LITERATURE REVIEW: MODERN PROBLEMS AND FEATURES OF PHARMACOTHERAPY OF RECURRENT HERPETIC INFECTION

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Resume:
The article examines current issues and features of the pharmacotherapy of recurrent herpes infection caused by the herpes simplex virus. It highlights the high prevalence of the infection, its ability to persist lifelong, as well as its immunosuppressive and oncogenic effects on the human body. Particular attention is given to the recurrent course of the disease, associated with reactivation of the virus from its latent state.

Key words: herpes infection; herpes simplex virus; recurrence; pharmacotherapy; antiviral drugs; acyclovir; valacyclovir; famciclovir; immunotherapy; interferons; interferon inducers; suppressive therapy; immunity; clinical pharmacology

АДАБИЁТЛАР ТАҲЛИЛИ: РЕЦИДИВИРУВЧИ ГЕРПЕТИК ИНФЕКЦИЯНИНГ ФАРМАКОТЕРАПИЯСИНИНГ ЗАМОНАВИЙ МУАММОЛАРИ ВА ХУСУСИЯТЛАРИ

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Аннотация:
Мақолада оддий герпес вируси (HSV) томонидан чақириладиган рецидивирувчи герпетик инфекциянинг фармакотерапиясининг замонавий муаммолари ва хусусиятлари кўриб чиқилади. Инфекциянинг юқори тарқалганлиги, унинг организмда умрбод персистенция қилиш қобилияти, шунингдек инсон организмига иммунодепрессив ва онкоген таъсири қайд этилади. Касалликнинг латент ҳолатдан вируснинг қайта фаоллашуви билан боғлиқ бўлган қайталанувчи кечишига алоҳида эътибор қаратилган.

Калит сўзлар: герпетик инфекция; оддий герпес вируси; рецидив; фармакотерапия; вирусга қарши препаратлар; ацикловир; валацикловир; фамцикловир; иммунотерапия; интерферонлар; интерферон индукторлари; супрессив терапия; иммунитет; клиник фармакология.

ЛИТЕРАТУРНЫЙ ОБЗОР: СОВРЕМЕННЫЕ ПРОБЛЕМЫ И ОСОБЕННОСТИ ФАРМАКОТЕРАПИИ РЕЦИДИВИРУЮЩЕЙ ГЕРПЕТИЧЕСКОЙ ИНФЕКЦИИ

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Резюме:
В статье рассматриваются современные проблемы и особенности фармакотерапии рецидивирующей герпетической инфекции, вызванной вирусом простого герпеса. Отмечается высокая распространённость инфекции, её способность к пожизненной персистенции, а также иммунодепрессивное и онкогенное воздействие на организм человека. Особое внимание уделяется рецидивирующему течению заболевания, связанному с реактивацией вируса из латентного состояния.

Ключевые слова: герпетическая инфекция; вирус простого герпеса; рецидив; фармакотерапия; противовирусные препараты; ацикловир; валацикловир; фамцикловир; иммунотерапия; интерфероны; индукторы интерферона; супрессивная терапия; иммунитет; клиническая фармакология.

Intraduction: At present, among viral diseases, herpes infection has become particularly relevant. Its causative agent is the herpes simplex virus (HSV). Firstly, this is due to its fairly widespread prevalence among populations in different regions; secondly, due to the lifelong persistence of the virus in the human body; thirdly, due to the immunosuppressive and oncogenic properties of the virus, as well as its negative impact on reproductive health and the high frequency of asthenic syndrome development. All of this significantly complicates the prognosis of the disease and reduces the quality of life in patients with this pathology.

Very often, herpes infection can take on a recurrent course. The problem is also that during recurrences, HSV, which had previously been in a latent state in the body, begins to actively replicate, clearly disrupting the body's defense mechanisms, while modern antiviral drugs can only temporarily halt viral replication during the period of their use.

Clinically, recurrences occur with signs of intoxication of varying severity and local symptoms affecting the skin and/or mucous membranes.

Like other viruses, HSV is an intracellular parasite. It is practically impossible to affect it with medications without damaging the cells of the host organism. In most cases, the use of antiviral drugs is not very effective, and the risk of adverse effects is quite high. Antiviral agents are drugs with a narrow therapeutic range. Maximum effectiveness can be achieved when they are used for preventive purposes or locally, when it is possible to create a high concentration. Since it is impossible to achieve complete elimination of the virus from the body using modern antiviral agents, the goal of pharmacotherapy (PT) for herpes infection (HI) is to transfer actively replicating viruses into a latent, inactive state.

