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PROTEFLAZID®: CLINICAL AND ECONOMIC SUBSTANTIATION FOR USE IN THERAPY OF HERPES INFECTION

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Epidemiological data indicate the widespread dissemination and constant dynamics of the incidence rate of herpesvirus infections due to a variety of forms and transmission paths of the virus, highly contagious and life-long persistence of the herpes virus in the body of the infected persons and the lack of effectiveness of existing treatments. Acyclic guanosine derivatives are the main group of antiviral drugs traditionally used for the causal treatment of herpes infections. They have a number of disadvantages, in particular formation of the virus resistance in a long-term use, the need to involve immunotherapy, as well as the high cost of treatment. The accumulated clinical experience with the original Ukrainian drug Proteflazid® (drops) in treating viral infections, including HHV- infections, shows its high clinical efficacy and safety. A relative estimation of the course treatment costs of herpes-induced infections using antiviral drugs has demonstrated the economic expediency of Proteflazid® with the purpose of treatment and maintenance therapy. Proteflazid® takes the medium sized niche among other antiherpetic drugs. In addition, due to the multi-vector nature of its pharmacodynamic effects (direct antiviral, immunomodulating, interferon-stimulating, antioxidant, apoptosis-modulating, etc.) Proteflazid® allows to exclude antioxidants, immunomodulators from the antiherpetic therapy scheme, or to adjust their use, and it can significantly reduce the cost per a course of treatment.

Among the viral diseases herpesvirus infections are the most commonly encountered due to the widespread dissemination of viruses, a variety of transmission paths of the virus, highly contagious and life-long persistence of the herpes virus in the body of the infected persons and the lack of effectiveness of existing treatments [19, 34]. The incidence of herpes infection is difficult to quantify, partly because of unrecognized or asymptomatic course of the disease. Nevertheless, the incidence of herpes infections in the North American and European populations is between 5 and 24 per 100 people per year [30]. Herpes viruses (HHV) are widespread in the industrialized countries. According to the epidemiological studies conducted in Europe, the USA and Canada, 95% of immunocompetent persons aged 50 years and older are seropositive for varicella zoster virus, and therefore, at risk of developing herpes zoster disease [27]. It has been also shown that the average age of adults infected with herpes zoster is 59.4 years, and 68% of cases occur in people aged 50 years and older. The incidence in women was significantly higher than that in men [33, 34]. Up to 45% of the population between the ages of 6 months to 79 years is seropositive for cytomegalovirus infections [21].

Getting into the human body the herpes virus stays in it for life, staying in a latent or persistent state and undergoing reactivation in favourable conditions. In this way a chronic, latent, recurrent or progressive infection and its complications is formed; it may cause temporary disability, the development of cancer and other complications, as well as disability or death [4]. The herpes infection disease leads to significant economic losses associated with both the incapacity of the patient, and difficulties and the duration of treatment of the disease [11]. This is due, first of all, to the complexity of the strategy of parasitism and opportunistic properties of these pathogens, multiple organ lesions, the presence of numerous complications and multi-vector nature of some lesions [4]. It is known that the main differences of the replicative cycle of the herpes family viruses are associated with the more complex structure of the genome compared to other DNA-containing viruses. Thus, these viral agent genes, which encode the protein structure, make up only 15% of the DNA since most of the genome is occupied by genes, which are responsible for the synthesis of enzymes and regulatory proteins. This makes it possible to show the herpes viruses parasitizing action, including the possibility of latent, persistent and reactivated state in the infected organism [4].

Due to the complexity of herpes treatment the cost of antiherpetic therapy, which is determined by the cost of drugs and duration of their use for the treatment of the disease and its complications and/or prophylactic use, is of significant importance. For example, the cost of Herpes Zoster (Varicella zoster – VZV, HHV III) therapy in France is 4206 € and more per a relapse; direct costs associated with the treatment of postherpetic neu-

