

Allergy to Carbidopa

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Background: D-Decarboxylase inhibitors, such as carbidopa or benserazide, have been used as adjunct therapy in Parkinson disease shortly after levodopa synthesis in the 1960s. These compounds increase intracerebral drug concentration and decrease adverse effects by blocking peripheral conversion to dopamine. Skin rash as part of an allergic reaction was previously described in subjects who were using levodopa in combination with carbidopa or benserazide; however, etiology was never clear. Allergic reactions to carbidopa have not previously been reported.

Methods: We report a case of a 77-year-old woman with a diagnosis of idiopathic Parkinson disease, who developed autonomic and dermatological signs: conjunctival injection, rhinorrhea, excessive sweating, hypertension, and pruritic generalized rash, among others, immediately after carbidopa/levodopa administration regardless of the manufacturer. Treatment with dexamethasone combined with chlorpyramine hydrochloride resulted in complete resolution of the hypersensitivity reaction each time it presented. The autonomic and dermatological manifestations did not reappear after treatment was replaced with benserazide/levodopa.

Conclusions: To the best of our knowledge, this is the first case report of an allergic reaction specific to carbidopa. Our case highlights the importance of identifying the source of a hypersensitivity drug response, whether it is caused by the active component or by the excipients.

Key Words: carbidopa, D-decarboxylase inhibitors, hypersensitivity reaction, yellow dye

(*Clin Neuropharm* 2018;00: 00–00)

Currently, levodopa remains the criterion-standard pharmacotherapy for symptomatic treatment of Parkinson disease (PD). After oral administration, 30% of the total drug dosage enters the systemic circulation. However, only 1% of it reaches the brain unmodified because of decarboxylation undertaken by the hepatic and intestinal metabolism. D-Decarboxylase inhibitors (DCIs) carbidopa and benserazide were added to levodopa in order to increase intracerebral drug concentration by blocking peripheral conversion to dopamine. This also led to a decrease in dopamine-related adverse effects in the periphery such as nausea, orthostatic hypotension, drowsiness, and possibly anxiety, depression, dyskinesias, hallucinations, and confusion.¹

Since the introduction of DCIs during the 1960s, there have been no published reports concerning hypersensitivity reactions involving these compounds. Drug hypersensitivity or allergic reactions are unexpected adverse drug effects.^{2,3} Allergic reactions to dopaminergic therapy are uncommon; however, cases of hemolytic anemia,^{4–7} nonhemolytic anemia,^{8,9} and skin rash^{10,11} have been reported. At present, there is no previous publication of an allergic reaction specific to carbidopa. We describe a case of a hypersensitivity reaction associated to carbidopa in a 77-year-old

woman who used different manufacturers of levodopa and carbidopa for the treatment of her PD symptoms.

CASE REPORT

The patient was a 77-year-old, right-handed woman with onset of rest tremor on her right hand at the age of 68 years. She had a history of arterial hypertension, rheumatoid arthritis, and allergy to cotrimoxazole. One of her siblings was diagnosed with PD when he was 60 years old.

During her first assessment, we identified the classic clinical manifestations of PD (resting tremor, bradykinesia, and rigidity over her right arm and leg) with a Unified Parkinson's Disease Rating Scale Part III score of 49 points and Hoehn and Yahr staging of 4. Benserazide/levodopa 25/100 mg was started at a dose of 1 tablet 4 times daily, resulting in an improvement of her symptoms. Six months later, we identified mild worsening of her motor symptoms, necessitating an increase in her levodopa dosage. Because benserazide/levodopa formulation in our country is available only as 25/100-mg tablets, and an increase in levodopa intake was needed, carbidopa/levodopa 25/250 mg was started instead, at a dosage of half tablet 4 times daily. This change was done in order to make levodopa administration easier, thus decreasing the quantity of tablets needed per day.

