

# Levodopa-carbidopa-entacapone overdose presenting as altered mental status, xanthoderma, and yellowish sclera

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## ABSTRACT

Levodopa-carbidopa-entacapone is a single combination drug consisting of levodopa (aromatic amino acid), carbidopa (dopa-decarboxylase inhibitor), and entacapone (catechol-O-methyltransferase inhibitor). The Food and Drug Administration approved levodopa-carbidopa-entacapone in 2003, as treatment for idiopathic Parkinson's disease in patients experiencing signs and symptoms of wearing-off. Although various adverse drug reactions of levodopa-carbidopa-entacapone have been recorded, there has been no reported case of levodopa-carbidopa-entacapone overdose. We report the first case of signs and symptoms of an overdose of levodopa-carbidopa-entacapone (levodopa: 3000 mg; carbidopa: 750 mg; entacapone: 6000 mg) in a suicide attempt, presenting as altered mentality, xanthoderma, and yellowish sclera without hyperbilirubinemia.

**Key words:** levodopa-carbidopa-entacapone, Parkinson's disease, drug overdose, xanthoderma, yellowish sclera, toxicology

## INTRODUCTION

Levodopa-carbidopa-entacapone is a triple combination drug containing levodopa, carbidopa, and entacapone. In 2003, this drug was approved by the Food and Drug Administration (FDA) and considered the main treatment option for Parkinson's

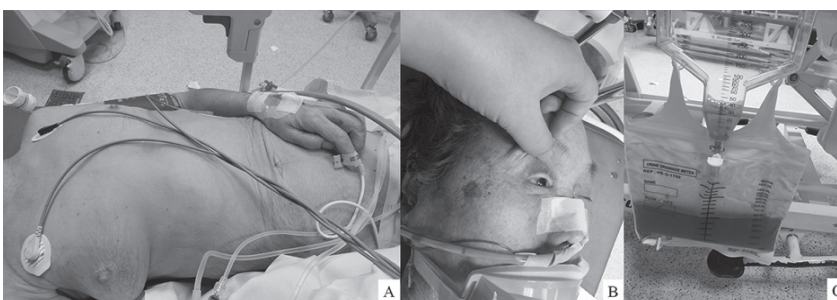


Figure 1. Photograph images of the patients' whole body (A), eye (B), and urine via Foley catheter (C). These show yellowish skin color (xanthoderma) (A) and yellowish sclera (B). Urine color is somewhat dark yellow to reddish (C).

disease (PD). (1) Adverse drug reactions associated with the recommended dose of levodopa-carbidopa-entacapone have been reported to be at least 3% greater than placebo incidences, and these include dyskinesia, urine discoloration, diarrhea, nausea, hyperkinesia, vomiting and dry mouth. (2)

Concerning the overdose of this drug, a few cases of levodopa alone or levodopa-carbidopa overdose have been reported. (3-6) However, there have been no reports on levodopa-carbidopa-entacapone overdose. We report the first case of a patient who ingested excess levodopa-carbidopa-entacapone in an attempt to commit suicide.

## CASE PRESENTATION

A 77-year-old woman presented at our emergency department, with complaint

from her son of altered mental status. She had a previous medical history of PD, for which she had received treatment for 4 years. In the morning, her son found her unconscious in the living room with 30 torn and remnants of the tablet. The last call was to her son 30 minutes before. Upon arrival, her vital signs were unstable (60/40 mmHg-110 beats/min-26 breaths/min-34°C) Physical examination showed the patient was in a state of stupor, with dilated pupils, sluggish light reflex, xanthoderma of the whole body (figure 1A) and yellowish sclera (figure 1B). Initial resuscitation included tracheal intubation, intravenous fluid infusions, inotropic agents, gastric lavage and orally administered activated charcoal. At that point, we suspected a case of hyperbilirubinemia, related to hepatic failure due to ingestion of an unknown drug.

The laboratory findings including liver function test (total bilirubin: 0.9 mg/dL;

Table 1. Reported studies of the drug overdosage in Parkinson's disease patients with levodopa therapy

Authors	Year	Age/Sex	Drug	No. of tables	Total drug dose	Symptoms	Abnormal laboratory finding at the time of the hospital visit	Interval between drug ingestion and hospital visit
Hoehn, et al <sup>3</sup>	1975	61/M	Levodopa alone	Not reported	Levodopa: upto 100 mg	Altered mentality, diaphoretic and restless, constant speech, jerk movement	Elevated serum CK, LDH, creatinine, glutamic oxaloacetic acid, glutarnic pyruvic acid transaminase	Several hours
Sporer <sup>4</sup>	1991	57/F	Levodopa-carbidopa	15	Levodopa: 1500 mg Carbidopa: 150 mg	Altered mentality, lethargy, choreiform movements	Elevated serum CK, LDH, hematuria, myoglobinuria	2 hours
Stuereburg et al <sup>5</sup>	1999	76/M	Levodopa-carbidopa	30	Levodopa: 6000 mg Carbidopa: 1500 mg	Altered mentality, anxious, depressed, agitated, subeuphoric, visual hallucinations	Not reported	About 1~2 hours
Delmas, et al <sup>6</sup>	2008	55/M	Levodopa-carbidopa	89	Levodopa: 17800 mg Carbidopa: 4450 mg	Psychomotor agitation, delirium, joviality, visual hallucinations, tachycardia, xerostomia	Elevated serum CK, aspartate aminotransferase	2.5 hours
Our case	2017	77/F	Levodopa-carbidopa-entacapone	30	Levodopa: 3000 mg Carbidopa: 750 mg Entacapone: 6000 mg	Altered mentality, xanthoderma, yellowish sclera, reddish urine	None	30 minutes~1 hour

