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SIDE EFFECTS OF ANTIVIRAL DRUGS USED IN RESPIRATORY INFECTIONS: A REVIEW

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Abstract

Since the 12th century, mankind has experienced more than 130 viral epidemics and influenza pandemics. The 21st century is no exception. The relatively "new" strains of influenza have been replaced by new infections, in particular, the coronavirus infection -COVID-19 (the official name SARS-CoV-2), the third peak of the pandemic of which we are now seeing. At the same time, the "old" viral infections have not disappeared anywhere. Using antiviral drugs in the treatment of respiratory infections, not only the medical and economic efficiency of the application must be taken into account, but also remember several side effects of the drugs, preventing them whenever possible and minimizing their consequences. The purpose of the publication is to systematize, analyze and summarize literature data on typical adverse reactions of antiviral drugs active against pathogens of acute viral respiratory infections.

Keywords: *antiviral drugs, side effects, respiratory infections.*

Since the 12th century, mankind has experienced more than 130 viral epidemics and influenza pandemics. The 21st century is no exception. The relatively "new" strains of influenza have been replaced by new infections, in particular, the coronavirus infection -COVID-19 (the official name SARS-CoV-2), the third peak of the pandemic of which we are now seeing. At the same time, the "old" viral infections have not disappeared anywhere [1].

The group of acute respiratory viral infections (ARVI) includes a large number of diseases characterized by damage to various parts of the respiratory tract and an aerogenic transmission mechanism [1]. In terms of frequency of occurrence, they rank first among all diseases. Every person during his life repeatedly suffers from ARVI. Concerning influenza alone, about 1 billion cases of the disease, 3-5 million severe cases, and 290-650 thousand deaths from influenza-associated respiratory dysfunctions are recorded annually in the world. In Ukraine, 10-14 million people suffer from ARVI every year, which is 25-30% of all cases and about 75-90% of infectious diseases [2]. In addition, ARVI is characterized by a lack of cross-immunity, which contributes to the formation of recurrent pathology.

ARVI can be caused by more than 200 viruses (influenza viruses, parainfluenza, coronaviruses, rhinoviruses, reoviruses, adenoviruses, respiratory syncytial virus (RS virus), some serotypes of Coxsackie viruses and ECHO, etc.), which makes it extremely difficult to diagnose [1, 3].

All these viruses belong to different families and genera, differ in biological properties. All representatives, except for adenoviruses, are RNA-containing viruses and are obligate intracellular parasites [1].

ARVIs are characterized by a short incubation period (usually up to 7 days), an acute onset, a combination of catarrhal phenomena with fever, and general intoxication. ARVI treatment is differentiated depending on the nosological form, the severity of the course of the disease, its complications, and the age of the patients. ARVI treatment is complex and consists of etiotropic, pathogenetic, and symptomatic therapy. Most patients tolerate ARVI relatively easily and are treated with symptomatic means at home [1]. However, with a more severe course, in some cases, the use of etiotropic antiviral agents is required [1].

The purpose of the publication is to systematize, analyze and summarize literature data on typical adverse reactions of antiviral drugs active against pathogens of acute viral respiratory infections.

Antiviral drugs can be divided into direct-acting agents (remantadine, oseltamivir, zanamivir, etc.) and indirect agents (interferon and interferon inducers) [1, 4, 5, 6, 7].

Derivatives of adamantane (rimantadine, amantadine) block a specific matrix protein of the virus (M2-protein), which forms ion channels in infected cells, providing endocytosis of the virus attached to the cell membrane, directly into the cytoplasm, as well as the release of nucleic acid from the viral particle. Also, these products disrupt the process of virions budding and their separation from the cell membrane.

Derivatives of adamantane inhibit the release of viral particles from the cell, i.e. interrupt the transcription of the viral genome. Previously, these drugs were widely used in the treatment of influenza caused by various strains of the influenza A virus (especially type A2), but now the overwhelming majority of currently circulating strains of influenza viruses are resistant to it, and they do not act at all on pathogens of other acute respiratory viral infections. Not effective in pandemic influenza A (H1N1) [1,4, 5].

