The use of aminocaproic acid for the prevention and treatment of influenza and acute viral respiratory infections

V.P. Lozitsky, A.S. Fedchuk, T.L. Gridina, S.V. Pozdnyakov

State Institution "Ukrainian I.I. Mechnikov Anti-Plague Research Institute", Ministry of Health of Ukraine, Odesa

Abstract. Developing methods and means aimed at preventing and treating influenza and acute respiratory viral infections (ARVI) is an urgent task faced by the healthcare system. The results of the study below provide grounds for using aminocaproic acid as an effective tool against influenza.

Keywords*: influenza and ARVI, chemotherapy and chemoprophylaxis of viral infections, aminocaproic acid, proteolysis inhibitor.*

Contact address: *Viktor Petrovych Lozitsky*
Phone: 066 013 81 07

INTRODUCTION

Influenza is the most common viral disease that causes significant harm to human health and massive economic damage. Annual influenza epidemics and post-influenza complications claim more human lives than any other existing infectious diseases. 2005 witnessed an outbreak of avian influenza caused by the H5N1 strain. Late April 2009 marked the beginning of a rapid global spread of an influenza virus with the strain name A/California/04/2009 (H1N1) and with the genome containing genes of avian, swine and human influenza viruses. The WHO announced an influenza pandemic and presented the Global Influenza Preparedness Plan to be adhered to by all the countries in case of a pandemic [1]. Within the framework of the Global Plan, the WHO recommends each country to create the necessary reserve of therapeutic chemical agents to be used for prophylaxis and treatment in situations of a sharp increase in influenza patients among the population.

Search for active therapeutic chemical agents against influenza remains an urgent and promising task. The development of new pharmacological substances is rather a time consuming and financially burdensome way of creating medicines. Therefore, the most promising and cost-effective strategy is to uncover antiviral properties of the officinal drugs that are already commercially manufactured (though intended for different medical uses), their activity and side effects being well-known due to their long-term use [2]. Besides, this approach allows to extend the indications for the use of such medicinal products.

In this context, the study below was aimed at collecting and systematizing available evidence regarding anti-influenza efficacy of the proteolysis inhibitor of aminocaproic acid (ACA) and updating the section on its use for preventing and treating influenza and ARVI in the Instructions for medical use of this medicinal product.

MATERIALS AND METHODS

The materials used in the study are as follows:

Cell culture: fragments of 11-14-day chick embryo chorioallantoic membrane (CAM).

Experimental animals: white outbred male mice; weight: 12-15 g.

Viruses: the A/PR/8/34 (H1N1) virus which is highly virulent for mice, the strain of influenza virus A/Hong Kong/1/68 (H3N2) from the museum collection of the Laboratory of immunobiological and therapeutic chemical agents of the State Institution "Ukrainian I.I. Mechnikov Anti-Plague Research Institute" of the Ministry of Health of Ukraine (UAPRI). The virus of avian influenza H5N3 used in the research was provided for the museum collection of the Laboratory above by the "Vidrodzhennya M" (Revival M) LLC (Odesa), and deposited by the Depository sector of the Scientific center for microorganism strains of the State Scientific Control Institute of Biotechnology and Strains of Microorganisms (Kyiv, Ukraine).

The study of anti-influenza activity of the medications used concomitantly *in vitro* was carried out according to the author's original modified method on the cell culture of 10-12-day chick embryo chorioallantoic membrane (CAM) which is currently recommended by the State Pharmacological Center [4, 5].

The study of anti-influenza protective efficacy was based on a model of experimental influenza in white mice that were intranasally infected with the mice-adapted influenza virus A/PR/8/34 (H1N1), or with the A/Hong Kong/1/68 (H3N2) strain.

The experiments were performed in compliance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and other Scientific Purposes (Strasbourg, 18 March 1986).

RESULTS

It has been established that the interaction between influenza virus and cell membranes with high sensitivity results in increased proteolysis that leads to cleavage of influenza virus hemagglutinin. This facilitates virions' entry into the cell and stimulates viral deproteinisation and subsequent replication. Proteolysis inhibitors (PIs), in particular, aminocaproic acid, block proteolysis activation and the viruses' entry into the cells, which reduces the viral harvest [6-8]. Numerous studies revealed a statistically significant proteolysis inhibitor aminocaproic acid facilitated blockage of replication of influenza viruses types A, B, parainfluenza, adenoviruses in various cell systems [8-10].

ACA preserves pulmonary vascular structure and blood flow, blocks the development of lung perivascular edema and hemorrhagic syndrome, thus preventing failures of aerohematic barrier. The medicinal product under consideration prevents secretory antibodies, non-specific viral inhibitors and interferon from destruction by proteases. Administration of aminocaproic acid to animals with experimentally induced influenza activates their defense reactions by stimulating lung secretion, inducing perivascular and peribronchial lymphoid infiltration, and by increasing the number of pulmonary granular cells [9].