CK, creatinine kinase; LDH, lactate dehydrogenase.

direct bilirubin: 0.3 mg/dL; aspartate aminotransferase: 46 u/L; alanine aminotransferase: 3 u/L, creatinine kinase (161 U/L), lactate dehydrogenase (330 U/L), and renal function tests (urea: 18.4 mg/dL; creatinine: 0.78 g/dL; urine neutrophil gelatinase-associated lipocalin (NGAL): 85 ng/mL) were within normal range. The results of urine toxicology screening were negative for benzodiazepine, tricyclic antidepressant, and barbiturate. Urine analysis showed no hematuria or pyuria, but her urine color was dark yellow to reddish (figure 1C). We performed brain computed tomography (CT), and an abdominal CT for evaluating the liver and kidney; however, there was no abnormal finding.

After initial resuscitation, her son brought along her remaining drug, which turned out to be a dose for the treatment of PD (single tablet: levodopa 100 mg+carbidopa 25 mg+entacapone 200 mg). After mental recovery, she confessed that she had intentionally taken an overdose of the drug for suicide. Thus, we diagnosed a levodopa-carbidopa-entacapone overdose (levodopa: 3000 mg; carbidopa: 750 mg; entacapone: 6000 mg). We can exclude effect of the rhabdomyolysis because creatinine kinase and lactate dehydrogenase were normal. She was admitted to the intensive

care unit for further management. On hospital day (HD)-3, she was extubated and recovered a normal skin, sclera, and urine color. On HD-10, she was discharged to a rehabilitation center for supportive care and rehabilitation. In order to exclude the effects of chronic levodopa-carbidopa-entacapone use on skin color, the patient was followed up once a month for 6 months and was free from any adverse events for a total follow-up period.

## DISCUSSION

Levodopa-carbidopa-entacapone is a single combination tablet consisting of levodopa (aromatic amino acid), carbidopa (dopa-decarboxylase inhibitor), and entacapone (catechol-O-methyltransferase (COMT) inhibitor). (1) Until now, an overdose of levodopa alone (3) or that of levodopa-carbidopa (4-6) has been reported (table 1). Based on previous reports, (3-6) the symptoms of altered mental status and hypotension in our patient may be related to levodopa since only levodopa could cross the blood-brain barrier freely, unlike carbidopa and entacapone. However, there was no report concerning the overdose of levodopa-carbidopa-entacapone. Especial-

ly, complications related to the overdose of entacapone have not been revealed, although its adverse reactions have been investigated. Common adverse reactions of the recommended dose of entacapone are dyskinesia and urine discoloration. Among these, urine discoloration was observed in our patient. This discoloration is due to the water-soluble metabolite of the entacapone (glucuronide conjugates). (2,7) However, the cause of the change in skin color (xanthoderma) is unclear because it has not been reported as an adverse reaction of levodopa, carbidopa, and entacapone in animal studies and post-marketing surveillance. We hypothesized three potential etiological mechanisms related to skin color change. The first hypothesis was that hyperbilirubinemia, due to the hepatic impairment, may have resulted in jaundice and icteric sclera, and the subsequent yellowish discoloration of the skin and sclera. The second hypothesis was that the stimulation of melanin production due to levodopa may have resulted in the change of the color of the skin. (8) The color of melanin is blue, dark blue, and black. (9) The third hypothesis was that high levels of the conjugated entacapone caused an accumulation of glucuronide conjugates in whole body tissues. Plasma entacapone

level is dose-dependent; thus by ingesting an excess of the entacapone, the glucuronide conjugates of the entacapone in the hepatocyte and the small intestine might increase. Although 90% of the glucuronide conjugate in the small intestine is excreted via feces, 10% remains in circulation. (2,8) As seen in discolored urine, the color of the glucuronide conjugate is dark yellow to reddish. In our patient's case, the skin and sclera color were yellowish, and liver function test including bilirubin was normal; thus, the third hypothesis provided a more likely explanation.

The differential diagnosis between xanthoderma with yellowish sclera related to the levodopa-carbidopa-entacapone overdose and jaundice with icteric sclera related to the hepatic impairment was important because the optimal treatment could be different. In the treatment of levodopa-carbidopa-entacapone overdose, hemodialysis is unlikely to be beneficial due to the high protein binding of the COMT inhibitors. Patients are therefore started gradually on inotropic agents, since COMT inhibitors may interfere with the metabolism of agents such as dopamine and nor-

epinephrine, thereby causing a prolonged response. (2)

Our case underscores the importance of the knowledge for new adverse reactions, related to levodopa-carbidopa-entacapone overdose. For optimal management, emergency physicians should keep in mind that an overdose of levodopa-carbidopa-entacapone in PD patients may be accompanied by altered mentality, xanthoderma and yellowish sclera.

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