

# COMPLEX THERAPY OF CHRONIC RECURRENT HERPETIC STOMATITIS

UDC 576.385.7:618.2+616.12-008.331.1-002.2

Received 12.09.2012



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**The aim of the investigation** was to assess the efficiency of complex use of famcyclovir (Famvir) to suppress herpes simplex virus infection, and interferon inducer Kagocel having immune modulating properties in patients with clinically diagnosed recurrences of herpetic stomatitis in past medical history.

**Materials and Methods.** We examined and treated 32 patients (26 female and 6 male) suffering from herpetic stomatitis, aged 20–63, with 2–8 disease recurrences a year indicated in the past history. The patients were divided into three groups: group 1 (n=12) patients were given Acyclovir, 1 tablet (200 mg) 5 times a day, for 5 days; group 2 (n=10) — Famvir, 1 tablet (250 mg) bid, for 5 days; group 3 (n=10) — Famvir, 1 tablet (250 mg) bid, for 5 days, and Kagocel: 2 tablets (12 mg) thrice daily, for 5 days. Local treatment for all patients was the same: Viru-Merz Serol gel was applied on problem areas.

**Results.** In combination therapy patients taking Famvir and Kagocel, acute manifestations of herpetic stomatitis (edema, hyperemia, and the presence of primary signs in oral cavity) were arrested in the shortest time — on day 6. These patients had the fewest recurrences within a year ( $1.8 \pm 0.5$ ,  $p < 0.001$ ), the average period of the first clinically confirmed episode was significantly larger (52.1 days;  $p < 0.05$ ). The patients of other groups were characterized by excess content of IgA and IgG in blood serum on day 10.

**Conclusion.** Complex therapy of herpetic stomatitis by antiviral medication Famvir and interferon inducer Kagocel results in maximum effect within a minimally short period of time, and enables to arrest clinical manifestations and achieve a stable and long remission.

**Key words:** chronic recurrent herpetic stomatitis; Famvir; Kagocel.

Herpes virus infections are referred by European Regional Bureau of WHO to a group of the diseases, on which the future of infectious pathology depends, since herpes infection and herpes morbidity rate in general population is getting ahead of the Earth growth population rate. More than 99% of urban population in all countries worldwide are infected by one or several serovariants of herpes simplex virus (HSV) [1].

Clinical manifestations of nasolabial herpes are generally associated with the replication of HSV type 1 (HSV-1). In recent years the prevalence rate of labial herpes caused by HSV type 2 (HSV-2) has increased. In addition, 50–70% of adults seeking medical advice have been found to have antibodies to HSV-2, though many of these patients have never had clinically manifested episodes of the disease [2, 3].

Herpes prevalence is growing from year to year [4, 5]. It is a continuing epidemic, in particular, due to the fact that HSV-infection in patients with subclinical or atypical diseases cannot be always diagnosed, and they are characterized by rare reactivation [6–9].

The primary objective of herpetic stomatitis (HS) management is to relieve the severity and duration of clinical manifestations of the infection, as well as decrease the number of recurrences annually. The researchers including those in Russia, who are engaged in HSV problem study, believe HS exacerbation to be

associated with unfavorable changes of the immune status, therefore, in frequently recurring course of herpetic infection, it is reasonable to carry out immunoprophylaxis of exacerbations including the administration of interferon-based products (IFN) or the stimulants of their endogenous synthesis [8].

**The aim of the investigation** was to assess the efficiency of complex use of famcyclovir (Famvir) to suppress herpes simplex virus infection, and interferon inducer Kagocel with immune modulating properties in patients with clinically diagnosed recurrences of herpetic stomatitis in past medical history.

