DOI: https://doi.org/10.5114/ait.2020.93137

A possible antiviral effect of amantadine in an AH1N1 influenza-infected patient – a case report

Piotr Palaczyński[1], Magdalena Garus[1], Magdalena Śliwczyńska[2], Hanna Misiołek[1]

[1]*Clinic of Anesthesiology and Intensive Therapy, Department of Anesthesiology, Intensive Therapy and Emergency Medicine, Medical University of Silesia, Katowice, Poland*
[2]*Postgraduate Study, Clinic of Anesthesiology and Intensive Therapy, Department of Anesthesiology, Intensive Therapy and Emergency Medicine, Medical University of Silesia, Katowice, Poland*

Anaesthesiol Intensive Ther 2020; 52, 1: 67–69

Dear Editor,

Acute respiratory infections caused by various viral strains are among the most frequent illnesses across the world [1]. Annual epidemics caused by influenza A viruses are one of the leading factors of morbidity and mortality. Therefore both prophylaxis and antiviral pharmacological treatment are the focal point of many past and ongoing studies.

Amantadine is a tricyclic water soluble amine, a derivative of adamantine. It was the first identified inhibitor of influenza virus that acts by blocking the virus M2 protein ion channel and inhibiting the early stages of virus replication [2]. Historically amantadine played a major role in antiviral treatment and prophylaxis, nowadays reduced due to the emergence of amantadine-resistant influenza strains [3]. The main mechanisms of resistance are based on mutations in the M2 protein that leads to the loss of the possibility of binding or action. Amino acid substitutions in the M2 protein prevent binding to the ion channel or modify its structure to allow it to operate in the presence of an active drug [4]. Most mutations responsible for the drug resistance do not cause deterioration of replicative functions and virulence [5].

In most cases influenza virus infection manifests as an upper airway inflammation, occasionally leading to bronchial hyper-reactivity, distal airway obstruction, impaired diffusion capacity, and severe alveolar inflammation that may cause respiratory failure. Currently treatment of severe influenza disease focuses on prompt antiviral therapy with neuraminidase inhibitors such as oseltamivir or zanamivir due to the fact that most circulating strains are susceptible to these agents. Possible therapeutic interventions also include immunomodulation and extracorporeal membrane oxygenation [6].

Beside its use as an antiviral agent, amantadine is a potent, multipurpose drug used in many clinical settings. Currently the main indications for the use of amantadine are Parkinson's disease, both in monotherapy and combined with other drugs [7], traumatic brain injury [8], autistic spectrum disorders, attention deficits, hyperactivity disorders, drug-induced extrapyramidal side effects and motor fluctuations during L-DOPA treatment. Current research assesses its use as an antidepressant [9] and antiepileptic drug [10]. Neurological effects are mainly attributed to the impact on the dopaminergic system through enhancement of dopamine release and inhibition of its reuptake in brain [11]. It is suggested that amantadine may have direct action on D2 receptors and increases the neosynthesis of those [12]. Noradrenergic regulation may contribute to some of its effects by increasing the norepinephrine levels [13]. Inhibition of NMDA receptor activation through the stabilization of ion channels and more rapid channel closure as well as immunomodulatory properties also contribute to the systemic effects of amantadine [14].

CORRESPONDING AUTHOR:

Piotr Palaczyński, Postgraduate Study, Clinic of Anesthesiology and Intensive Therapy, Department of Anesthesiology, Intensive Therapy and Emergency Medicine, Medical University of Silesia, Katowice, Poland, e-mail: piotrpalaczynski@gmail.com

A seventy-year-old woman was admitted to the Intensive Care Unit (ICU) due to acute respiratory failure from the Department of Surgery, where she was treated for cellulitis of the lower limbs. In the 24 hours preceding admission to the ICU the general condition of the patient deteriorated, mechanical ventilation was introduced due to respiratory failure, and exacerbation of chronic circulatory and renal failure symptoms were observed. Medical history of the patient included atrial fibrillation, lower limb ischemia caused by atherosclerosis, and chronic heart and renal failure.

