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**Repurposing of
Adamantanes for the
Potential Prevention
or Treatment of COVID-19**

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Adamantanes for the Prevention of COVID-19: A Review of Case Reports

Abstract

Clinical evidence is reviewed for the possible use of the adamantanes amantadine and memantine, for the prevention and/or treatment of COVID-19. Literature searches revealed three series of case reports authored by independent teams of international investigators. Subjects were comprised principally of patients receiving amantadine or memantine for several weeks as part of their treatment regimen for Parkinson's disease, Multiple Sclerosis or Cognitive impairment prior to their infection by SARS-CoV-2. All patients tested positive for SARS-CoV-2 confirmed by RT-PCR of nasopharyngeal swabs. Interestingly, the majority of cases manifested age-related vulnerabilities to COVID-19 as well as the presence of co-morbidities resulting from either severe neurological disorders or type-2 diabetes. Amantadine appeared to prevent the appearance of typical COVID-19- related clinical manifestations of infectious disease in 23/24 cases. In addition, one patient with type-2 diabetes treated with amantadine for 14 days showed clear improvements in clinical status and in oxygen saturation levels; by day 6 he could breathe without the need for oxygen supplementation and was discharged from hospital on day 14. It is necessary to now confirm these findings by randomized controlled trials in order to objectively evaluate the use of these agents for the prevention and/or treatment of COVID-19.

Introduction

Case reports are detailed reports of the symptoms, signs, diagnosis, treatment and follow-up of individual patients. In general they describe a novel finding that, at times, may contribute to new ideas in medicine. They are by their very nature descriptive accounts that are almost always uncontrolled and cross-sectional in nature. With these issues in mind, a search was made by the author relating to the clinical evidence for efficacy of a family of pharmaceutical agents known as adamantanes for the prevention and/or treatment of COVID-19. Three published articles were retrieved relating to the topic and, in all cases, they came in the form of case reports.

Adamantanes and COVID-19

The incursion of a new coronavirus isolated for the first time in Wuhan, China diagnosed on November 17th m 2019 has since been classified by WHO as a global pandemic [1,2]. In the ensuing months, innumerable prophylactic strategies have been proposed and widely adopted including the use of face masks, continuous hand washing, the use of hydroalcoholic gel and social distancing of 1.5-2 meters.

From the pharmacological standpoint, an increasing number of attempts are currently being made to repurpose existing agents including antivirals, antibiotics, antimalarials, anticoagulants, plasma transfusions and many more [3]. Although a significant number of these agents including the antimalarials chloroquin and hydroxychloroquin showed some initial promise, subsequent controlled clinical trials were less impressive [4].

An area of growing interest has started to emerge namely the



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repurposing of the family of agents known as the adamantanes a number of which have established antiviral properties. Two examples namely amantadine and memantine will suffice to illustrate this point. It has been proposed the amantadine has the capacity to block the viroporin channel of the E protein of SARS-Cov-2 the virus responsible for COVID-19 [5]. In a High throughput gene screening of agents able to inhibit the host cell protease *Cathexin L*, amantadine was found to be among the most effective resulting in decreased viral entry into the host cell and impaired replication [6].

Given the fact that COVID-19 pandemic has only been a matter of everyday discussions and preoccupations for less than 1 year for the vast part of the world, and given the even more recent interest in the repurposing of members of the adamantane family of agents many of which are known to possess antiviral potential, it is not surprising that there have, to date been no published results of randomized controlled trials to assess the efficacy of these agents to say nothing of systematic reviews or meta-analyses of any published findings. Consequently, we must rely for the moment on the reports of individual cases, generally uncontrolled and observational in nature. There are currently three published reports involving a total of 24 patients in which there is subjective evidence of a protective effect of an adamantane against COVID-19 [7-9].

Adamantanes, Neurodegenerative diseases and COVID-19

Adamantanes such as amantadine and memantine are widely used for the treatment of neurodegenerative diseases such as Parkinson's Disease, Multiple sclerosis and Alzheimer's Disease [10-12]. Patients in these groups frequently are prescribed amantadine for relatively long periods of time. Hence if one of these patients taking amantadine is exposed to SARS-CoV-2 and given the evidence base for an antiviral action of amantadine described above, it is conceivable that such patients may experience some protective effect of amantadine against COVID-19. Consequently the following Case report relates to the protective effect of amantadine against COVID-19.

Amantadine, Parkinson's Disease and COVID-19

Amantadine is widely used for the treatment of Parkinson's

Disease [PD] and its related dyskinesias [Butt] Patients with PD frequently are prescribed amantadine for relatively long periods of time. Hence if one of these patients taking amantadine is exposed to SARS-CoV-2 and given the evidence base for an antiviral action of amantadine described above, it is conceivable that such patients may experience some protective effect of amantadine against COVID-19. Case reports #1 and #2 illustrate such a possibility.

Case report #1

In this study, 5 patients with PD [mean age: 68+/-15 yr, 3 males, 2 females, all receiving L-Dopa] tested positive for COVID-19 after documented person-to-person contact. All were quarantined for 14 days after exposure; all had been receiving amantadine 100 mg/d for at least 3 months prior to infection exposure. None of the 5 patients developed clinical manifestations of infectious disease.

