and was then transferred to psychiatry unit for detailed evaluation.

The patient was a student and had no relevant past medical or psychiatric history and belonged to lower socioeconomic status with significant family conflict. There was family history of obsessive-compulsive disorder in father. The current psychiatric assessment revealed active suicidal ideation and a potential underlying psychiatric condition which led to intentional overdosing. The Brief Psychiatry Rating Scale (BPRS) [8] score was 40/126 and Intensity of Ideation score on Columbia suicide severity rating scale(C-SSRS) [9] was 22/25 indicating psychosis and active suicidal ideation. He was started on antipsychotics and lithium. He was discharged in a clinically stable condition and was advised for regular follow ups.

3. Discussion

Melatonin acts as an “internal sleep facilitator” and promotes sleep due to its "hypnotic" effect. It is considered as a chronobiotic molecule, i.e. a substance that reinforces oscillations or adjusts the timing of the central biological clock located in the suprachiasmatic nuclei of the hypothalamus to stabilize bodily rhythms [10]. Circadian rhythms can be altered in terms of their three main components (i.e., period, amplitude, and phase) by a variety of stimuli that include light, non-photic stimuli, and a plethora of chemical perturbations that can influence the biological clock. In the presence of time cues, the biological clock and rhythms are adjusted to an exact 24-h period. In humans, the biological clock is maintained mostly by the light/dark cycle which is perceived by the visual pathways. However, the rhythmic release of the hormone melatonin is also of utmost importance. The normal levels of melatonin are typically less than 0.0001mg/L during daytime and up to 0.0009 mg/L at peak time which occurs around 3–4 **a.m.** [6]. This basal fluctuation is negligible in cases of overdose and there is currently no comparable literature that delineates the average changes [6].

Melatonin is not an FDA-regulated drug; therefore, the effective dose range is not well defined and the dose range varies from 0.5 to 10mg [7]. After oral administration, the plasma concentration peak arises within 60 min. It may cause minor adverse drug reactions, such as headache, insomnia, rash, gastritis, and nightmares at supraphysiological doses. Melatonin appears to have a favourable safety profile, however, there is a dearth of evidence regarding the same [11,12]. Our case, provides evidence that acute intoxication with melatonin even at a dose, as high as 900mg, did not produce any severe adverse effects (patient was vitally stable and only sedation was reported).Regarding its chronic administration at 1000mg daily in adults, no toxicity was seen as reported by Cuesta et al. [13].

When consumed along with benzodiazepines (like alprazolam, diazepam, clonazepam), it reduces mean melatonin levels in healthy volunteers by 50–70 % [14].They are also associated with the suppression of endogenous melatonin levels and have been reported to cause increased episodes of arousal during sleep, restlessness, and hang over effects [15]. As our patient has consumed such high dose of melatonin along with a benzodiazepine, this may account for reduced effects of melatonin.

The overdose experience with melatonin is very limited. There have been few previous reported case reports on melatonin overdose. In one, adverse effects were noted after an oral dose of 24mg resulting in lethargy and disorientation, whereas the other described lethargy and severe delayed hypotension after an oral dose of 180mg [16].

The third reported case was of combined Diphenhydramine (DPH) and melatonin toxicity where the individual died due to overdose. The patient had a potential oral ingestion of up to 480mg of melatonin [17]. The toxicology analysis of postmortem specimens in that patient revealed melatonin concentration of 3.9mg/l in iliac blood, 4.4mg/l in cardiac blood and 130mg/l in gastric contents. The patient had also alprazolam levels of 0.05mg/L. It was concluded that both DPH and melatonin were deemed to be the predominant contributors to the decedent’s cause of death. In our patient, we were not able to analyse the plasma and urinary melatonin due to logistic issues and financial constraints on part of patient. However, the dose of melatonin consumed by our patient was nearly double of the patient reported by Zimmerman et al., 2023 and almost 90 times the normally recommended dose. Contrary to their report, our patient was a male teenager and alprazolam levels in our patient were higher but would not be solely responsible for such severe signs and symptoms observed in our patient.

Patients with melatonin overdose are managed in emergency department with use of activated charcoal and other aggressive procedures that do not have any evidence. Flumazenil, a specific central-type Benzodiazepine antagonist, can be used in melatonin overdose by enhancement of BZ-$GABA_A$ receptor signalling [18].

A psychiatric assessment should also be arranged as appropriate to know about the cause of overdose (suicide or accidental) or to diagnose any underlying psychiatric condition. This case of melatonin overdose in a young male underscores the complex interplay between acute medical management, drug misuse, and an underlying psychiatric illness. A holistic approach, encompassing both acute stabilization and long-term psychiatric care, is essential for optimizing patient outcomes and preventing future adverse events.

4. Conclusion

The purpose of this case report is to highlight the fact that abuse of melatonin is gradually increasing due to lack of regulatory concerns and easy availability. Despite having low potential for toxicity, side effects are of concern. Death has also been reported in combination with other drugs. Supportive measures and control of vital signs are crucial for the treatment. This case report also warrants immediate attention to over the counter (OTC) drugs misuse. Public health strategies such as regulated access and altered packaging (such as blister packs) are needed.

CRediT authorship contribution statement

Richa Tripathi: Writing – review & editing, Supervision, Formal analysis, Conceptualization. **Hina Bano:** Writing – original draft, Methodology, Investigation. **Mohd Rashid Alam:** Writing – original draft, Supervision, Investigation, Conceptualization.

Declaration of competing interest

Authors declare none.

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