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Table 1

Drugs used for treatment of herpes infections

Parameter		Proteflazid	Acyclovir	Valacyclovir	Ganciclovir	Famciclovir
Bioavailability		High, more than 80%	Low, 8-10%	Moderate, 50-60%	Low, up to10%	High, up to 77%
T ½, h		5-9	2-3	≥3	3-4	2-2.8
Pharmacodynamic effects		Antiviral, immuno-stimulating, antioxidant, apoptosis-modulating	Antiviral	Antiviral	Antiviral	Antiviral
Indications for for diseases caused by viruses:	HSV I	+	+	+	–	–
	HSV II;	+	+	+	–	+
	HHV III – VZV	+	+	+	–	+
	HHV IV – EBV	+	–	–	–	–
	HHV V – CMV	+	–	+	+	–
	HHV VI	-	–	–	–	–
	HHV VII	-	–	–	–	–
	HHV VIII	-	–	–	–	–
The presence of resistance		-	+	+	+	+
Children		Since birth	Over 2 years	Over 12 years	Over 12 years	Over 12 years
Pregnancy / lactation		Permitted	Undesirable / prohibited	Undesirable	Prohibited	Undesirable
Dosage form		Drops	Tablets	Tablets	Tablets	Tablets

ralgia in Sweden are up to € 939, or more than 19 million € per 100 000 population [17, 29].

Over the past decade a significant number of antiherpetic drugs, which are different in origin (natural, synthetic), the structure and properties, has been introduced in clinical practice [23]. Herbal drugs have been also applied in the treatment of herpes infections. Among them Proteflazid® – the Ukrainian original drug with the antiviral effect due to flavonoid glycosides containing in wild grasses of *Deschampsia caespitosa L.* and *Calamagrostis epigeios L.* should be mentioned [1, 5, 28]. Thanks to the direct antiviral action, as well as the ability of biologically active substances of Proteflazid to activate the humoral and cellular immunity and induce the synthesis of endogenous interferon, the drug has shown a high clinical efficacy in the treatment of viral infections, including those caused by HHV.

Table 1 shows the main drugs traditionally used to treat herpes infections. According to the modern requirements the ideal antiviral agent should have a wide spectrum of the antiherpetic action (the activity against herpes viruses I and II types, Varicella zoster (VZV – HHV III), Epstein-Barr (EBV – HHV IV), cytomegalovirus (CMV – HHV V) and etc.), low toxicity, the absence of adverse effects on the immune system, a good ability to penetrate a cell, act on a virus with a high selectivity, have the minimal general cytotoxicity, do not induce resistance and do not cumulate in the organism. The pharmacokinetic characteristics of antiherpetic drugs such as the rapid achievement of the infected cells, the prolonged presence of the drug in the active form, as well as ease of the dosing regimen (1-2 times daily), are also important. Specific requirements are imposed to safety – an antiherpetic drug must be safe in short-term use (especially in the elderly, pregnant women and children, including newborns), and in a long-term suppressive therapy.

As a rule, all antiviral drugs have low toxicity – their LD_{50} value ranges from 2.000 mg/kg to 20.000 mg/kg after a single intragastric introduction in animals [24]. However, a lot of them have a wide spectrum of undesirable side reactions, in particular, ganciclovir possesses significant toxic effects, and the expressed hematotoxicity (thrombocytopenia, neutropenia, etc.) is inherent to it. It should be also noted that because of the high toxicity and mutagenic activity of antiviral drugs the effective methods of contraception should be used by patients of the reproductive age during the treatment and up to 90 days after the end of therapy [26]. To some extent it narrows the niche of the drug use (severe cases of cytomegalovirus infection (CMV), infections in transplantation, patients with HIV/AIDS, etc.) [15, 25]. Inadequate study or any potential negative effect significantly restrict the use of most antiherpetic drugs in children and women during pregnancy and lactation when the

practical therapist faces the problem of assessing the "risk-benefit" for the patient. In pediatrics, especially in young children, the assortment of antiherpetic drugs is markedly narrow and often limited to acyclovir (over 2 years), inosine pranobex (over one year), as well as Proteflazid®, which can be used from the first days of the child's life [28]. It should be noted that only Proteflazid® has no direct contraindications for use during pregnancy and lactation [5].