Typical side effects of adamantane derivatives are agitation, hallucinations, insomnia; irritability, sleep disturbance, difficulty concentrating, convulsions, and some other central nervous system disorders. Digestive tract disorders include nausea, dyspepsia, and hepatotoxicity. In elderly patients with arterial hypertension, its use increases the risk of developing hemorrhagic stroke, in patients with epilepsy, the risk of developing an epileptic seizure increases [5, 6, 8, 9].

Neuraminidase inhibitors (oseltamivir, zanamivir, laninamivir, peramivir) [1, 5, 9] block the active center of the enzyme that controls the release of mature viral particles from the membranes of infected cells and the penetration of influenza viruses into the patient's cells. This disrupts the penetration of the virus into healthy cells and the exit of virions from the infected cell, which limits the spread of infection in the body.

Neuraminidase inhibitors have anticytokine activity, reduce the production of IL-1, tumor necrosis factor-alpha, thereby reducing the severity of inflammation and clinical manifestations of the disease (fever, muscle, and joint pain, etc.).

Neuraminidase inhibitors are currently first-line drugs and are recommended by WHO for the treatment and prevention of influenza infection caused by seasonal influenza viruses and new strains of influenza with pandemic potential [1,10].

Neuraminidase inhibitors are effective for the treatment of influenza when administered no later than 24–48 hours after the onset of clinical symptoms of the disease, but are not used to treat other acute respiratory viral infections.

Antineuraminidase drugs do not significantly reduce the frequency of hospitalizations and complications of influenza, for example, viral pneumonia [13, 14], but significantly reduce the frequency of patients connecting to mechanical ventilation.

Oseltamivir is administered orally, zanamivir and laninamivir are administered by inhalation due to their low bioavailability, and peramivir is administered intramuscularly. Some scientists recommend using oseltamivir in combination with other antiviral drugs, interferon inducers, which will enhance the effectiveness of treatment and prevent viral resistance.

When using oseltamivir, the typical adverse reactions are nausea, vomiting, diarrhea, abdominal pain, nephrotoxicity, hepatotoxicity, arrhythmias, cough. Uncommon are headaches, dizziness, weakness, and insomnia.

Insomnia may occur with peramivir; cases of arterial hypertension, a decrease in the number of neutrophils have been described [12].

Zanamivir has a low bioavailability, as a result of which it is used only in inhalation form, which limits its use for preschool children and elderly patients. In addition, several adverse reactions are possible, including sore throat, rarely bronchospasm, headaches, dizziness, and laryngeal edema [4, 5].

A trimerization inhibitor, ribonucleoproteins (pentanedioic acid imidazolyl ethanamide - ingavirin) is active against influenza viruses of type A (A/H1N1, A/H3N2, A/H5N1) and type B, adenovirus, parainfluenza virus, respiratory syncytial virus. In preclinical studies, activity was established against coronavirus, metapneumovirus, enteroviruses, incl. Coxsackievirus and rhinovirus [15,16,17].

The action of the drug is realized at the level of infected cells by stimulating factors of innate immunity, suppressed by viral proteins. Under conditions of infection, the drug stimulates the production of the antiviral effector protein MxA, which inhibits the intracellular transport of ribonucleoproteins of various viruses, slowing down the process of viral replication, stimulates and normalizes the reduced α-interferon-producing ability of blood leukocytes, and stimulates the γ-interferon-producing ability of white cells. An increase in the density of interferon receptors leads to an increase in the sensitivity of cells to signals from endogenous interferon. The anti-inflammatory effect of Ingavirin is due to the suppression of the production of the pro-inflammatory cytokines (tumor necrosis factor (TNF-α), interleukins (IL-1β and IL-6)), a decrease in the activity of myeloperoxidase [15].