To animals with experimental influenza, ACA was administered through intranasal, peroral or parenteral routes,

according to the therapeutic scheme, emergency prophylaxis scheme and long-term prophylaxis scheme (for 5 days with re-infection 15-45 days later). It is important to note that animals treated with aminocaproic acid displayed a considerably higher resistance to re-infection after a 30-day interval, compared to those in the placebo-treated control group. Due to ACA etiotropic, pathogenic and immunomodifying action on animals with experimental influenza, there was a statistically significant decrease in lethality, as well as a substantial reduction of infectious virus titers in the lungs of mice both infected with a non-lethal strain of A/Hong Kong/1/68 (H3N2), and with a lethal strain of the highly virulent virus A/PR/8/34 (H1N1) [8].

Concomitant use of ACA and specific immunoglobulin developed by the Institute resulted in potentiating their anti-influenza effect in experimental conditions. This data was confirmed in the course of clinical observations, which proved the expediency of recommending concomitant use of these medications for purposes of health care [10]. That led to using significantly lower effective doses of immunoglobulin, lower drug loads and less expensive treatment.

Concomitant use of ACA and the nationally produced antivirus agent Amizon resulted in potentiating anti-influenza effect. The effect was observed *in vitro*, both for human and avian influenza virus. A potentiated anti-influenza effect was also observed in mice that were infected with the highly virulent virus A/PR/8/34 (antigenic formula H1N1) and concomitantly administered ACA and Amizon.

The results above prove it possible to make anti-influenza therapy more effective by means of using an integrated scheme based purely on nationally produced medicinal products, which is especially relevant in view of rapidly spreading influenza pandemic.

Concomitant use of ACA and the neuraminidase inhibitor oseltamivir (Tamiflu) that is considered the most effective Based on the results of the studies and on the expert opinions provided by the State Pharmacological Center of the Ministry of Health of Ukraine, the range of medications officially approved for the prevention and treatment of influenza and ARVI in adults and children, including infants in the first year of life, has been extended to include aminocaproic acid. This is of vital importance in the situation of influenza pandemic ripping through Ukraine.

Contraindications for the use of aminocaproic acid are high individual sensitivity, a tendency to thrombosis and embolism, any inheritable and secondary thrombophilia, disseminated intravascular coagulation, macrohematuria, severe kidney diseases, pregnancy and lactation.

Peroral administration of aminocaproic acid to patients with influenza and ARVI normally lasts for 3 to 7 days. The duration of the treatment depends on the severity of the disease and is determined by the doctor in each individual case. The doctor can also change the dosage and recommend a repeat course of treatment.

In order to be provided with prophylactic protection during influenza epidemics, children and adults should be administered ACA solution via intranasal instillation (3 to 4 times a day). For persons in the focus of infection and in direct contact with the sick, ACA intranasal instillations should be combined with its peroral uses, according to the therapeutic scheme.

The treatment of influenza and ARVI in adults can be based on the ACA doses recommended for teenagers. If necessary, aminocaproic acid can be used in combination with other existing antiviral medications (amizon, oseltamivir, etc.), as well as with interferon or its inductors, which increases the efficacy of the treatment.

In case of severe and hypertoxic forms of influenza or ARVI, the ACA dose can be increased by 30-40%, with half of the daily dose administered through intravenous infusions. Intravenous infusions should be performed under the control of coagulogram.

The topical (local) route of ACA administration has also proved to be effective. We recommend placing into the nostrils wound cotton swabs soaked with a 5% solution of aminocaproic acid or powder dissolved in unsweetened water, for 5 to 10 minutes, every 2 to 3 hours. Alternatively, it is recommended to drip 3 to 5 drops of this solution into each nostril, with the same intervals (2-3 hours). The solution can also be used for inhalations.

