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Amantadine Enhances Recovery from Delayed Neuropsychiatric Effects Caused by Carbon Monoxide Poisoning: A Case Report

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Abstract **Case Report**

Carbon monoxide (CO) poisoning causes severe brain damage, including delayed neuropsychiatric sequelae (DNS), which occur after a lucid interval following recovery from the insult of acute CO poisoning. Delayed neuropsychiatric syndrome (DNS) is a well-known complication following carbon monoxide (CO) poisoning and develops in up to 50 % of adult survivors. The syndrome is probably immunologically mediated. We describe a 19-year-old female who developed DNS, including slowness, Parkinsonism; irritability and cognitive impairment. All symptoms, including cognitive impairment, were dramatically improved by amantadine monotherapy. The present case illustrates the possibility of amantadine treatment for cognitive impairment and parkinsonism induced by CO poisoning.

Keywords: Amantadine; carbon monoxide poisoning; delayed neuropsychiatric sequelae; NMDA-R antagonist.

INTRODUCTION

Carbon monoxide (CO) is notorious for causing both immediate and long-term brain damage. When someone suffers from acute CO poisoning, they may experience delayed neuropsychiatric sequelae (DNS) even after apparent recovery. These sequelae are characterized by a range of symptoms such as cognitive issues, difficulties with bodily functions, impaired movement, and other neuropsychiatric problems. Despite the common practice of administering hyperbaric oxygen therapy after CO exposure in clinical settings, there's uncertainty about its effectiveness in preventing DNS. Consequently, there's no established treatment for DNS resulting from CO poisoning. In this case study, we present a patient who developed DNS due to CO poisoning. Interestingly, treatment with amantadine (AMA), a blocker of glutamine/N-methyl-D-aspartate receptors (NMDA-R), not only alleviated symptoms of Parkinsonism but also improved cognitive impairment.

CASE PRESENTATION

A 19-year-old woman experienced carbon monoxide poisoning due to a gas leak while bathing, leading to her admission to the emergency department at Sanit Rmel Hospital in Tetouan. She fell into a severe coma but received hyperbaric oxygen therapy, which successfully brought her out of the coma. Brain magnetic resonance imaging revealed symmetric hyperintense lesions in the globus pallidus on both fluid-attenuated inversion recovery imaging (FLAIR) and diffusion-weighted imaging (DWI), indicating acute necrosis of the globus pallidus caused by the carbon monoxide poisoning.

We received the patient two months later in the psychiatric hospital for cognitive impairment, irritability and parkinsonism. The Mini-Mental State Examination (MMSE) score was reduced to 20/30. Routine blood laboratory studies were not remarkable. Her electroencephalography showed normal background activity (10 Hz). Based on the clinical course and MR images, DNS due to CO poisoning was drastically developing and progressing in this case.

AMA administration (100 mg/day, per os) was started against Parkinsonism induced by CO poisoning, and the dosage was gradually increased up to the maximal approved dose of 300 mg/day. About three weeks after AMA administration, memory function improved and the MMSE score was fully recovered, again reaching 30/30, whereas cognitive impairment, including disturbance associated with verbal fluency, attention/processing speed, and executive function, remained to be observed.

FLAIR and DWI showed a decrease in the hyperintense white matter lesions. In total, she was treated with AMA (50–300 mg/day) for 200 days. She no longer showed recurrence of neurological abnormalities even after AMA administration was stopped about a half year after the CO exposure. On follow-up FLAIR and DWI, the globus pallidus lesions remained; however, the subcortical white matter lesions had disappeared.

DISCUSSION

Generally, hyperbaric oxygen therapy is considered to be the first-line medication against CO poisoning in patients who have exposure intervals greater than 24 h, loss of consciousness, or higher carboxyhemoglobin concentration [6]. Approximately 70% of patients who survive CO poisoning exhibit various transient symptoms only during the acute phases, and 10% exhibit DNS, representing recurrent neuropsychiatric symptoms occurring after an interval of apparent normality after the apparent resolution of acute symptoms [1, 7, 8]. Contrary to the acute phase, effective medication for improvement and/or prevention of chronic neuropsychiatric symptoms and DNS is yet to be clarified. The mechanism of brain damage caused by CO exposure is quite complex [1]. It has been established that brain hypoxia induced by forming carboxyhemoglobin is the major mechanism of various types of brain damage [9]. Hypoxia generates several neurotoxic reactions, including increased glutamatergic transmission and activation of redox reactions [10, 11]; however, delay until the occurrence of DNS after improvement of hypoxia cannot be fully explained by hypoxia-induced deficiencies. Therefore, the exact pathomechanism of CO-poisoning-induced DNS is more complex than that of CO-induced hypoxia. Inhibition of excitatory glutamate receptors, such as NMDA-R and glutamate/α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, prevented the deficits of astroglial glutathione synthesis induced by CO exposure [12]. Furthermore, there is an approved NMDA-R antagonist, AMA-activated system xc-, which is the rate-limiting molecule in the glutathione synthesis pathway [11]. The first highlight of this case was that the AMA dramatically improved cognitive function as well as Parkinsonism in DNS induced by CO poisoning.

Indeed, the follow-up brain MR image on Day 390 showed improvements in hyperintense white matter lesions. A case study reported that a combined treatment of methylprednisolone and memantine hydrochloride improved Parkinsonism due to CO poisoning [13]. We previously reported that memantine inhibited NMDA-R with activation of system xc- [14], resembling AMA. The preclinical studies could not detect the effects of AMA on dopamine or muscarinic acetylcholine receptor subtypes around therapeutic AMA concentrations [15], whereas clinical studies suggest several types of side effects associated with mild anticholinergic or hyperdopaminergic functions, such as hallucination, dry mouth, and blurred vision [16]. It has been known that anticholinergic agents negatively affect cognitive function [17]. To prevent the dopaminergic and anticholinergic side effects induced by AMA, we gradually decreased the dose of AMA as soon as possible after detecting improvement in scores of the Clinical Global Impressions Severity of Illness scale (CGI-S: 3). Taken together with previous findings, the present case report suggests that multiple pharmacologic targets of AMA (i.e., NMDA-R antagonism and system xc- activation) contribute to recovery from/prevention of DNS induced by CO poisoning.

CONCLUSION

The present case suggests that AMA is effective against the cognitive impairments and Parkinsonism in DNS induced by CO poisoning. We consider that AMA might become a therapeutic option for DNS due to CO poisoning. Further clinical trials are needed to support the present finding.

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