After admission the patient was sedated, mechanical ventilation with high doses of oxygen was continued, and pressor amines and hemodynamic monitoring due to persistent hypotension and continuous venovenous hemodiafiltration were introduced. Samples for blood and bronchoalveolar lavage culture were secured. A broad-spectrum antibiotic therapy with vancomycin administered due to its blood concentration and imipenem in a dose of 500 mg with cilastatin in a dose of 500 mg administered four times a day were introduced, later deescalated to ciprofloxacin in a dose of 400 mg three times a day in accordance with bacteriological culture results. Oseltamivir was used as an antiviral agent in a dose of 75 mg orally two times a day and fluconazole was used as an antifungal agent in a dose of 400 mg two times a day. Initial chest radiograph revealed patchy, confluent consolidations in the central and lower area of right lung and possible pleural effusion in the right pleural cavity. Bronchoalveolar lavage cultures revealed infection of *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Candida albicans* and influenza A H1N1 virus. The general condition of the patient gradually improved, both clinical and laboratory indicators of inflammation decreased, and continuous hemodiafiltration and pressor amines therapy were ceased. The sedation was terminated, yet the patient remained unresponsive and a poor neurological outcome was prognosed. Due to the necessity of mechanical ventilation, percutaneous tracheotomy was performed.

On the 24th day after admission symptoms of inflammation reemerged. Bronchoalveolar lavage culture was positive for *Enterobacter cloacae* and influenza A H1N1 virus; hence antibiotic therapy was extended to colistin 2 000 000 IU three times a day intravenously and 2 000 000 IU two times a day by inhalation. Also, oseltamivir was reintroduced in a dose of 75 mg orally two times a day. Afterwards the patient's clinical condition improved yet influenza A H1N1 virus was persistently positive in consecutive tests. Due to neurological condition amantadine in a dose of 100 mg orally was administered for 9 days. Gradual improvement of psychomotor function was observed, inflammatory indicators normalized and bronchoalveolar lavage tested negatively for any pathogens. After 55 days of hospitalization the patient was discharged home in optimal neurological condition with no need of invasive ventilation via a tracheotomy tube.

In the presented case amantadine was initially used as a neuroprotective factor in order to decrease the range of damage in the patient's nervous system and to improve psychomotor recovery, which is consistent with studies concerning the subject [15]. Rapid neurological improvement was observed probably due to the use of the drug and other factors such as intense rehabilitation.

Bronchoalveolar lavage tested for influenza A resulted in persistently positive outcomes after initial therapy with oseltamivir, even though clinical condition of the patient improved. The study of Ngyuen *et al*. [16] suggested that a combination of antiviral factors (amantadine, oseltamivir and ribavirin) may be more efficient than monotherapy or double combinations of aforementioned factors in vitro. Preclinical data of use of triple antiviral therapy on mice proved more beneficial even in adamantine-resistant influenza strains [17]. Unfortunately, a large blinded, randomized, controlled trial conducted by Beigel *et al*. on triple antiviral therapy did not present beneficial clinical outcomes in the study group, although a statistically significant decrease in viral shedding was noted [18]. The reason for the dissonance between shortening of viral shedding and no clinical effect is yet to be revealed. In this case oseltamivir and amantadine were used consecutively, so a possible synergistic effect is debatable. Nevertheless, a cause and effect relationship may be seen amid the implementation of amantadine therapy and cessation of viral shedding.

Another aspect and limitation of our study is the fact that no viral resistance for oseltamivir and amantadine was tested in the secured material. Studies show mostly high yet variable amantadine resistance in different types of influenza across the world [19]. There is scarce evidence on up to date profiles of resistances on different antiviral agents in Poland [20], which we see as an opportunity for further research and can greatly help to combat cases of severe viral pneumonia such as that presented.

Amantadine is much cheaper and more easily accessible in comparison with other antiviral factors and recommended forms of therapy in severe viral pneumonia, bearing in mind different indications of use. In this case cessation of viral shedding ended the need of long isolation of the patient, which contributed to reduction of the costs of treatment.

To conclude, in this case of severe AH1N1 viral pneumonia which caused multisystem organ failure and central nervous system disorder amantadine served as a neuroprotective agent and possibly led to cessation of viral shedding, which contributed to the positive outcome and discharge from the ICU. Amantadine is a pleiotropic, multipurpose, easily accessible drug. It could be a useful implementation in cases of severe viral pneumonia with neurological disorders. However, further research and confirmation of its effects are needed. We hope that the presented case will spark the interest in the role of amantadine in the ICU

because cases of severe viral pneumonia are becoming more frequent.