- teenagers: 5-8 g (5-8 bags or 10-16 tablets) daily taken with water and divided into 4-5 intakes, 1-2 bags each, or 100-160 ml of a 5% solution (divided into 4-5 intakes). ACA in the form of tablets can be administered to children no younger than 3 years of age.
- children 7 to 10 years of age: 4-5 g (4-5 bags or 8-10 tablets) daily taken with water, or 80-100 ml of a 5% solution (divided into 4-5 intakes);
- children 2 to 6 years of age: 2-4 g (2-4 bags or 4-8 tablets) daily, (40-80 ml of a 5% solution) divided into 4 intakes, 1-2 tablespoons each;
- infants in the first two years of life: 1-2 g (1-2 bags) daily (20-40 ml of a 5% solution) divided into 4 intakes, 1-2 teaspoons each. The medication can be taken with food or drinks;

In case of peroral administration, the medicinal product is administered in the doses below:

Instructions for the use of aminocaproic acid for anti-influenza purposes are as follows:

For influenza A, B and other acute respiratory viral infections, aminocaproic acid is administered through the enteral and topical routes. For peroral administration, the product is taken in the forms of powder or tablets, as well as a pre-made 5% solution. Alternatively, ACA powder is previously dissolved in boiled, cooled and sweetened water in the proportion 1 g (1 bag) of ACA for 20 ml (2 tablespoons) of water, which yields a 5% solution. A more accurate preparation or dosage of the solution requires the use of a 10 or 20 ml medical syringe without needle.

It is worth mentioning that in Ukraine aminocaproic acid as a substance is produced by the “Chemical Technology” State Enterprise (Severodonetsk). As a medicinal product in the form of solution it is produced by six companies, in the form of powder – by one company, in the form of tablets – by one company. The UAPRI has prepared necessary modifications to the Instructions for medical use of different dosage forms of aminocaproic acid (solution, powder, tablets) and has submitted them to the State Pharmacological Center. The Institute has also developed a booklet and a patient information bulletin containing the information on how to use ACA for preventing and treating influenza and ARVI in children and adults.

It should be emphasized that ACA is a nontoxic medication and, unlike all the existing anti-influenza agents, is allowed to be used by children as early as in the first year of life. Moreover, aminocaproic acid prevents the development of toxic shock syndrome and hemorrhagic syndrome or reduces their intensity, which is crucial in view of the fact that these syndromes contribute to numerous complications, particularly pneumonia.

It is important to mention that the Institute has developed a technology targeting children of this age group. The technology is designed to produce bispecific immunoglobulin directed against influenza and staphylococcus. This anti-influenza bispecific immunoglobulin contains high levels of antibodies to current influenza virus strains and is also rich in anti-staphylococcal alpha-toxin antibodies. The medicinal product has undergone thorough experimental and clinical studies. Its clinical studies carried out in the clinic of the Department of Children's Diseases at Odesa Medical

University (OMU) and at the Research Institute of Influenza (RII, St. Petersburg, Russia) proved its high clinical efficacy. Those of the children diagnosed with influenza and ARVI who were administered bispecific immunoglobulin with high levels of antibodies to current influenza virus strains and rich in anti-staphylococcal alpha-toxin antibodies, demonstrated a significantly lower number of complications and pneumonias, as well as a shorter duration of fever and inpatient care.

The results of the experimental studies and clinical observations were submitted to the State Pharmacological Center of the Ministry of Health of Ukraine (the Center). The Director of the Center V.T. Chumak in his letter No. 6780/212-8 of 16 November 2009 reported the following, "At its meeting held on 29 October 2009, the scientific advisory board of the Pharmacological Center of the Ministry of Health of Ukraine adopted the decision to recommend the inclusion of the clause "*treatment and prophylaxis of influenza and ARVI in children and adults*" in the Therapeutic Indications section of Instructions for medical use of aminocaproic acid, with all the necessary amendments made in the Posology and Method of Administration section."

According to the analysis of epidemiological efficacy of aminocaproic acid, children who were administered ACA tended to display significantly lower influenza incidence rates, compared to those displayed by children not immunized with it [13]. The tendency persisted also for the following 4 months. The number of children who caught influenza and ARVI up to 6 times a year was reduced by 60%. The prevention course shortened the duration of one disease by 2.7 days on average.

The prophylactic efficacy of aminocaproic acid in 3 to 6-year-old children with recurrent infections was revealed in the course of observations carried out in preschools [13]. The first prevention course was held for 2 weeks in September. The children were immunized with 0.5 ml of a 5% ACA solution two times a day (in the morning and evening), through a device to secure intranasal delivery. The second analogous prevention course was carried out during the period when the influenza epidemic was at its height.

Aminocaproic acid has been found to be particularly effective when administered at early stages of the disease, due to its ability to prevent the development of toxic shock syndromes, as well as to reduce the occurrence of secondary bacterial infections (by 50% and more). Locally administered ACA promotes speedy restoration of the ratio of cylindrical and flat epithelium, reduces the viral antigen host period and the duration of cytotoxic effect of the virus [12].

Clinical observations conducted jointly with the scientists of Odesa State Medical University demonstrated the efficacy of aminocaproic acid preparations used for treating children of various age groups diagnosed with influenza and other acute respiratory viral infections [11, 12].