After the first dose of carbidopa/levodopa, the patient began experiencing drowsiness, heartburn, excessive sweating, bilateral tearing, conjunctival injection, and rhinorrhea. She became hypertensive with blood pressures ranging from 160/100 to 200/115 mm Hg and tachycardic. Within 3 hours of the first dose, a pruritic rash involving mainly her face, neck, and chest was observed (Fig. 1).

There was resolution of these symptoms after treatment with 8 mg of intravenous dexamethasone followed by 20 mg of chlorpyramine hydrochloride intramuscular injection. Other manufacturers of carbidopa/levodopa were tried, including carbidopa/levodopa/entacapone formulations, resulting in the same allergic reaction each time (Table 1).

Finally, benserazide/levodopa 25/100 mg 2 tablets 4 times daily was restarted, with no allergic reactions seen with this formulation.

DISCUSSION

D-Decarboxylase inhibitors, either carbidopa or benserazide, increase levodopa bioavailability and decrease peripheral conversion, thus augmenting intracerebral drug concentration and decreasing its peripheral adverse effects. They act as noncompetitive inhibitors of the aromatic L-amino acid decarboxylase, which catalyzes the decarboxylation of L-3,4-dihydroxyphenylalanine (L-dopa; Fig. 2) to dopamine, L-5-hydroxytryptophan to serotonin, and L-tryptophan to tryptamine. Benserazide is also a partial competitive inhibitor of catechol-O-methyl transferase, which catalyzes the methylation of levodopa to 3-O-methyldopa (a plasma metabolite with a half-life of 15 hours), and a weak inhibitor of monoamine oxidase.^{12,13}

Carbidopa [(2S)-3-(3,4-dihydroxyphenyl)-2-hydrazinyl-2-methylpropanoic acid hydrate (Fig. 3)] is a white crystalline compound soluble in water with a molecular weight of 244.3 and a

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Informed consent was obtained from the patient prior to publication.

The authors have no conflicts of interest to declare.

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DOI: 10.1097/WNF.0000000000000270

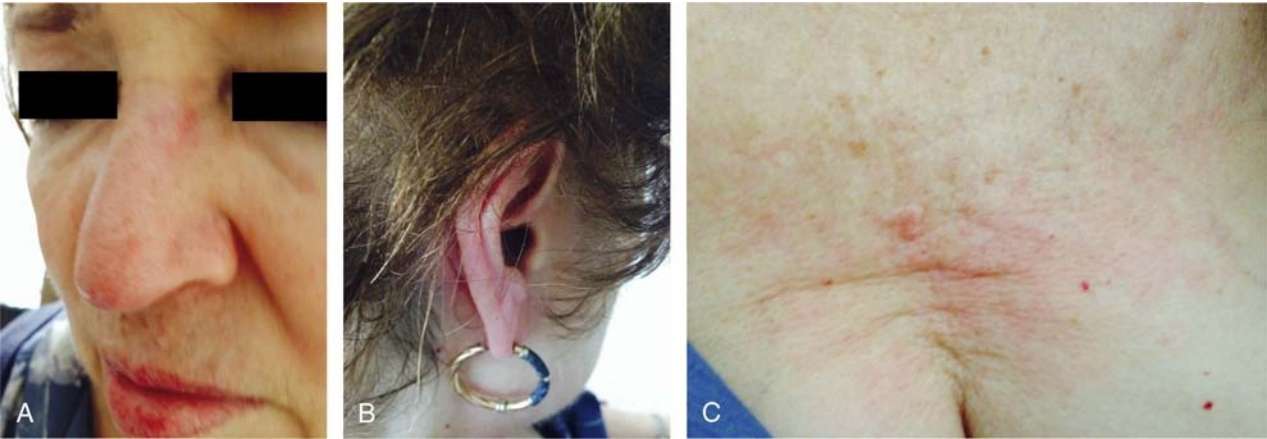


FIGURE 1. Rash affecting the face (A), ears (B), and chest (C).