As noted above, when choosing a medication the pharmacokinetic properties of drugs are important as they determine the rate and completeness of delivering an active agent to the target. As a rule, acyclic guanosine analogues, among which is the "golden standard" of antiherpetic drugs – acyclovir, reveal a low bioavailability [22]. Actually most antiherpetic drugs widely used in the clinical practice are acyclovir modifications obtained in order to increase its bioavailability while preserving the activity that is at least not inferior to that of acyclovir [7]. Another important pharmacokinetic characteristic, which determines the efficacy and frequency of prescribing an antiherpetic drug is its elimination half-life [31]. In this aspect, proteflazid exceeds acyclovir and other antiherpetic drugs since its T1/2 of about 12 hours determines its therapeutic frequency – twice a day. Antiherpetic drugs used at the pharmaceutical market of Ukraine, except penciclovir, which found the optimal use in external applications, and foscarnet commonly used in resistance of strains to other drugs in the form of injection, are arranged in the following order by the level of bioavailability: proteflazid ≥ famciclovir > valacyclovir > ganciclovir > acyclovir (Table 1).

Another important requirement for antiherpetic drugs is the range of the antiviral action [18]. It is well known that modern antiviral drugs should have a high specificity to the causative agents of herpes infections – herpes simplex virus I and II (HSV I and HSV II), CMV, EBV, human herpes virus type VI A (HHV VI A) and VI B (HHV VI B), etc. Generally, most antiherpetic agents have the activity against different strains of herpes viruses differing on sensitivity to them, and it determines the choice of a drug for the treatment of the disease. It is known that ganciclovir unlike acyclovir, famciclovir, proteflazid and other drugs is more effective against cytomegalovirus infection rather than for the treatment of herpes simplex virus [9, 20, 26]. It has been shown that most EBV-infection symptoms are not associated with the direct cytopathic effect of the virus in the infected tissues, but with the indirect immunopathological response to EBV-infected B-lymphocytes circulating in the blood and being in the cells of the affected organs. That is why the nucleoside analogues (acyclovir, ganciclovir, etc.) and polymerase inhibitors (foscarnet) inhibiting the replication of EBV and reducing the content of the virus in saliva (but not sanitizing it entirely) do not have a clinical effect on severity and duration of symptoms of the EBV-infection, particularly in infectious mononucleosis. In this context, a significant advantage of proteflazid over other antiherpetic drugs is the fact that it has the immunomodulating effect that potentiates the clinical efficacy [5, 28]. The attention should be paid to a serious drawback, which all acyclic nucleosides without exception have: by their mechanism of action they inhibit only actively reproducing (replicating) herpesviruses. Consequently, even the most efficient course of a single use of a chemotherapeutic agent in no way does not prevent a possible recurrence of the same herpes virus infection, or, moreover, a new herpesvirus infection by the related strain or a new type of herpesvirus. This is probably the most serious limitations of the existing chemotherapy of herpesvirus infections [2]. It should be also noted a significant resistance to acyclovir and other acyclic nucleosides in patients (up to 10%), but concerning proteflazid such data are not available [7]. Thus, in the practice of choosing the optimal antiherpetic drug and taking into account all of the above, the range of products considerably narrows and largely determined by the price of the drug, more specifically by the cost of the course of treatment giving the best result.

The therapy of herpes diseases, depending on their complexity, is long, and usually it is not limited to one drug. Duration of the therapy of herpetic infection is determined approximately and depends on many factors (severity of the disease, the immune system, the properties of the antiherpetic drug, etc.). The clinical experience shows that treatment of herpes infections (in particular, HHV III-V types) is divided into a number of stages [8, 10]. The first stage is the treatment in the acute phase of the disease (or relapse). The antiviral drugs often prescribed topically and orally (parenterally) at the same time are used for the treatment, the course of treatment usually lasts for 5-10 days. The second phase is the treatment in remission. After decline of the main clinical manifestations in order to stimulate completeness of the immune response immunomodulators or herbal adaptogens are used. Drugs of interferon or inducers of their products are also used; symptomatic, health-promoting, physiotherapeutic treatment, and sanitation of sites of infection are performed; the therapy of chronic inflammatory diseases continues. The phase duration is 30-60 days, depending on the clinical and laboratory parameters of the disease activity [2, 4, 32]. Specific antiviral drugs are the main products at the first stage, and are also used at the second stage