According to the data of a double-blind, randomized, placebo-controlled multicenter clinical trial involving 190 patients aged 3-6 years, the use of Ingavirin leads to a significant reduction in the period of fever, accelerates the resolution of symptoms of intoxication and catarrhal symptoms, and reduces the recovery time compared to placebo [16].

The drug effectively protects contact persons from disease in the focus of infection, has a wide spectrum of activity against influenza viruses, adenovirus, parainfluenza virus. The drug has proven itself well as a means for emergency intralesional prophylaxis during the period of the rising incidence of influenza and other acute respiratory viral infections in adults and children [18, 19].

According to the data of a prospective non-interventional study conducted by Russian researchers, in patients with COVID-19, the use of Ingavirin in addition to the commonly recommended therapy leads to faster achievement of clinical improvement, an adequate level of saturation (the proportion of patients with adequate saturation and not requiring oxygen support was two times higher than in the standard therapy group by the seventh day of treatment) and

positive integral clinical dynamics. In addition, the use of Ingavirin reduces the risk of cytokine storm in COVID patients [17].

The drug is contraindicated during pregnancy and lactation. Side effects include allergic reactions.

An inhibitor of viral replication - inosine pranobex (isoprinosine) - has a wide spectrum of action, inhibits the replication of various DNA and RNA-containing viruses, slows down the synthesis of viral i-RNA (violation of transcription and translation) [5].

The immunomodulatory effect is due to the effect on T-lymphocytes and an increase in the phagocytic activity of macrophages. Inosine pranobex prevents post-viral weakening of cellular synthesis of RNA and protein in infected cells, helps reducing the viral load on the body [20]. The medicine is used in the treatment of influenza, RS virus, parainfluenza, herpes type I, II, III, hepatitis B.

The efficacy and safety of inosine pranobex were confirmed by data from a randomized, placebo-controlled, double-blind study in patients with clinically diagnosed infections caused by influenza A or B, parainfluenza, RSV, adenovirus [21].

Of the adverse reactions, allergic reactions, diarrhea, dyspeptic disorders, and headache are observed. The medicine may increase the level of uric acid in blood plasma and urine for a short time (caused by the metabolism of inosine) transaminase, alkaline phosphatase [4, 5, 6].

A hemaglutinin inhibitor (umifenavir) inhibits the fusion of the lipid envelope of viruses - causative agents of ARVI (influenza, parainfluenza, rhinovirus, respiratory syncytial virus, etc.) with the cell membrane, which reduces the possibility of internalization of the virus inside the host cells [22, 23, 24]. The drug also has interferon-inducing activity [25, 26, 27].

It is used for non-specific prophylaxis and treatment during an epidemic of influenza and other acute respiratory viral infections, in the complex therapy of recurrent herpes infection [25].

In coronavirus infection, umifenavir (arbidol) blocks the trimerization of the SARS-CoV-2 spike glycoprotein (necessary for fusion with the host cell membranes) and prevents the virus from binding to host cells [5]. The use of umifenovir for the treatment of COVID-19 infection, according to Russian and Chinese researchers, helps reducing mortality and reduces hospitalization time [28, 29, 30].

According to data from an open, randomized controlled trial of umifenovir in patients with COVID-19 including peripheral oxygen saturation, requiring ICU admissions, duration of hospitalization [31].

Side effects of the drug are manifested in the form of allergic reactions.

The guanine analog favipiravir is a prodrug; it metabolizes in cells to ribosyl triphosphate favipiravir (RTF favipiravir) and is an inhibitor of viral RNA-dependent RNA polymerase [4, 32, 33, 34, 35]. It also integrates into the viral RNA chain, preventing its further lengthening.

Favipiravir was approved in 2014 for the treatment of pandemic influenza in Japan, but due to its teratogenic effect, it has only been used in emergency cases. Favipiravir is active against influenza viruses H3N2, H3N2, H5N1, and H1N1, as well as West Nile virus, yellow fever virus, etc. [1]. It is widely used in the treatment of coronavirus infection.