half-life of 1.5 to 2 hours. Peak plasma levels of carbidopa occur within 0.5 to 5 hours after oral administration. It is mainly excreted in feces (40%–55%), and the acid metabolites are eliminated in urine as glucuronide conjugates. Benserazide hydrochloride {2-amino-3-hydroxy-N'-[(2,3,4-trihydroxyphenyl)methyl] propanehydrazide hydrochloride (Fig. 4)} has a molecular weight of 293.704 g/mol. Its maximum plasma levels occur 1 hour after dosage. It undergoes hydroxylation in the intestinal mucosa and liver, generating trihydroxybenzylhydrazine, a potent

inhibitor of the aromatic L-amino acid decarboxylase. Initially, it is rapidly excreted in urine, but later the elimination rate decreases so that approximately 60% of the oral dose is eliminated after 7 days.^{12–14} Once a DCI is administered along with levodopa, the peripheral decarboxylation of levodopa into dopamine in the gastrointestinal tract and blood vessels is decreased. This allows a greater amount of unmodified levodopa to cross the hematoencephalic barrier and reduces the extracerebral adverse effects.¹⁵

TABLE 1. Levodopa/Carbidopa Formulations Used by Our Patient

Trademark	Presentation	Active Component	Excipient
CLOISONE*†	Tablet	Carbidopa 25 mg Levodopa 250 mg	Corn starch Indigotin (E132)
SINEMET‡	Tablet	Carbidopa 25 mg Levodopa 250 mg	Microcrystalline cellulose Corn starch Pregelatinized corn starch Magnesium stearate Indigotin (E132)
TERNOVAG§	Tablet	Carbidopa 25 mg Levodopa 250 mg	Pregelatinized corn starch Microcrystalline cellulose Corn starch Quinoline yellow (E104) Magnesium stearate
STALEVO	Tablet	Carbidopa 31.25 mg Levodopa 125 mg Entacapone 200 mg	Croscarmellose sodium Hydroxypropyl cellulose Trehalose dehydrate Anhydrous sodium sulfate Cellulose Microcrystalline sodium Magnesium stearate Special film cover: Partially hydrolyzed polyvinyl alcohol Talc Titanium dioxide (E171) Red iron oxide (E172) Sodium lecithin Yellow iron oxide (E172)

*Pharmaceutics data (active substances and excipients) of every levodopa/carbidopa trademark were obtained directly from the pharmaceutical company at issue.
†Psicofarma.
‡Merck Sharp & Dohme.
§Novag.
||Novartis.

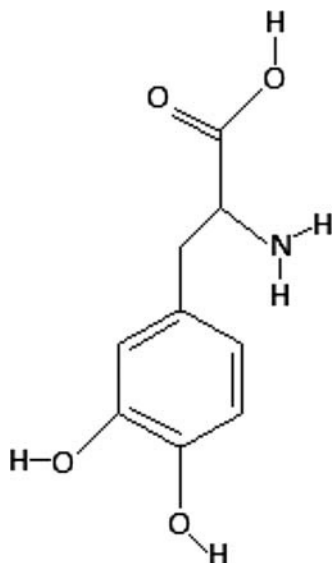


FIGURE 2. L-3,4-Dihydroxyphenylalanine (L-dopa).

Commonly reported adverse effects of carbidopa/levodopa include dyskinesias, nausea, drowsiness, and hypotension and less commonly psychiatric manifestations (anxiety, depression, hallucinations, and confusion).¹ Hypersensitivity reactions to carbidopa have been rarely described; all of them suggesting the yellow dye excipient as the causative agent (Table 2). The first carbidopa/levodopa hypersensitivity reaction was published in 1979 by Bernstein et al,⁷ who described a 71-year-old French man treated with SINEMET 25/100 who developed severe autoimmune hemolytic anemia, after 1 year of therapy.⁷ The incidence of SINEMET 25/100 skin rash attributed to yellow dye is infrequent. Goetz¹¹ suggested that yellow dye present in SINEMET 25/100 formulation was responsible for the generalized maculopapular rash developed in 5 of his patients. The allergic reaction resolved promptly after discontinuation of the drug. The use of yellow dye-free formulations, either SINEMET 25/250 or SINEMET 10/100, did not cause rash.

