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Dextromethorphan Overdose with Refractory Status Epilepticus and Reversible Cranial Nerve Reflex Loss: A Case Report

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Manuscript Preparation E
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Patient: Female, 21-year-old
Final Diagnosis: Dextromethorphan overdose with refractory status epilepticus and reversible cranial nerve reflex loss
Symptoms: Status epilepticus
Clinical Procedure: —
Specialty: Toxicology

Objective: Unusual clinical course

Background: Dextromethorphan is a widely used over-the-counter antitussive medication. Generally safe within the recommended dosages, its misuse can lead to severe adverse effects, particularly in large amounts. However, comprehensive descriptions of severe overdose cases – including pharmacokinetic data of dextromethorphan and its active metabolite (dextrorphan) – are scarce.

Case Report: A 21-year-old woman with schizophrenia ingested 20 280 mg of dextromethorphan along with other prescribed medications during a suicide attempt. She was discovered semiconscious and experienced a generalized seizure en route to the hospital. Despite intensive treatments – including endotracheal intubation and administration of propofol and midazolam – she continued to experience refractory status epilepticus. Subsequent neurological examination revealed cranial nerve reflex loss. The serum concentration of dextromethorphan was 5.8 mg/L on admission and decreased to 2.2 mg/L by day 1 and 1.1 mg/L by day 2, contrasting with that of dextrorphan, which remained within the therapeutic limits. By day 4, her condition stabilized; she became alert, responsive to commands, and was successfully extubated. She was discharged on day 9 without any sequelae.

Conclusions: This report describes the case of a patient who survived a massive dextromethorphan overdose, who presented with refractory status epilepticus followed by reversible suppression of cranial nerve reflexes. The pharmacokinetic profiles suggested that dextromethorphan, rather than dextrorphan, was responsible for the symptoms. High-dose dextromethorphan ingestion can lead to varied and potentially fatal outcomes, especially when compounded by metabolism-altering factors such as CYP2D6 inhibition, genetic variability, or co-ingested medications. This case underscores the importance of prompt, intensive supportive care in managing severe dextromethorphan toxicity.

Keywords: Dextromethorphan • Dextrorphan • Serotonin Syndrome • Toxicology

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Introduction

Dextromethorphan, commonly accessible as an over-the-counter cough suppressant, inhibits the cough reflex by acting on the cough center in the medulla oblongata. It is generally well-tolerated at therapeutic doses, causing minimal adverse effects. Recently, there has been increasing concern regarding the misuse and abuse of dextromethorphan. A national survey in the United States in 2022 reported that over 2 million people aged ≥12 years had misused nonprescription cough and cold medicines, including dextromethorphan [1].

A recent review emphasized that dextromethorphan at high dose interacts with multiple channels and receptors, thereby triggering various clinical symptoms [2]. Dextromethorphan toxicity is dose-dependent, presenting in 4 distinct stages or plateaus: 100-200 mg causes mild stimulation (stage 1); 200-400 mg leads to euphoria and hallucinations (stage 2); 300-600 mg induces a dissociative state (stage 3); and >600 mg results in complete dissociation and coma (stage 4). Therapeutic dosing maintains blood concentrations at <0.05 mg/L. Supportive care remains the primary management approach for acute intoxication [2].

Recent case reports describe massive overdoses in young adults who ingested 1665 mg [3] and 4500 mg of dextromethorphan [4], each requiring endotracheal intubation for refractory status epilepticus. Status epilepticus has not typically been related to dextromethorphan toxicity in known dose stages [2], indicating that significantly higher doses can provoke this severe outcome.

Blood concentrations provide a more accurate estimate of toxicity than ingested doses alone, considering the variability in individual metabolism, drug interactions, and differences in gastrointestinal absorption rates following large overdoses. However, limited clinical data exist on the pharmacokinetics of dextromethorphan and its active metabolite, dextrorphan, in the context of significant overdoses [4-7]. This makes the correlation between blood concentrations and clinical symptoms difficult to establish. Furthermore, pharmacologic interactions of dextromethorphan cause atypical or intensified symptoms, especially when taken concurrently with multiple other medications [5,8,9].