The objectives of pharmacotherapy in this case are to suppress viral reproduction during exacerbation in order to reduce the severity or duration of recurrence, as well as to restore adequate immune system function to prevent post-recurrence viral reactivation and to increase the duration of the recurrence-free period.

Antiherpetic drugs include tebrofen, reodoxol, idoxuridine, vidarabine, acyclovir, valacyclovir, and famciclovir. All of them disrupt the synthesis of viral nucleic acids, that is, they block replication.

Currently, there are two main approaches to the treatment of herpes infection (HI):

1. antiviral chemotherapy;
2. a comprehensive treatment method, in which immunotherapy (specific and nonspecific) is combined with antiviral therapy and the use of topical agents.

All antiherpetic drugs are divided into two groups:

Group 1 – agents of etiotropic pharmacotherapy:
a) direct antiviral chemotherapeutic agents (abnormal nucleosides): acyclovir, valacyclovir,

famciclovir;
b) interferon preparations: natural – leukinferon and recombinant – viferon;
c) interferon inducers – cycloferon, neovir, amixin, ridostin.

Group 2 – agents of pathogenetic therapy (immunotropic agents). These include:
a) drugs that restore T- and B-cell immunity and phagocytosis – thymalin, T-activin, immunofan, immunomax, galavit, myelopid, polyoxidonium, methyluracil;
b) immunoglobulins – standard immunoglobulin, antiherpetic immunoglobulin;
c) drugs with metabolic effects – glutoxim, mildronate;
d) drugs with mixed mechanisms of action – derinat, hepon;
e) herpes vaccine.

The prescription of immunotropic drugs should be based on clinical and immunological examination, with mandatory consultation by a clinical immunologist.

At present, acyclovir is considered the "gold standard" of HI therapy. As an abnormal nucleoside, it has pronounced antiherpetic activity and relatively low toxicity. A key feature of acyclovir, as well as other abnormal nucleosides, is that it acts only on intracellular HSV that is in an active state. After discontinuation of therapy, viral replication resumes.

Side effects of acyclovir include: local irritation (with topical use), dyspeptic symptoms (nausea, vomiting, diarrhea), hepatotoxicity, headache, increased fatigue, and skin reactions. It should be noted that there are cases of primary resistance to acyclovir or resistance that develops during treatment (in 5–7% of patients).

Based on acyclovir, valacyclovir (Valtrex) and famciclovir (Famvir) have been developed. Valacyclovir is advantageous because after administration it achieves blood and tissue concentrations comparable to intravenous acyclovir, which ultimately allows for reduced dosing frequency. In terms of suppressing HSV replication, famciclovir is considered the most effective; however, from a pharmacoeconomic perspective, acyclovir remains the more justified choice.

It is important to note that early administration of systemic and topical antiviral agents contributes to more effective and prolonged suppression of viral replication.

There are two methods of oral administration of synthetic nucleoside analogs:

1. episodic therapy (a 5–10 day course) – prescribed during the first episode of HI in a patient's life, and can also be used during the prodromal period of mild HI;
2. suppressive (preventive) therapy, in which the drug is prescribed for months or even years, but in lower doses than in episodic treatment, in order to prevent recurrence.

In cases of recurrent herpes infection of moderate severity and severe herpes infection, the most justified approach is the use of antiviral drugs in a subsuppressive regimen (administration of acyclovir for 4–6 weeks) or a suppressive regimen (see Tables No. 1 and 2)

Table 1.
Recommended regimens for episodic therapy of herpes infection (CDC, *Sexually Transmitted Diseases*, 2002)

Drug	Episodic therapy for HI with rare recurrences	First episode of HI
Acyclovir	400 mg per dose, 3 times daily, for 5 days	
200 mg per dose, 5 times daily, for 5 days		
800 mg per dose, 2 times daily, for 5 days	400 mg per dose, 3 times daily, for 7–10 days	
200 mg per dose, 5 times daily, for 7–10 days		
Valacyclovir	500 mg per dose, 2 times daily, for 3–5 days	
1000 mg per dose, once daily, for 5 days	1000 mg per dose, 2 times daily, for 7–10 days	
Famciclovir	125 mg per dose, 2 times daily, for 5 days	250 mg per dose, 3 times daily, for 5 days

Table 2.
Recommended regimens for suppressive therapy of herpes infection (CDC, *Sexually Transmitted Diseases*, 2002, with modifications)

Drug	Treatment regimen
Acyclovir	400 mg per dose, 2 times daily, continuously
Famciclovir	250 mg per dose, 2 times daily, continuously
Valacyclovir	500 or 1000 mg per dose, once daily, continuously
or 500 mg per dose, 2 times daily, continuously	

Depending on the nature of changes in interferon status, interferon (IFN) preparations or interferon inducers (IFI) are used for the pharmacotherapy (PT) of patients with herpes infection (HI).