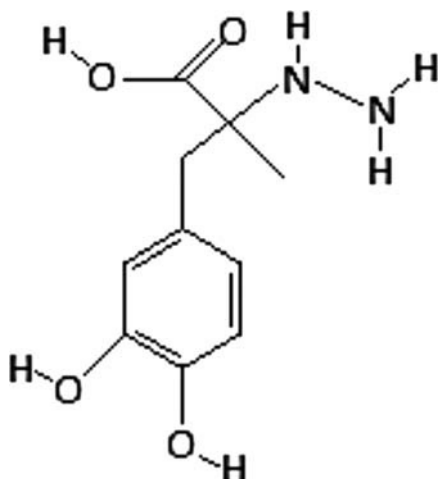


FIGURE 3. (2S)-3-(3,4-dihydroxyphenyl)-2-hydrazinyl-2-methylpropanoic acid hydrate (carbidopa).

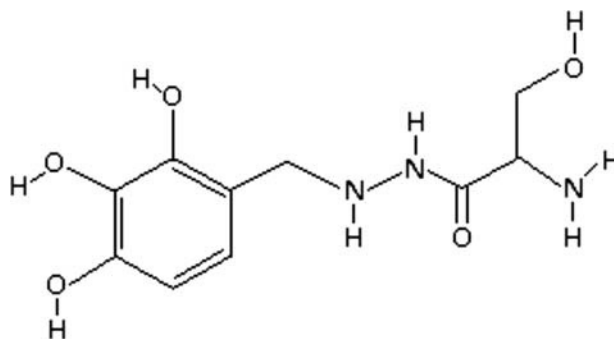


FIGURE 4. 2-Amino-3-hydroxy-N'-[(2,3,4-trihydroxyphenyl)methyl] propanehydrazide hydrochloride (benserazide).

The most recent study proposing the yellow dye excipient as the trigger of the skin rash was published by Chou and Stacy,¹⁶ in which 2 subjects developed maculopapular pruritic rash after the administration of SINEMET 25/100. Use of levodopa formulations free of D&C yellow 10 and FD&C yellow 6 dyes, such as STALEVO 100/25/200 and STALEVO 50/12.5/200, did not provoke an allergic reaction. No other publications regarding levodopa/carbidopa allergic reactions have been reported until now.

In 2016, Esteban-Fernandez et al¹⁷ described the first case of carbidopa-induced eosinophilic fasciitis in a subject with chronic carbidopa/levodopa 25/100 therapy. Suspecting carbidopa-induced eosinophilic fasciitis, his therapy was modified to benserazide/levodopa 50/200 in addition to corticosteroids, resulting in a complete recovery. However, the authors did not specify the manufacturers or excipients present in the formulations used. Eosinophilic fasciitis is a rare immune-mediated connective tissue disease affecting predominantly men (range, 30–60 years). The pathophysiology is not fully understood, but it is thought that eosinophils induce fibrosis due to transforming growth factor β 1 synthesis. It can be elicited by drug exposure, trauma or vigorous activity, autoimmune disorders, and some neoplasias, among others.^{18,19}

Because of the initial suspicion of a yellow dye-induced allergic reaction, we trialed a yellow dye-free formulation of carbidopa/levodopa (Table 1); however, it resulted in the same clinical manifestations. After the use of multiple formulations, it was deduced that carbidopa was the only common excipient among those formulations provoking an allergic reaction (Table 2). After reintroduction of benserazide/levodopa, anaphylactic symptoms did not reappear. Therefore, we have concluded that carbidopa was the cause of the hypersensitivity reaction seen in our patient. An allergic background in our patient was known, because she manifested the same problem with cotrimoxazole, reinforcing the concept of an allergic reaction due to carbidopa usage.