Case report #2

In this study, a 75 yr-old woman with PD diagnosed 17 years previously. Under medical supervision by her neurologist was receiving opicapone 50 mg/d, pramipexole 2.1 mg/d, levodopa 1000 mg/d, benzaride 250 mg/d, and amantadine 100mg/d. She also received levothyroxine 25 mg/d for her hyperthyroidism. % years ago, the patient was diagnosed with gastric cancer that was treated surgically [Billroth II gastrectomy] and with chemotherapy before and after surgery was currently cancer free. After 7 days of oscillating fever [37.5-38.8 deg C] together with a sporadic cough, mild diarrhea and fatigue, the patient's husband tested positive for COVID-19 by RT PCR that led to hospital admission for SARS-CoV-2 infection with bilateral pneumonia. Despite drug treatment, high-flow oxygen [Monaghan mask] he died some days after admission. The wife of the above and object of this clinical case did not manifest any symptoms of COVID-19, neither fever, cough, diarrhea, anosmia despite having lived with her husband in an intimate manner, sharing the same bed and exposed to her husband's persistent cough. Once her husband had been admitted to hospital, she was isolated at the home of her daughter who, after the death of her father, she assumed the role of main caregiver. Both her daughter and her daughter's husband tested negative for COVID-19 [9].

Amantadine, Multiple Sclerosis and COVID-19

Patients with Multiple Sclerosis are also regularly prescribed amantadine for the management and treatment of MS-related fatigue and this is strongly recommended by the German Multiple Sclerosis Society [GMSS]. Typically patients receive 100mg bid for periods of 1 month [11]. As was the case for the PD cases described above, it is conceivable that such patients may benefit from some degree of protection against COVID-19. Case Report #3 examines this possibility.

Case report #3

In this study, 10 patients with multiple sclerosis, [mean age: 38+/-10 yr, 3 males 7 females] tested positive for CoVID-19 by RT-PCR of nasopharyngeal swabs and were receiving amantadine in stable registered doses for at least 3 months prior to exposure to infection. Two week quarantine was observed in all cases following documented exposure. None of the 10 patients developed clinical manifestations

of infectious disease [8].

Memantine, Cognitive Impairment and COVID-19

Cognitive impairment resulting from a range of conditions including brain injury is increasingly being treated by adamantanes [10]. Moreover, memantine, an adamantane analogue is now routinely prescribed to patients with cognitive impairment related to Alzheimer's Disease and there is evidence to support a role for memantine as an antiviral [13]. The findings reported in Case Report #4 are consistent with this notion.

Case report #4

In this report, 7 patients, mean age: 71+/- 10 yrs, 4 males, 3 females with duration of cognitive impairments of 7+/- yrs had been administered Donepezil [n=5] or Rivastigmine [n=2]. All 7 patients became infected by SARS-CoV-2 confirmed by RT-PCR. All 7 patients were being treated with memantine [10 mg bid] for at least 3 months prior to exposure to the virus and all were quarantined for two weeks following documented exposure to the virus. None of the 7 patients went on to develop clinical manifestations of infectious disease [8].

Amantadine, Type-2 Diabetes and COVID-19

Patients with Type-2 diabetes are more likely to have increased severity of COVID-19. In a cohort of 7337 patients with COVID-19 with or without type-2 diabetes, it has been shown that those with diabetes required increased interventions during their hospital stay compared to the non-diabetics. Furthermore, it was shown that patients with poor glucose control suffered higher mortality rates [14]. It is therefore essential that new therapies be tested in such patients. Case Report #5 may offer one possible alternative that may be worthy of follow up.

Case report #5

A 57 yr old man with type-2 diabetes had cold symptoms, muscle pain and persistent cough tested positive for COVID-19 by RT-PCR was prescribed amantadine [100 mg bid] for 14 days, nebulized, 500 mg aspirin added for 5 days. Patients wife [54 yr] and daughter [33 yr] also tested positive for COVID-19 and were asymptomatic were each prescribed amantadine [100 mg bid for 14 days] as a preventive measure. The patients clinical status and oxygen saturation levels improved with combination therapy and by day 6 he could breathe without oxygen supplementation. The patient was released from hospital on day 14. The two family members who were in contact with the patient and who had tested positive for COVID-19 had been receiving amantadine [100 mg/d, 14 days] did not go on to develop symptoms [9].

Conclusion

This review is by way of a summary of clinical evidence for the possible use of the adamantanes amantadine and memantine, two agents with established antiviral properties for the prevention and/or treatment of COVID-19. Due to the short lapse of time since the appearance of SARS-CoV-2, the only available published data is in the form of case reports. Literature searches revealed three such reports authored by three independent teams of investigators from

Spain, Poland, Mexico and Portugal.

Subjects identified were made up principally of patients who had been receiving one of the adamantanes [amantadine or memantine] for several weeks as part of their treatment regimen for PD, MS or Cognitive impairment prior to infection by SARS-CoV-2. All patients tested positive for SARS-CoV-2 confirmed by RT-PCR of nasopharyngeal swabs. The majority of cases manifested age-related vulnerabilities to COVID-19 as well as the presence of co-morbidities resulting from severe neurological disorders or type-2 diabetes. In spite of this, amantadine appeared to prevent the appearance of typical COVID-19- related clinical manifestations of infectious disease. In addition, one patient with type-2 diabetes treated with amantadine for 14 days showed clear improvements in clinical status and in oxygen saturation levels; by day 6 he could breathe without the need for oxygen supplementation and was discharged from hospital on day 14.

Clearly, information of this nature garnered from case reports with their inherent biases due to limited numbers of patients together with confounding factors related to the use of concurrent medications in some cases will necessitate the confirmation of these findings followed, if appropriate by randomized controlled trials in order to further evaluate the usefulness of these agents for the prevention and/or treatment of COVID-19.

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