Thus, the results obtained from *in vitro and in vivo* experimental studies provide convincing evidence of high anti-influenza activity of aminocaproic acid.

It is established that aminocaproic acid protects viral antigens from autolysis in the process of preserving inactivated vaccines, thus prolonging their shelf life and increasing the protective effect of the vaccines (*Patent of Ukraine No. 9574 of 17 October 2005. Bulletin No. 10.3 "The method of antiviral vaccine production"*). Combination therapy with ACA and natural interferon inductor stimulates interferon production and increases the degree of protection in animal models with experimentally induced viral infection (*Patent of Ukraine "Interferon induction method". Patent No. 14402 of 15 May 2006. Bulletin No. 5. International Patent Classification (2006) A61K 45/00*).

Through the combination above, the already available amount of oseltamivir can be used for preventing and treating influenza in a considerably bigger number of patients. Furthermore, there have been an ever increasing number of reports on oseltamivir-resistant strains, as well as on adverse effects associated with the use of oseltamivir, especially in children. Therefore, the problem of lowering the dose of oseltamivir used for preventing and treating influenza still persists. One of the most effective ways to solve the problem can be combination therapy with oseltamivir and aminocaproic acid. Also, combined use of medications with different mechanisms of antiviral action is known to prevent viruses from developing drug-resistance.

- reducing the cost of treatment.
- minimizing the incidence of toxic effects of using oseltamivir;
- lowering drug loads;

Concomitant use of ACA and the neuraminidase inhibitor oseltamivir (Tamiflu) that is considered the most effective treatment against influenza caused by the strain A/California/04/2009 (H1N1), also resulted in potentiating anti-influenza effect. In a mouse model of severe lethal infection with the highly virulent virus A/PR/8/34 (antigenic formula H1N1), oseltamivir and ACA in doses lower than minimum effective doses demonstrated a statistically significant protective effect only when administered in combination. This testifies to the fact that the combination therapy above is capable of: view treatment against influenza caused by the strain A/California/04/2009 (H1N1), also resulted in potentiating anti-influenza effect. In a mouse model of severe lethal infection with the highly virulent virus A/PR/8/34 (antigenic formula H1N1), oseltamivir and ACA in doses lower than minimum effective doses demonstrated a statistically significant protective effect only when administered in combination. This testifies to the fact that the combination therapy above is capable of:

- lowering drug loads;
- minimizing the incidence of toxic effects of using oseltamivir;
- reducing the cost of treatment.

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DISCUSSION

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various age groups diagnosed with influenza and other acute respiratory viral infections [11, 12].

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- children 2 to 6 years of age: 2-4 g (2-4 bags or 4-8 tablets) daily, (40-80 ml of a 5% solution) divided into 4 intakes, 1-2 tablespoons each;
- children 7 to 10 years of age: 4-5 g (4-5 bags or 8-10 tablets) daily taken with water, or 80-100 ml of a 5% solution (divided into 4-5 intakes);
- teenagers: 5-8 g (5-8 bags or 10-16 tablets) daily taken with water and divided into 4-5 intakes, 1-2 bags each, or 100-160 ml of a 5% solution (divided into 4-5 intakes). ACA in the form of tablets can be administered to children no younger than 3 years of age.

The topical (local) route of ACA administration has also proved to be effective. We recommend placing into the nostrils wound cotton swabs soaked with a 5% solution of aminocaproic acid or powder dissolved in unsweetened water, for 5 to 10 minutes, every 2 to 3 hours. Alternatively, it is recommended to drip 3 to 5 drops of this solution into each nostril, with the same intervals (2-3 hours). The solution can also be used for inhalations.

In case of severe and hypertoxic forms of influenza or ARVI, the ACA dose can be increased by 30-40%, with half of the daily dose administered through intravenous infusions. Intravenous infusions should be performed under the control of coagulogram.

The treatment of influenza and ARVI in adults can be based on the ACA doses recommended for teenagers. If necessary, aminocaproic acid can be used in combination with other existing antiviral medications (amizon, oseltamivir, etc.), as well as with interferon or its inductors, which increases the efficacy of the treatment.

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Contraindications for the use of aminocaproic acid are high individual sensitivity, a tendency to thrombosis and embolism, any inheritable and secondary thrombophilia, disseminated intravascular coagulation, macrohematuria, severe kidney diseases, pregnancy and lactation.

CONCLUSIONS

Based on the results of the studies and on the expert opinions provided by the State Pharmacological Center of the Ministry of Health of Ukraine, the range of medications officially approved for the prevention and treatment of influenza and ARVI in adults and children, including infants in the first year of life, has been extended to include aminocaproic acid. This is of vital importance in the situation of influenza pandemic ripping through Ukraine.

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