This report details the case of a woman who survived a massive dextromethorphan overdose, characterized by refractory status epilepticus followed by reversible suppression of cranial nerve reflexes, compounded by an overdose of medications prescribed for schizophrenia. It also includes serial serum concentrations of dextromethorphan and dextrorphan.

Case Report

A 21-year-old, 68-kg woman with schizophrenia was found semiconscious by her brother at 16: 10. Emergency services arrived after 10 min to find empty packages nearby corresponding to 1352 Medicon Sekidome-Jou Pro® tablets (totaling 20 280 mg of dextromethorphan) along with her prescribed schizophrenia medications, consisting of triazolam (18 tablets of 0.25 mg), alprazolam (24 tablets of 0.4 mg), risperidone (27 tablets of 0.5 mg), duloxetine (2 tablets of 30 mg), and brotizolam (5 tablets of 0.25 mg). Her brother reported that she appeared to be in her usual health at approximately 12: 00; however, the exact time of ingestion remains unclear.

During the hospital transfer at 16: 50, the patient experienced a 30-s generalized tonic-clonic seizure, subsequently slipping into a coma. She arrived at the emergency department (ED) at 17: 00, with a Glasgow Coma Scale score of 5 (eye of 1, verbal of 2, and motor of 2). Her vital signs upon arrival indicated a blood pressure of 57/12 mmHg; pulse of 141 beats/min; respiratory rate of 20 breaths/min; and oxygen saturation of 86% despite receiving 10 L/min of oxygen through a reservoir mask. Her pupils were 5.0 mm in diameter and were reactive. Widespread skin flushing without urticaria and warm extremities were noticed. Auscultation revealed no wheezing in both lung fields and no stridor. Arterial blood gas analysis revealed severe metabolic acidosis with a pH of 7.008, partial pressure of carbon dioxide ($PaCO_2$) of 50.9 mmHg, bicarbonate of 12.8 mmol/L, and lactate of 14.7 mmol/L. The patient continued to experience brief, recurrent, and generalized seizures despite the intravenous administration of diazepam (20 mg). Fentanyl (0.1 mg) was administered to facilitate endotracheal intubation, followed by continuous midazolam infusion to manage her status epilepticus. Initial fluid resuscitation (2000 mL) and norepinephrine infusion (0.36 µg/kg/min) improved her blood pressure to 101/68 mmHg. Acute drug intoxication was initially suspected as the primary diagnosis, considering the patient's presentation and the circumstances of her discovery. A nasogastric tube was inserted after intubation, and aspiration revealed white, cloudy gastric contents with solid material presumed to be tablets. Meanwhile, the differential diagnosis considered alternative causes of metabolic acidosis and seizures, including glucose metabolism disorders, such as diabetic ketoacidosis, as well as alcoholic ketoacidosis, alcohol withdrawal, sepsis, uremia, cerebrovascular events, and electrolyte disturbances. The patient had no reported alcohol consumption. Laboratory studies revealed a leukocyte count of 10.6×10^3/µL; hemoglobin of 14.1 g/dL; platelets of 258 000/µL; C-reactive protein of 0.1 mg/dL; blood urea nitrogen of 6.4 mg/dL; creatinine of 0.71 mg/dL; sodium of 142 mEq/L; chloride of 106 mEq/L; potassium of 3.6 mEq/L; glucose of 144 mg/dL; albumin of 3.5 g/dL; total bilirubin of 0.3 mg/dL; aspartate aminotransferase of 29 U/L; alanine aminotransferase of 13 U/L;

