



Amantadine in the prevention of clinical symptoms caused by SARS-CoV-2

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Abstract

Background Amantadine is a drug that can help in the prevention of SARS-CoV-2 symptomatology, as has been demonstrated in observational clinical studies.

Methods We searched in the PubMed database Clinical Studies of coronavirus-infected patients who have been treated with amantadine in a preventive manner as well as patients with Parkinson's disease.

Results Four clinical studies were found in which relatives of patients with COVID-19 had been prescribed the use of amantadine in a preventive manner to avoid the symptoms caused by the coronavirus.

Conclusion Amantadine is a drug that can be prescribed as a prophylactic that prevents symptomatology caused by SARS-CoV-2 coronavirus.

Keywords Amantadine · SARS-CoV-2 · Prevention

Introduction

In December 2020, it will be 1 year since the SARS-CoV-2 viral disease was first reported. On March 11, 2020, the World Health Organization declared that this new disease caused by a coronavirus had been elevated from a public health problem to a pandemic [1]. Infections have occurred practically all over the world and the number of deaths is increasing every day. The efforts to find a drug that helps to decrease the clinical manifestations caused by the coronavirus have been practically constant.

Several medications have been used to decrease the clinical manifestations caused by the virus, such as hydroxychloroquine [2], ivermectin [3], dexamethasone [4], remdesivir [5].

Remdesivir and dexamethasone have been approved for the treatment of people with severe symptoms caused by the virus [6].

We have studied an adamantane derivative to treat the effects of SARS-CoV-2. Adamantane derivatives have been used as drugs with different biological activities. The best known are amantadine and memantine [7].

We have used a drug to treat the clinical symptoms caused by SARS-CoV-2 that has been approved by the FDA since 1976 for treatment of H1N1 influenza. Amantadine is a small molecule of low-molecular weight whose formula is $C_{10}H_{17}N$ and which is also used as an anti-Parkinsonic, since it seems to be involved in the release of dopamine from the nerve terminals [8]. Amantadine enters the E channel of SARS-CoV-2 and prevents the virus to discharge its genetic content into the cell to generate new viral particles [9].

Materials and methods

A search was carried out on Pubmed of recent literature on studies conducted on patients treated with amantadine and that also the relatives who were in direct contact with the patients have been treated with this drug as a way to prevent the symptoms caused by COVID-19. We also searched for people with Parkinson's disease who are taking amantadine

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as part of their treatment, and who have been infected with SARS-CoV-2.

Results

Amantadine in the prevention of SARS-CoV-2

An observational study has shown that amantadine is an effective drug in the treatment of symptoms caused by SARS-CoV-2 [10].

It has been observed that patients with Parkinson's disease who were prescribed with amantadine as part of their treatment and were infected with the coronavirus did not develop the symptomatology caused by COVID-19 [11, 12].

In recent literature, there are few clinical cases related to the hypothetical role as preventive use of amantadine.

Aranda et al. studied a total of 15 patients of different ages who presented symptoms compatible with COVID-19. The average age of the patients studied was 48 ± 16 years. Ten of them were women and the rest were men. Four percent were suffering from hypertension and three percent from type 2 diabetes mellitus. Only one person reported cardiac disease. The main symptoms they reported were fever, dyspnea, headache, nausea and nasal congestion. Ten of the patients lost their sense of taste and smell. The treatment consisted of 100 mg of amantadine, one tablet in the morning and one in the evening, for a period of 14 days. Most of them were prescribed 500 mg of azithromycin, 200 mg of celecoxib and 500 mg of aspirin for a period of 6 days. Three patients had to receive nebulizations with ipratropium bromide/salbutamol, 3 times a day for 5 days. Two of the patients were administered oxygen (4Lpm) because their oxygen saturation was below 90%. All patients recovered with amantadine treatment and none had to go to the hospital for mechanical ventilation. Family members who were in contact with them were prescribed amantadine 100 mg twice daily as a prophylactic measure [10].

Cortés presents a 75-year-old woman with Parkinson's disease diagnosed 17 years previously is presented. Under medical supervision by her neurologist, the patient was receiving opicapone, 50 mg/day, pramipexole, 2.1 mg/day, levodopa, 1000 mg/day, benserazide, 250 mg/day and amantadine, 100 mg/day and for hyperthyroidism levothyroxine, 25 mg/day. Five years ago, the patient was diagnosed with gastric cancer treated surgically (Billroth II gastrectomy) and with chemotherapy before and after surgery, currently without recurrence of her cancer. After 7 days with a fever oscillating between 37.5 and 38.8 °C together with an unusual sporadic cough, mild diarrhea and fatigue, the patient's husband was diagnosed by PCR with COVID-19 which led to his hospital admission with a diagnosis of SARS-CoV-2 infection with bilateral pneumonia. Despite drug treatment

and the administration of high-flow oxygen with a Monaghan mask, he died 5 days after admission. The female patient and wife of the above, did not present any symptoms of coronavirus infection: neither fever, nor cough, nor diarrhea, nor anosmia, despite having lived with her husband in a very intimate way, sharing a bed and exposed to the aerosols produced by her husband's persistent cough. Once her husband was admitted to hospital, she was isolated at the home of her daughter, who, after the death of her father, assumed the role of main caregiver. Both her daughter and her daughter's husband tested negative for COVID-19 by PCR [11].