**Materials and Methods.** We examined and treated 32 patients (26 females and 6 males) suffering from HS, aged 20–63. The recurrence rate of the disease was from 2 to 8 exacerbations per year. The diagnosis was made based on the typical damage of oral mucosa (OM), vermilion border and red face skin, as well as by polymerase chain reaction (PCR) that enabled to reveal in saliva HSV-1, HSV-2, Epstein-Barr virus, cytomegalovirus, and human herpes virus of type 6. Depending on the therapy type, the patients were divided into three groups. Group 1 (n=12) patients were given Acyclovir, 1 tablet (200 mg) 5 times a day, for 5 days. Group 2 (n=10) patients took Famvir, 1 tablet (250 mg) bid, for 5 days. Group 3 (n=10) patients were given Famvir, 1 tablet (250 mg) bid, for 5 days, and Kagocel: 2 tablets (12 mg) thrice daily, for 5 days. Local

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treatment for all patients was the same: Viru-Merz Serol gel was applied on problem areas of OM and vermilion border 4–5 times a day, for 5 days. In case of the disease recurrence, the patients were administered the repeated therapy.

We performed test examination: on day 1 of clinical manifestations and on day 10 after the treatment. The indices of cell immunity were studied by the reaction with monoclonal antibodies in blood serum. Titers of IgM, IgA and IgG were determined using enzyme immunoassay of blood serum.

The findings were statistically processed using Kruskal-Wallis test and  $\chi^2$  Pearson criterion.

**Results and Discussion.** Famvir (INN — famciclovir) is a new antiviral medication (NOVARTIS PHARMA, AG, Switzerland). After intake it rapidly passes into penciclovir, which is active in relation to human herpes virus including Varicella zoster virus (herpes zoster virus) and Herpes simplex type 1 and 2, as well as Epstein-Barr virus and cytomegalovirus.

Penciclovir enters the virus infected cells, and under the effect of thymidine kinase rapidly passes into monophosphate, which in its turn, with the participation of cell enzymes passes into triphosphate. Penciclovir triphosphate is in the virus infected cells for more than 12 h suppressing the replication of viral DNA in them. The concentration of penciclovir triphosphate in non-infected cells does not exceed minimum concentration; therefore, in therapeutic concentrations penciclovir does not have effect on non-infected cells.

Penciclovir is active in relation to newly found acyclovir-resistant strains of Herpes simplex with changed DNA-polymerase. The frequency of Famvir (penciclovir) resistance does not exceed 0.3%, in patients with dysimmunity — 0.19%. Famvir has been found to decrease significantly the intensity and duration of post-herpetic neuralgia in patients with herpes zoster. Penciclovir bioavailability after oral administration of Famvir is 77%. Maximum concentration of penciclovir in blood after Famvir intake in the dosage of 250 mg is reached on average 45 min later and is 1.6  $\mu$ mL. Plasma protein binding of penciclovir and its 6-deoxy-precursor is less than 20%. In repeated intake there has been found no accumulation of the drug. Plasma elimination half-life of penciclovir in final stage after a single dose and repeated doses is about 2 h. Famvir is eliminated mainly in the form of penciclovir and its 6-deoxy-precursor, which are excreted unchanged with urine.

A new Russian interferon inducer, Kagocel (INN — Kagocel) is a high-molecular weight compound synthesized on the basis of sodium carboxymethyl cellulose and low-molecular weight gossypol polyphenol isolated from cotton plant. This medication has no antigenic activity. Kagocel contains bound gossypol (3%), which does not release in metabolism.

The medicament has interferon-inducing and antiviral action; it is active in relation to influenza viruses and HSV. It can prevent virus-specific cytopathic effect in relation to herpes virus strains included into the study. Kagocel can also suppress the reproduction of HSV-1 strain that is Acyclovir-resistant, and the reproduction of the strain,

which is resistant to Acyclovir and phosphor-acetic acid.

The basic mechanism of Kagocel action is the ability to induce interferon production. It promotes the production of the so called late interferon in the body, which is the combination of alpha- and beta-interferons with high antiviral activity. It induces the production of physiological number of gamma interferon, causes interferon production in all cell populations participating in antiviral response of the body: T- and B-lymphocytes, macrophages, granulocytes, fibroblasts, endothelial cells. Kagocel is not toxic, does not accumulate in the body when administered in therapeutic doses. It has no mutagenic and teratogenic properties, embryotoxic action, is not carcinogenic.