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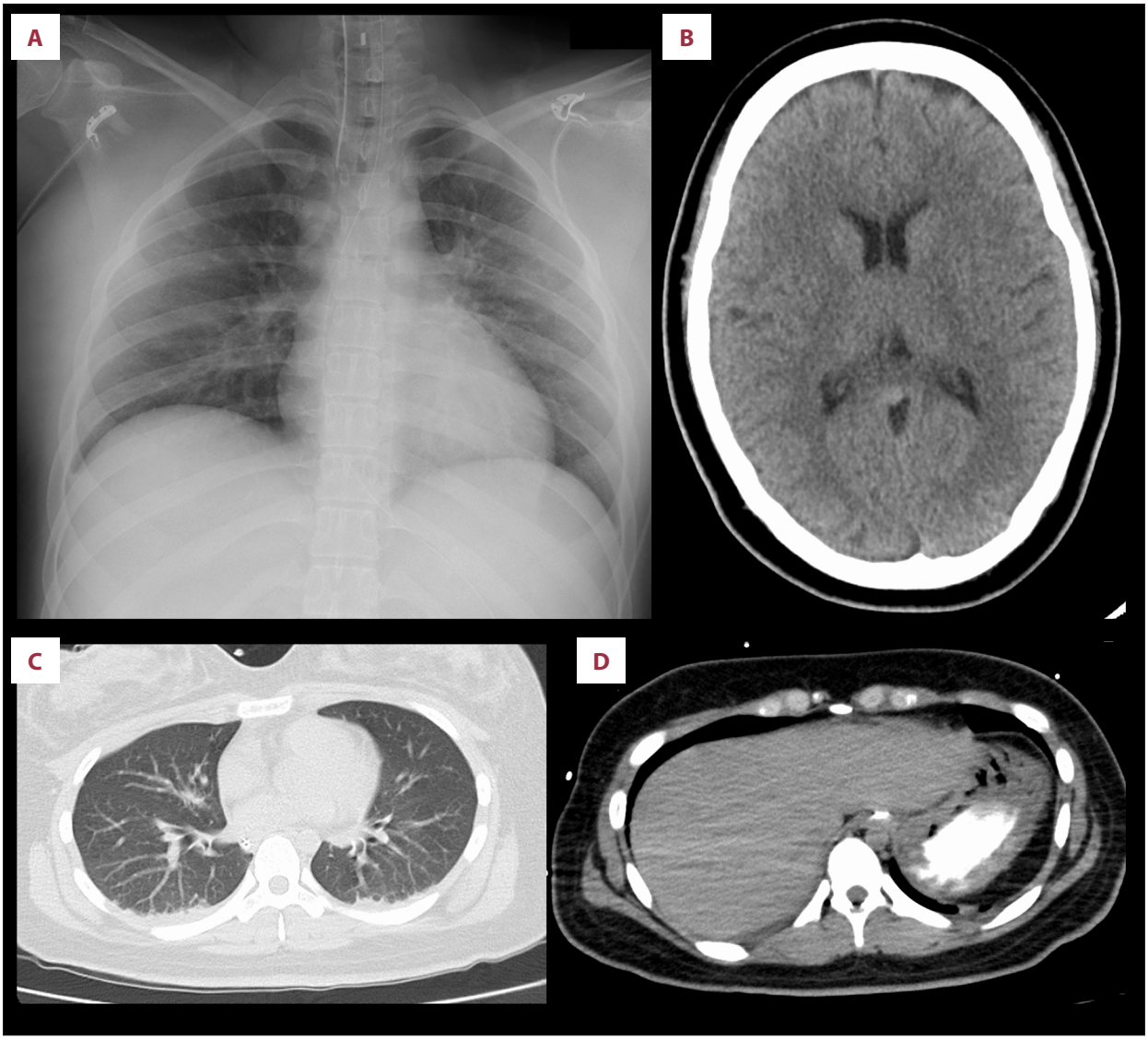