According to several meta-analyses, there was a significant clinical improvement in the group of patients with COVID-19 who received favipiravir [33]. Also, this group of patients had 7% less need for additional oxygen therapy [34].

According to a prospective, randomized, controlled, open-label, multicenter study, for moderate COVID-19 in adult patients [32], favipiravir was accelerating the resolution of fever, cough, and breathing difficulties more effectively than umifenovir.

The most commonly observed adverse events associated with taking favipiravir are hyperuricemia, hypertriglyceridemia, hypertransferasemia, diarrhea [35].

Also described are cases of hyperthermia when using favipiravir in patients with COVID-19, which persisted against the background of a reduction in the symptoms of the disease and decreased after discontinuation of the drug [36].

Given the teratogenic effect of favipiravir [6, 32], when using it in the fertile population, it is necessary to use the most effective methods of contraception (condom with spermicide) during and after treatment with the drug: within 1 month for women and within 3 months for men.

The adenosine triphosphate analog remdesivir is widely used to treat viral infections. Remdesivir is a prodrug. The mechanism of action is associated with inhibition of RNA-dependent RNA polymerase, ie, a decrease in the replication of the viral genome and its further production [4, 5, 37, 38]. Remdesivir was used to treat HIV infection, to treat infections caused by the Marburg virus and the Ebola virus, and is now widely used in the complex therapy of COVID-19 [38, 39].

It is better to prescribe Remdesivir in the first 5 days from the onset of the first symptoms of the disease, but it is possible to use it at a later stage of the disease if there are clinical indications. According to [41], it increases the rate of recovery in critically ill patients with COVID-19 and reduces the death rate of patients.

The composition of dosage forms for parenteral administration of remdesivir includes an excipient, the sodium salt of sulfobutyl ester-β-cyclodextrin (SBECD). SBECD is excreted by the kidneys and may be delayed in patients with impaired renal function. It is recommended to determine the estimated glomerular filtration rate (eGFR) before starting and daily during the use of remdesivir in adult patients [37].

Typical side effects are hypersensitivity reactions, including infusion and anaphylactic reactions, hypotension, hypertension, tachycardia, bradycardia, nausea, cholestatic hepatitis, increased transaminase levels, renal dysfunction, hyperhidrosis, tremors, rash. Significantly rarely may develop bronchospasm, hyponatremia, hypertriglyceridemia, a decrease in the total level of protein, hypoxic-ischemic encephalopathy, obstruction of the urinary tract, respiratory thoracic and mediastinal disorders, generalized convulsive seizures [41, 42].

Slower infusion (maximum infusion time ≤120 minutes) can potentially prevent these reactions. Remdesivir should not be used in patients with blood alanine aminotransferase (ALAT) levels more than 5 times the upper limit of normal. Remdesivir may cause nausea, vomiting [43].

There are also pieces of evidence of cardiovascular toxicity cases. Cases of the respiratory distress syndrome development against the background of the use of the drug [44], as well as the occurrence of acute pancreatitis [45], have been described.

Interferons (IFN) are species-specific low molecular weight proteins (glycoproteins) with a molecular weight of 20-30 kDa, which are produced by cells in response to viral, antigenic, or mitogenic effects on the body and protect the body from infection with viruses, bacteria, fungi, protozoa, potentiate immune responses, inhibit the growth of malignant cells [1, 46].

This group of compounds is produced by the cells of the body when exposed to viruses in the early stages of viral infection, as well as biologically active substances of endogenous and exogenous origin. They do not directly affect the vital activity of viruses. They increase the resistance of cells to damage by viruses. They are characterized by a wide antiviral spectrum, although they do not possess specificity of action against individual viruses. There is no resistance to interferons in viruses [1, 46].

IFs bind to specific receptors on the cell surface, triggering a complex intracellular signaling mechanism and rapid activation of gene transcription. Genes stimulated by IF modulate many biological effects, including suppression of viral replication in infected cells, suppression of cell proliferation, and immunomodulation. There are two types of receptors: for ⍺- and ⍺-IFN and for ⍺-IFN [1, 46,47, 48].