ACKNOWLEDGEMENTS

1. Financial support and sponsorship: none.
2. Conflict of interest: none.

REFERENCES

1. Monto AS. Epidemiology of viral respiratory infections. Am J Med 2002; 112: 4-12. doi: 10.1016/S0002-9343(01)01058-0.
2. Nicholson KG, Wood JM, Zambon M. Influenza. Lancet 2003; 362: 1733-1745. doi: 10.1016/S0140-6736(03)14854-4.
3. Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006; 367: 303-313. doi: 10.1016/S0140-6736(06)67970-1.
4. Bright RA, Medina MJ, Xu X, et al. Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. Lancet 2005; 366: 1175-1181. doi: 10.1016/S0140-6736(05)67338-2.
5. Abed Y, Goyette N, Boivin G. Generation and characterization of recombinant influenza A (H1N1) viruses harboring amantadine resistance mutations. Antimicrob Agents Chemother 2005; 49: 556-559. doi: 10.1128/AAC.49.2.556-559.2005.
6. Wieruszewski PM, Linn DD. Contemporary management of severe influenza disease in the intensive care unit. J Crit Care 2018; 48: 48-55. doi: 10.1016/j.jcrc.2018.08.015.
7. Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease: a review. JAMA 2014; 311: 1670-1683. doi: 10.1001/jama.2014.3654.
8. Meythaler MJ, Brunner RC, Johnson, A, Novack TA. Amantadine to improve neurorecovery in traumatic brain injury-associated diffuse axonal injury: a pilot double-blind randomized trial. J Head Trauma Rehabil 2002; 17: 300-313. doi: 10.1097/00001199-200208000-00004.
9. Raupp-Barcaro IF, Vital MA, Galduroz JC, Andreatini R. Potential antidepressant effect of amantadine: a review of preclinical studies and clinical trials. Braz J Psychiatry 2018; 40: 449-458. doi: 10.1590/1516-4446-2017-2393.
10. Turner AL, Perry MS. Outside the box: medications worth considering when traditional antiepileptic drugs have failed. Seizure 2017; 50: 173-185. doi: 10.1016/j.seizure.2017.06.022.
11. Fletcher EA, Redfern PH. The effect of amantadine on the uptake of dopamine and noradrenaline by rat brain homogenates. Br J Pharmacol 1970; 22: 957-959. doi: 10.1111/j.2042-7158.1970.tb08486.x.
12. Stone TW. Responses of neurones in the cerebral cortex and caudate nucleus to amantadine, amphetamine and dopamine. Br J Pharmacol 1976; 56: 101-110. doi: 10.1111/j.1476-5381.1976.tb06964.x.
13. Moryl E, Danysz W, Quack G. Potential antidepressive properties of amantadine, memantine and bifemelane. Pharmacol Toxicol 1993; 72: 394-397. doi: 10.1111/j.1600-0773.1993.tb01351.x.
14. Wandinger KP, Hagenah JM, Kluter H, Rothermundt M, Peters M, Vieregge P. Effects of amantadine treatment on in vitro production of interleukin-2 in de-novo patients with idiopathic Parkinson's disease. J Neuroimmunol 1999; 98: 214-220. doi: 10.1016/s0165-5728(99)00093-4.
15. Tomruk SG, Bakan N, Karaören G, Salvarcý A. Amantadine sulfate treatment in cases with brain injury in the ICU: a retrospective clinical trial. Crit Care 2015; 19: 453. doi: 10.1186/cc14533.
16. Nguyen JT, Hoopes JD, Smee DF, et al. Triple combination of oseltamivir, amantadine, and ribavirin displays synergistic activity against multiple influenza virus strains in vitro. Antimicrob Agents Chemother 2009; 53: 4115-4126. doi: 10.1128/AAC.00476-09.
17. Nguyen JT, Smee DF, Barnard DL, et al. Efficacy of combined therapy with amantadine, oseltamivir, and ribavirin in vivo against susceptible and amantadine-resistant influenza A viruses. PLoS One 2012; 7: e31006. doi: 10.1371/journal.pone.0031006.
18. Beigel JH, Bao Y, Beeler J, et al. Oseltamivir, amantadine, and ribavirin combination antiviral therapy versus oseltamivir monotherapy for the treatment of influenza: a multicentre, double-blind, randomised phase 2 trial. Lancet Infect Dis 2017; 17: 1255-1265. doi: 10.1016/S1473-3099(17)30476-0.
19. Barr IG, Deng YM, Iannello P, Hurt AC, Komadina N. Adamantane resistance in influenza A(H1) viruses increased in 2007 in South East Asia but decreased in Australia and some other countries. Antiviral Res 2008; 80: 200-205. doi: 10.1016/j.antiviral.2008.06.008.
20. Stephenson I, Clark TW, Pareek M. Antiviral treatment and prevention of seasonal influenza: A comparative review of recommendations in the European Union. J Clin Virol 2008; 42: 244-248. doi: 10.1016/j.jcv.2008.04.001.