Figure 1. (**A**) Chest radiograph illustrating no abnormalities in the lung fields. (**B**) Computed tomography scan of the head with no abnormalities detected. (**C**) Chest computed tomography scan demonstrating mild atelectasis in the bilateral dorsal regions. (**D**) Abdominal computed tomography scan revealing a hyperdense area in the stomach, indicative of residual drug clumps.

and alkaline phosphatase of 46 U/L. Imaging studies supported our assessment, consisting of a chest radiograph revealing no lung field abnormalities (**Figure 1A**); a head computed tomography (CT) scan to rule out intracranial causes, revealing no abnormalities (**Figure 1B**); and a chest CT detecting mild atelectasis in the dorsal regions bilaterally (**Figure 1C**). An abdominal CT scan was performed to evaluate for residual drug clumps in the gastrointestinal tract, considering the partially undigested tablets aspirated from the nasogastric tube, indicating recent ingestion. The scan revealed a hyperdense area in the stomach (**Figure 1D**), which prompted gastric lavage to limit further absorption. Activated charcoal was administered every 4 h after repeated gastric lavage. Naloxone (0.2 mg) was administered, but there was no response.

At 19: 00, 2 h after arrival and upon intensive care unit (ICU) admission, the patient still had refractory status epilepticus despite a continuous midazolam infusion (2.5 µg/kg/min), prompting the administration of propofol (37 µg/kg/min) for seizure management and adjustment of the norepinephrine dose to 0.76 µg/kg/min. She became noticeably diaphoretic. At 20: 00, a neurological examination revealed flaccid quadriplegia with absent deep tendon reflexes in the bilateral biceps, triceps, brachioradialis, patellar, and Achilles tendons. No tremor, myoclonus, clonus, or muscle rigidity was observed. The pupils were mydriatic (6.0 mm/6.0 mm) with an absent pupillary light reflex. In addition, corneal, oculocephalic, gag, and cough reflexes were not observed. During mechanical ventilation, she exhibited no spontaneous respiratory effort. On the

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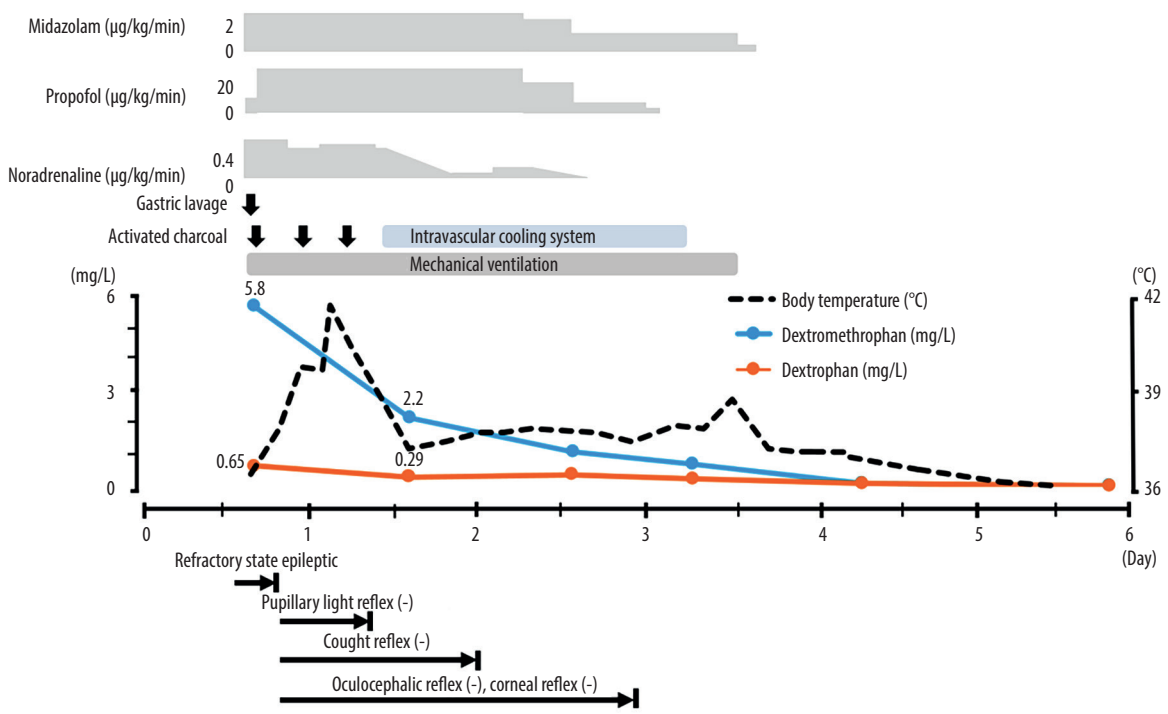