With the help of IFN preparations, replacement therapy is carried out; however, this may suppress the production of the body's own endogenous interferon, which must be taken into account when prescribing long courses (more than 2 weeks), especially with genetically engineered IFN. Therefore, an intermittent (discrete) regimen of their use is preferable. It should be noted that if there is hyperproduction of endogenous α- and/or γ-interferons, the use of IFN preparations should be avoided.

IFN preparations can be used in various dosage forms depending on the severity of HI. For example, leukinferon has antiviral and immunocorrective effects, accelerates the differentiation of immune cells, and is mainly used in severe HI. The drug viferon, in the form of rectal suppositories, contains recombinant α2b-interferon and vitamins C and E, which ensures longer circulation of interferon in the blood, although at a lower concentration than with parenteral administration; therefore, it is more often used in moderate HI and less frequently causes adverse effects.

IFI (interferon inducers) exhibit all the effects characteristic of IFN preparations but have a number of advantages (provided that the body's cells retain the ability to produce interferon): interferon synthesis induced by these agents is balanced and regulated by the body itself; moreover, inducers are not antigenic, which prevents side effects typical of interferon therapy. The regimen of their use is determined by the individual characteristics of the patient's interferon status, the clinical course of the disease, and the pharmacological properties of the specific IFI used.

The approaches to the use of the herpes vaccine are as follows:

1. the herpes vaccine is used at the beginning of HI pharmacotherapy according to the standard regimen, in combination with immunotropic and etiotropic drugs;
2. the herpes vaccine is administered after completing one or several courses of комплексной PT, once stable clinical and laboratory improvement is achieved (positive dynamics of immune status, negative immunofluorescence test results for HSV).

Although the latter approach is more justified, in some patients stimulation of hyperimmunoglobulinemia may provoke allergic and autoimmune processes, thereby worsening the course of herpes infection.

The treatment strategy for patients with herpes infection (HI) depends on the severity of the infection, the nature of comorbid conditions, and the patient's reproductive plans.

Pharmacotherapy (PT) of recurrent mild HI is often limited to the use of acyclovir in an episodic regimen or a short course (2 weeks), interferon inducers (cycloferon, amixin), along with pathogenetic therapy (thymic factors that mainly affect the T-cell component of immunity and drugs influencing the monocyte-macrophage system—polyoxidonium or methyluracil). In mild HI, polyoxidonium and methyluracil have comparable clinical effectiveness. However, since treatment costs are more favorable with methyluracil, it is preferable to use thymic factors and methyluracil in combination with etiotropic PT as first-line therapy. In addition, combined vitamin preparations with antioxidant effects (aevit, triovit) may be used.

Pharmacotherapy for patients with moderate HI should include antiviral drugs (acyclovir, valacyclovir) in a subsuppressive regimen, interferon preparations or interferon inducers, combined with immunotropic PT (according to changes in immune status).

In severe HI and continuously recurrent forms (more than once per month), suppressive antiviral therapy (acyclovir, valacyclovir) for 3–6 months is indicated, along with immunotropic PT.

The use of vegetotropic and autonomic-modulating drugs, combined with qualified reflexotherapy and psychotherapy, is considered promising for patients with HI of any severity.

At any severity of HI, the use of topical agents is advisable. Topical antiviral drugs (such as acyclovir cream or ointment) are necessary to reduce clinical manifestations at the lesion site, accelerate epithelialization, and shorten the duration of viral shedding. Local use of interferon inducers (cycloferon liniment, epigen) and cytokine preparations (superlymph) reduces inflammation, stimulates phagocytosis and fibroblast proliferation, and improves regeneration of mucous membranes.

In Conclusion, Thus, the above highlights the clear need for further development of standards for immunoactive and etiotropic pharmacotherapy for HI, based on clinical and laboratory polymorphism of the disease and the pharmacological characteristics of the drugs. Unfortunately,

the use of modern antiviral agents does not achieve complete elimination of the virus from the body, and data on vaccine effectiveness remain contradictory. Moreover, unified standardized protocols for immunoactive and etiotropic pharmacotherapy are still lacking.

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