Viru-Merz Serol gel (INN — tromantadin) is an antiviral medication for external use (Germany), contains active substance — tromantadin hydrochloride, 10 mg/g, and a filler. It is active in relation to Herpes simplex virus type 1 and 2, Herpes zoster, inhibits absorption and penetration of viruses. It inhibits absorption and penetration of viruses into a cell; causes no resistance of viruses to the medication. Viru-Merz Serol relieves pain, itching and stinging typical of herpetic infection manifestations, reduces the course of the disease, and lengthens remission periods. The intake within first 2–3 h after the onset of the disease prevents its further development. The medication is applied on infected areas 3–5 times a day (and more frequently if necessary) slightly rubbing in the skin.

Acyclovir (INN — aciclovir) is an antiviral medication, effective in relation to HSV, herpes zoster and smallpox. The similar structure of Acyclovir and deoxy-guanidine enables Acyclovir to interact with viral enzymes; it results in virus replication interruption. After medication penetration into a virus-infected cell, in response to thymidine kinase produced by a virus, Acyclovir turns into acyclovir monophosphate, and then — into an active form — acyclovir triphosphate that blocks viral DNA replication. The medication affects viral DNA synthesis selectively. Acyclovir triphosphate practically has no effect on the replication of a host cell DNA.

The treatment of HS patients using Famvir and Kagocel contributed to more rapid arrest of clinical symptoms of the disease including the relief of pain, itching in the rash area, edema and erythema, and the number of locations involved. Generally, acute HS manifestations in group 1 disappeared on day 9, in group 2 — on day 6, and in group 3 — on day 6.

10 days after the therapy, in group 1, the pain syndrome was arrested by 83%, edema and hyperemia in infected OM and lips were still observed in 12% of cases, the number of erosions decreased. 10 days after the therapy, in group 2, the pain syndrome was arrested by 93%, edema and hyperemia in involved areas of OM and lips persisted in 3% of cases only, and there were no erosions. In group 3, the pain syndrome was arrested by 98%, edema and hyperemia in affected areas of OM and lips were revealed only in 3% of cases, and on day 10 after the treatment there were no erosions.

On day 10 after the therapy, the saliva reanalysis in all patients did not revealed DNA and early proteins of the virus that indicated the virus replication termination. The

Indices of immune status in patients with herpetic stomatitis before and after treatment (X±m)

Groups	IgG		IgA		IgM	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Acyclovir + Viru-Merz Serol (group 1)	18.940±0.032	17.2400±0.0264	3.9300±0.0088	3.8000±0.0084	1.8200±0.0042	1.8400±0.0041
Famvir + Viru-Merz Serol (group 2)	16.260±0.029	17.9900±0.0199	3.5700±0.0078	3.8200±0.0088	1.6400±0.003	1.5700±0.0041
Famvir + Kagocel + Viru-Merz Serol (group 3)	14.330±0.029	14.170±0.025	3.220±0.007	2.8600±0.0075	1.5200±0.0028	1.670±0.003

Note: p<0.05 — statistically significant differences of IgG values before and after treatment; p<0.001 — for IgA and IgM values before and after treatment.

study of specific immunity showed the change of IgG, IgA, IgM content in blood serum to be within the norm.

8 patients had an excess IgG content before the treatment. On day 10 its content exceeded the norm only in 3 patients (these patients received Acyclovir monotherapy). 11 patients had an increased IgA content before the treatment. The control study 10 days after the therapy revealed the same IgA content in 3 patients, and increased IgA in blood serum was recorded in 2 patients (these patients were given Acyclovir monotherapy and Famvir monotherapy). The IgM value in blood serum before and after the therapy was the same (See Table).

The positive effect of a complex therapy was also manifested in recurrence reduction within a year: on average about 4.7±0.4 recurrences per year — in group 1; 4.0±0.4 recurrences — in group 2; and 1.8±0.5 recurrences — in group 3 (p<0.001). An average remission duration in group 1 was 28.9±2.3 days, in group 2 — 30.0±2.9 days, in group 3 — 52.1±8.1 days (p<0.05).

**Conclusion.** Complex therapy of herpetic stomatitis by antiviral medication and interferon inducer (Famvir and Kagocel) enables to achieve a maximum effect within a minimally short period of time, particularly, succeed in arresting clinical manifestations (pain syndrome, edema, hyperemia) and achieve a stable and long remission, reduce the number of recurrences, and normalize IgG, IgA, IgM indices in blood serum.

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