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 2
Leukocyte ($\times 10^3$/μL)	10.6	16.6	19.4	15.3	12.8	8.7
Hb (g/dL)	14.1	14.6	11.3	9.5	9.7	9.4
PLT ($\times 10^4$/μL)	25.8	29.5	18.5	14.8	13.9	19.0
AST (U/L)	29	89	61	63	58	48
ALT (U/L)	13	23	20	21	26	28
ALP (U/L)	14	43	37	42	44	63

Figure 2. Clinical course of a 21-year-old female patient following a massive dextromethorphan overdose, complicated by refractory status epilepticus and subsequent reversible cranial nerve reflex suppression. ALP – alkaline phosphatase; ALT – alanine aminotransferase; AST – aspartate aminotransferase; Hb – hemoglobin; PLT – platelet. *This figure was created by OA and NY.*

second day, 12 h after ICU admission, her core body temperature increased to 41.5°C, requiring an intravascular cooling system to reduce it to 37.5°C. Transcranial Doppler ultrasound revealed no signs of increased intracranial pressure, and an electroencephalogram conducted 20 h after admission revealed no epileptic activity. Midazolam (2.5 μg/kg/min) and propofol (37 μg/kg/min) infusions were continued, whereas norepinephrine was gradually tapered to 0.12 μg/kg/min. By day 3, brainstem reflexes and deep tendon reflexes had recovered, and movements in the extremities were also observed. Despite reducing sedative administration, the patient experienced no further seizures or agitation and achieved hemodynamic stability, allowing for the cessation of norepinephrine administration. On day 4, she became alert and responsive to commands and was extubated. Hyperthermia was not observed after the cooling system was stopped. Arterial blood gas analysis revealed a pH of 7.376, a $PaCO_2$ of 43.8 mmHg, bicarbonate of 25.1 mmol/L, and lactate of 0.8 mmol/L. Laboratory studies demonstrated a leukocyte count of 15.3×10^3/μL; hemoglobin of 9.5 g/dL; platelets of 148 000/μL; albumin of 2.5 g/dL; total bilirubin of 0.6 mg/dL; aspartate aminotransferase of 63 U/L; alanine aminotransferase of 21 U/L; and alkaline phosphatase of 42 U/L. She disclosed that she had bought a large amount of Medicon sekidome-jou Pro® cough tablets from a pharmacy to commit suicide and had ingested all the tablets at once, along with her regularly prescribed medications for schizophrenia. She made a full recovery and was discharged on day 9.

Liquid chromatography coupled with quadrupole time-of-flight mass spectrometry upon admission revealed that the serum concentrations of dextromethorphan and its metabolite, dextrorphan, were 5.8 mg/L (therapeutic range: 0.01-0.04 mg/L) [10] and 0.65 mg/L, respectively (**Figure 2**). As shown in **Figure 2**, the serum levels of dextromethorphan and its metabolite, dextrorphan, decreased significantly. In addition, other detected drugs included triazolam at 0.02 mg/L (therapeutic range:

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Table 1. Adult survival cases of dextromethorphan overdose in which blood dextromethorphan and dextrorphan concentrations were specifically documented.