CONCLUSIONS

To the best of our knowledge, this is the first case of an allergic reaction to carbidopa. Previous reports of allergic reactions to carbidopa/levodopa were thought to be triggered by the yellow dye excipient present in carbidopa. However, the allergic reaction recurred only when our patient was re-exposed to carbidopa. This was proven by the administration of various formulations, including some that were yellow dye-free. The reaction resolved after treatment with steroids and an antihistamine. The latter was absent once benserazide/levodopa was reintroduced, indicating a true allergic reaction to carbidopa. Our case highlights the importance of

TABLE 2. Current Levodopa Formulations

Trademark	Presentation	Active Component	Excipient
MADOPAR RETARD* [†]	Capsule	Benserazide 25 mg Levodopa 100 mg	Hypromellose Hydrogenated vegetable oil Dibasic calcium phosphate anhydrous Mannitol Povidone Talc Magnesium stearate
MADOPAR [†]	Capsule	Benserazide 50 mg Levodopa 200 mg	Mannitol Dibasic calcium phosphate Microcrystalline cellulose Pregelatinized corn starch Polyvinylpyrrolidone Magnesium stearate Ethyl cellulose Silicic acid Red iron oxide (E172) Sulfosuccinate dioctyl sodium
SINEMET [‡]	Tablet	Carbidopa 25 mg Levodopa 250 mg	Microcrystalline cellulose Corn starch Pregelatinized corn starch Magnesium stearate Indigotin (E132)
SINEMET PLUS [‡]	Tablet	Carbidopa 25 mg Levodopa 100 mg	Microcrystalline cellulose Corn starch Pregelatinized corn starch Magnesium stearate Quinoline yellow (E104)
SINEMET RETARD [‡]	Tablet	Carbidopa 50 mg Levodopa 200 mg	Red iron oxide (E172) Quinoline yellow (E104) Hydroxypropyl cellulose Poly(vinyl acetate-co-crotonic acid) Magnesium stearate
SINEMET PLUS RETARD [‡]	Tablet	Carbidopa 25 mg Levodopa 100 mg	Red iron oxide (E172) Hydroxypropyl cellulose Poly(vinyl acetate-co-crotonic acid) Magnesium stearate
STALEVO [§]	Tablet	Carbidopa 12.5–50 mg Entacapone 200 mg Levodopa 50–200 mg	Croscarmellose sodium Magnesium stearate Corn starch Mannitol (E421) Povidone K30 (E1201) Especial film-cover: Glycerol 85% (E422) Hypromellose Magnesium stearate Polysorbate 80 Red iron oxide (E172) Saccharose Titanium dioxide (E171) Yellow iron oxide (E172)
RYTARY	Capsule, extended release	Carbidopa 23.75–61.25 mg Levodopa 95–245 mg	Tartaric acid Microcrystalline cellulose Mannitol Ethylcellulose Hypromellose 2910 Sodium starch glycolate type A potato Sodium lauryl sulfate Povidones Talc Methacrylic acid Triethyl citrate Croscarmellose sodium Magnesium stearate
DUODOPA [¶]	Enteral suspension	Carbidopa 5 mg/mL Levodopa 20 mg/mL	Carmellose sodium Purified water

*Pharmaceutics data (active substances and excipients) of every levodopa/carbidopa trademark were obtained directly from the pharmaceutical company at issue.

[†]Roche Farma.

[‡]Novag.

[§]Novartis.

^{||}Impax.

[¶]AbbVie Spain.

identifying and reporting the source of an allergic drug response, whether it is caused by the active component or by the excipients present in the formulations.

ACKNOWLEDGMENT

The authors thank Gabriel Moreno, MD, for providing assistance in the development of this article.

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