Rejda et al. studied 22 patients (10 with multiple sclerosis, 5 with Parkinson's disease and 7 with cognitive impairment) positive for SARS-CoV-2 and were receiving treatment with amantadine or memantine (100 mg q.d and 10 mg b.i.d, respectively) for at least 3 months prior to exposure to infection. All patients were tested after reported person-to-person contact with SARS-CoV-2 infected subjects and confirmed viral infection with SARS-CoV-2 PCR testing of upper and lower respiratory tract specimens. All of them were in quarantine for two weeks from the exposure documented, and none developed clinical manifestations of infectious disease. They also reported no significant change in neurological status in the course of primary nervous system disease [12].

Aranda et al. conducted a clinical study of a 57-year-old person who presented cold symptoms and body pain, with glucose levels of 200 mg/dL, and was prescribed paracetamol (500 mg every 6 h) and naproxen (550 mg daily for 5 days). The patient continued with his treatment for type 2 diabetes mellitus. Due to the persistent cough, azithromycin (500 mg) was added for a period of 3 days; however, the symptomatology continued, so it was decided to perform a real-time PCR test for SARS-CoV-2, which was positive. The treatment prescribed was 100 mg of amantadine twice a day for 14 days. His asymptomatic relatives (wife and daughter) positive for SARS-CoV-2 were prescribed 100 mg of amantadine twice daily as a preventive measure. The patient improved satisfactorily on the sixth day of treatment. The wife and daughter were symptom-free during the 14 days of treatment with amantadine [13].

Table 1 shows cases where amantadine has been used as a treatment and family members have been administered this drug as a measure to prevent them from getting symptoms from SARS-CoV-2 infection

Currently, there are a group of investigators who subscribe to the hypothesis that amantadine offers a protective effect to prevent the replication of the virus in patients who are taking it regularly.

Tipton and Wszolek from the Mayo Clinic suggest that "we must explore all possible options to prevent and seek treatment for COVID-19. The use of low-cost and readily available

Table 1 Studies carried out with amantadine

Clinical Studies	Treatment with amantadine	Prevention of symptoms with amantadine
15 Patients infected with SARS-Cov-2 [10]	Yes	Family members received amantadine 100 mg twice a day and had no symptoms
Clinical case [11]	Yes	SARS-CoV-2 infection, PCR positive did not present symptoms
22 Patients, 10 Multiple Sclerosis, 5 with Parkinson's and 7 with Cognitive Impairment [12]	Yes	SARS-CoV-2 infection, PCR positive did not present symptoms
Clinical case [13]	Yes	Wife and daughter SARS-CoV-2 PCR positive, took amantadine 100 mg in the morning and 100 in the evening, showed no symptoms

drugs is a low-risk and cost-effective approach. We propose amantadine and memantine as two possible candidates" [14]. Aranda-Abreu et al. demonstrate that amantadine blocks the viroporin channel of COVID-19, preventing the release of the viral nucleus in the cell cytoplasm and states that "the use of amantadine when the first symptoms of COVID-19 occur can mitigate the effects of the disease" [9].

In addition, Smieszek et al., conclude that "amantadine could be used as a potent agent to lower viral load if administered early enough in the course of COVID-19 infection and that the cumulation in lysosomes, if effective could reduce viral load, decrease organ spread within the host and decrease the severity and progression of associated disease." They suggest that more studies are needed to examine the role of amantadine [15].

Rejdak and Grieb in a study of patients with a range of neurological disorders concluded that "although their study had limitations due to the small sample size and cross-sectional approach, it indicated that the adamantanes amantadine or memantine exert a protective antiviral effect" and that, if confirmed, adamantanes could be useful in limiting SARS-CoV-2 infection and its clinical neurological sequelae" [12].

Cimolai expressed a view that, although not commonly discussed, the adamantanes should also be reevaluated at least in preliminary in vitro studies for various human coronaviruses [16]. Araujo et al. concluded that "In the absence of a vaccine or medication to help prevent or decrease the effects of the disease, we suggest that amantadine may reduce the effects of COVID-19" [17]. Wiwanitkit says there are many classic drugs that might be useful for management of COVID-19. Amantadine is an antiviral agent that is in that category. Its exact effect has to be further studied [18].

Conclusion

Amantadine due to its lipophilic nature can easily cross the biological membranes. Molecular docking studies have shown that amantadine can interact at the receptor binding domain of the S protein of SARS-CoV-2 [19].

In the case that the virus enters the cell, amantadine would interact with the E-channel, inhibiting the release of RNA into the cell.

This drug can be used preventively by personnel who are constantly exposed to the coronavirus, such as doctors, nurses, pharmacists, as well as people suffering from a disease, and the elderly can receive this drug as a protective measure in the sense that they can become infected with the coronavirus but not develop the characteristic symptoms of the disease.

Amantadine is well absorbed when administered orally and is also well tolerated by the digestive system. The recommended dose for an adult is one 100 mg tablet twice daily for at least 14 days if the person is or has been exposed to SARS-CoV-2.

If the person does not have severe kidney failure, it may be taken indefinitely during the pandemic or if no vaccine is available. Amantadine has a moderate diuretic effect and is excreted unchanged in the urine via glomerular filtration.

In the Drug-bank database, it mentions that the reported lethal dose is 2 g, the half-life is 10–14 h.

In general, amantadine can be used in combination with other medications such as antihypertensives or antidiabetics [17].

At a time when the coronavirus has caused new outbreaks in some countries in Europe, the use of amantadine could prevent the development of symptoms of the disease in case an infection has occurred.

Author contributions Both authors designed and wrote the article.

Compliance with ethical standards

Conflict of interest No conflict of interest.

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