Author, year [ref. no.]	Age (years)	Gender	Ingested dextromethorphan amount	Concomitant drugs	Serum dextrome-thorphan concentration (mg/L)	Serum dextrorphan concen-tration (mg/L)	Clinical symptoms
Kuwana et al, 2024 [4]	Older adolescent	Male	4,500 mg	Flunitrazepam	3.7	N/A	Altered mental status, tachycardia, mydriasis, shock, hyperthermia, refractory status epilepticus, muscle rigidity, flushed skin, and serotonin syndrome
Monte et al, 2010 [5]	19	Male	Up to 1,440 mg	Chlorphe-namine	0.25	N/A	Agitation, delirium, hypertension, tachycardia, hyperthermia, hyperreflexia, mydriasis, ocular clonus, and inducible ankle clonus
Schwartz et al, 2008 [6]	20	Male	Unknown	Escitalopram, chlorphe-niramine, benztropine, aripiprazole	0.95	N/A	Confusion, tremor, hyperthermia, hypertension, hyperthermia, ankle clonus, muscle rigidity, hyperreflexia, mydriasis, and diaphoresis
Ganetsky et al, 2007 [7]	18	Male	Up to 480 mg	Chlorphe-niramine	0.93	N/A	Tachycardia, agitation, diaphoresis, mydriasis, ocular clonus, muscle rigidity, tremor, and hyperreflexia
Present case	21	Female	Up to 20,280 mg	Triazolam, alprazolam, risperidone, duloxetine, brotizolam	5.8	0.65	Altered mental status, tachycardia, mydriasis, shock, hyperthermia, refractory status epilepticus, reversible suppression of cranial nerve reflexes, and flushed skin

N/A – not applicable.

0.002-0.02 mg/L), alprazolam at 0.083 mg/L (therapeutic range: 0.005-0.08 mg/L), risperidone at 0.099 mg/L (therapeutic range: 0.002-0.02 mg/L), duloxetine at 0.27 mg/L (therapeutic range: 0.03-0.12 mg/L), and brotizolam at 0.022 mg/L (therapeutic range: 0.001-0.02 mg/L) [10]. However, due to the time required for external processing, these results became available only after the patient's condition had significantly improved and thus did not affect immediate treatment adjustments.

Discussion

Table 1 shows cases of adults surviving dextromethorphan overdose in which blood dextromethorphan concentrations were specifically documented [4-7]. In the current case, the amount of dextromethorphan absorbed into the bloodstream was approximately 1972-2366 mg based on an estimated Cmax of 5.8 mg/L (the dextromethorphan serum concentration upon admission),

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a volume of distribution of 5.0-6.0 L/kg [2], and a body weight of 68 kg. In comparison, up to 10 140 mg would be expected to have entered systemic circulation, considering the patient-reported ingestion of 20 280 mg and assuming a bioavailability of approximately 50%, as typically observed with therapeutic doses [11]. The difference between the absorbed amount (1972-2366 mg) and the expected amount (up to 10 140 mg) indicates that gastric lavage and repeated activated charcoal administration may have effectively removed a portion of the dose. Naloxone (0.2 mg) was administered as a possible specific treatment, but the dose may have been suboptimal [6,12], with inconclusive evidence regarding its efficacy in dextromethorphan toxicity [2,13]. However, this case represents the highest recorded concentration in a surviving patient to date. To the best of our knowledge, this is the first report to describe serial blood concentrations of both dextromethorphan and dextrorphan in an overdose context.