The antiviral activity of IFN is not associated with a direct effect on the virion but is a consequence of changes in metabolic processes at the cellular level. The mechanism of antiviral action ⍺- and ⍺-IFN is to suppress the synthesis of viral proteins and block the release of virions from the cell. ⍺-IFN directly affects the cells of the immune system (T-, NK-cells, macrophages, granulocytes) and enhances the expression of antigens of the major histocompatibility complex. IFNs cause significant physicochemical and structural changes in the cell membrane, increasing the expression of antigens of classes I and II of the major histocompatibility complex. This changes the topography of the membrane, leads to disruption of the attachment of viruses to it, and prevents them from entering the cell. By activating the cytotoxic activity of T-lymphocytes, IFNs stimulate the lysis of cells infected with the virus. Thus, IFNs prevent the infection of uninfected cells, and also suppress the

reproduction of viruses at the stage of synthesis of virus-specific proteins [1,46, 47, 48].

The immunomodulatory effect of IFN is to stimulate phagocytosis, natural killer cell activity, stimulate the formation of antibodies, activate and modulate B-lymphocyte differentiation, and express antigens of the major histocompatibility complex of class I and II. The antibacterial activity of IFN is, apparently, due to an increase in phagocytic activity, synthesis of immunoglobulins, increased cytotoxicity of natural killer cells [1, 46].

Interferon preparations are classified into natural (human leukocyte IFN, human fibroblast IFN, human immune IFN) and recombinant (α-2a, α-2b, α-2c. β-1a, β-1b) [1, 4, 5, 46, 49].

There is evidence of the advisability of using a combination of rectal and local dosage forms of interferons with antioxidants for the treatment of ARVI [1, 46, 50].

Interferon preparations are widely used in the prevention and treatment of respiratory infections, influenza, hepatitis, cancer, multiple sclerosis, etc. [1, 46, 50].

Several publications are devoted to the use of IFN-α interferon preparations in the early stages of COVID-19, which helps to alleviate symptoms and shorten the duration of the disease. At the same time, IFN-α2b in the early stages can reduce nosocomial mortality in the early stages of COVID-19, but in the later stages, it increases mortality [51, 52, 53].

Side effects with the use of interferons are very diverse. When using them, a patient may develop allergic reactions, "flu-like syndrome" (myalgia, fever, chills, headache, malaise, arthralgia, back pain); dyspeptic disorders (decreased appetite, nausea, vomiting, diarrhea, change in taste, "metallic" taste in the mouth, dry mouth, abdominal pain, weight loss, rarely - ulcerative stomatitis, constipation, flatulence, heartburn, increased peristalsis, cytolysis syndrome); syndrome of vascular manifestations (hypo or hypertension, swellings, arrhythmia, cyanosis, increased capillary permeability, thrombocytopenia, etc.); syndrome of neurological manifestations (dizziness, paresthesia, tremor, less often - depressive disorders, convulsions), thyroid dysfunction [4, 6, 46, 53].

It should be remembered that with parenteral administration of IF, the formation of anti-interferon antibodies is not excluded, which requires the termination of IFN therapy [47]. Many side effects of antiviral drugs are dose-dependent and often reversible [54].

It is also necessary to pay attention to the excipients that make up the preparations. For example, methyl parahydroxybenzoate, which is included in the composition of nazoferon nasal spray, laferobionum nasal spray (interferon alfa-2b) can cause allergic reactions, including delayed, extremely rare - bronchospasm [5, 55].

Thus, when using antiviral drugs in the treatment of respiratory infections, not only the medical and economic efficiency of the application must be taken into account, but also remember several side effects of the drugs, preventing them whenever possible and minimizing their consequences. The optimal method for the prevention of viral respiratory diseases is compliance with the sanitary and epidemiological regime and vaccination.

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