Intriguingly, dextromethorphan serum levels were markedly high, whereas dextrorphan levels remained within the therapeutic range throughout the event – a pharmacokinetic profile that contrasts sharply with what is typically observed at standard dosages [14]. Dextromethorphan is rapidly absorbed and primarily metabolized in the liver by the cytochrome P450 enzyme CYP2D6 into its active metabolite, dextrorphan. The observed pharmacokinetic profile could be attributed to the rapid saturation of the CYP2D6 enzyme activity, caused by the excessive intake of dextromethorphan. Moreover, the genetic variability of CYP2D6, which results in unique metabolic rates for dextromethorphan due to differences in enzyme activity, could also account for this phenomenon [15], although a direct analysis was not performed. Furthermore, the concurrent use of duloxetine (60 mg), a moderate CYP2D6 inhibitor, may have further intensified the inhibition of the metabolism from dextromethorphan to dextrorphan [16]. These may explain the stark contrast in the serum levels of dextromethorphan and dextrorphan observed in our patient.

This stark contrast may explain the clinical presentation of the refractory status epilepticus observed in our case. A previous study involving rats administered equipotent analgesic doses of dextromethorphan and dextrorphan [17], and only dextromethorphan induced seizures, whereas dextrorphan did not. Another previous study on rats found that high-dose intraperitoneal dextromethorphan (80 mg/kg) administration induced convulsive behaviors via GluN2B/NMDA receptor signaling pathway activation [18]. These results indicate that the pharmacological differences between dextromethorphan and dextrorphan, along with the unusually high serum dextromethorphan levels, may have collectively contributed to the occurrence of refractory status epilepticus in this case.

Dextromethorphan is a serotonergic drug, and severe overdoses are related to serotonin syndrome [19], which is characterized by mental status changes, autonomic hyperactivity, and neuromuscular abnormalities. Typical vital sign alterations include tachycardia and hypertension, with severe cases potentially developing hyperthermia and marked blood pressure fluctuations, as seen in this case. The key diagnostic features – hyperreflexia, inducible clonus, and rigidity – were absent throughout hospitalization, although suggestive signs, such as mydriasis, skin flushing, diaphoresis, and hyperthermia, were observed. Consequently, the patient did not meet the Hunter criteria for a definitive diagnosis of serotonin syndrome [20]. A previous systematic review revealed that serotonin syndrome, which typically originates from multiple receptor activations, does not occur with dextromethorphan alone [5]. Consistent with these results, the absence of co-ingested serotonergic drugs in our case may have prevented the full manifestation of serotonin syndrome.

Reportedly, several drugs cause a reversible loss of brainstem reflexes [21]. However, no study has specifically implicated dextromethorphan in the reversible suppression of cranial nerve reflexes. Forensic case studies suggest that generalized central nervous system depression was the probable cause of mortality in 5 cases of dextromethorphan overdose in which postmortem blood concentrations were 0.95-3.2 mg/L [22]. The high serum concentration of dextromethorphan, drug interactions with co-ingested overdoses, and the high doses of sedatives administered to control refractory status epilepticus may have contributed to the transient cranial nerve reflex suppression observed in this case, although the precise mechanism remains unclear.

Conclusions

This case highlights the complexities of managing refractory status epilepticus followed by reversible suppression of cranial nerve reflexes triggered by a severe dextromethorphan overdose. Rapid CYP2D6 enzyme saturation, genetic CYP2D6 metabolism variability, and pharmacologic interactions – including co-ingestion of a CYP2D6 inhibitor – may have contributed to the atypical pharmacokinetic profile for both dextromethorphan and dextrorphan. These combined factors likely caused a unique clinical presentation, manifesting as refractory status epilepticus with transient brainstem reflex suppression. The absence of serotonergic co-ingestants in this case may have prevented its full manifestation, although serotonin syndrome is a well-recognized complication of dextromethorphan toxicity.

Clinicians should remain vigilant for life-threatening atypical presentations in dextromethorphan overdose, especially when metabolism-altering factors, such as CYP2D6 inhibition, genetic variability, or co-ingested medications are observed. Prompt, intensive supportive care is crucial in such severe cases and can be lifesaving. Further research is warranted to confirm the association between dextromethorphan and dextrorphan serum concentrations and their clinical manifestations.

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Declaration of Figures' Authenticity

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