Table 2

The cost of treatment of herpes virus infections

Drug, dose	The average retail price per a pack	Nosology	A course of treatment	Cost of a course
Proteflazid®, 30 ml	~11$ / 274 UAH	herpes zoster CMV Infectious mononucleosis	7 drops twice a day for 3 days; 12-15 drops twice a day for the following 2-4 weeks; *Maintenance therapy:* 10 drops a day for 2-4 months without interruption	33$ / 830 UAH
Acyclovir, 200 mg, No. 20	from 0,9$ (22 UAH) to 5,6$ (140 UAH)	herpes zoster	800 mg 5 times a day for 7 days; *Combination Therapy*: additionally, interferon alfa-2b 1 million IU intramuscularly + 2 million IU subcutaneously into several points around the area, up to 7 days	from 7$ (175 UAH) to 40$ (1000 UAH) additionally from 138 $ (~3470 UAH)
Valacyclovir, 500 mg No. 10	from 5,2$ (131 UAH) to 9$ (230 UAH)	herpes zoster	1000 mg for 7 days; *Combination Therapy*: additionally, immunostimulant (e.g. polyoxidonium 6 mg / day) for 5 days; antioxidants (vitamin B and C groups) intramuscularly five times at intervals every other day	50$ (~1250 UAH) additionally to 40 $ (~1000 UAH)
		CMV	2000 mg four times a day for 90 days	520$ (~13000 UAH)
Ganciclovir, 450 mg, No. 60	from 400$ (10 000 UAH) to 650$ (16 500 UAH)	CMV	900 mg (2 tablets a day) for 21 days	from 400$ (10 000 UAH) to 650$ (16 500 UAH)
Famciclovir 500 mg, No. 14	107$ (~2700 UAH)	herpes zoster	1500 mg (3 tablets a day) for 7 days	160$(~4050 UAH)

of the therapy. Taking into account duration and complexity of herpes treatment the cost of treatment, as well as prophylactic use of antiherpetic drugs, are the main factors. The cost of drugs for treating herpes varies from tens to thousands of US $ (foscarnet). Considering the low purchasing power of the Ukrainian population the basic price segment of drugs for treating herpes simplex based on the cost of the pack is about $ 60. Today the range of products for the treatment of infections caused by herpes viruses is limited by the list given in Table 2.

Acyclovir takes one of the central places in the treatment of herpetic infections; it is presented at the Ukrainian market by a significant number of manufacturers (company "Stada Arzneimittel AG", Germany; JSC "Lekhim-Kharkiv", corporation "Arterium", Ukraine, etc.). The average retail price of acyclovir drugs in Ukraine (as for March 2016) ranged from 0.9-1.1 $ (22-28 UAH) per a pack of domestic producers (Acyclovir, 200 mg, No. 20 produced by PrJSC "Pharmaceutical Firm "Darnitsa", Ukraine) to 5.6 $ (140 UAH) of foreign manufacturers (Acyclovir, 200 mg, No. 25 produced by "Stada Arzneimittel AG", Germany) [6]. As a rule, duration of the acyclovir treatment for herpes zoster (the acute phase of the disease) is up to seven days. The frequency of administration of the drug – 800 mg 5 times a day – is associated with poor pharmacokinetic properties and often requires the immunomodulatory therapy [22]. The cost of the course of therapy in the acute stage of the disease ranges from $ 7 to $ 40 (from 175 to 1000 UAH) depending on the manufacturer of the drug. There are actually proportional expenses with preventive (anti-relapse) use of acyclovir. Valacyclovir presented at the Ukrainian market by a number of manufacturers (JSC "Farmak", Ukraine – Valavir®, JSC "Kyivmedpreparat", Ukraine – Valtrovir, company by "GlaxoSmithKline", UK – Valtreks™, etc.), has better pharmacokinetic properties, allowing it to apply three times in the dose of 1000 mg for 7 days in the treatment of herpes zoster. The weighted average cost of the drug varies depending on the manufacturer – from $ 5.2 (131 UAH) (Valtrovir, 500 mg, No. 10) to $ 9 (230 UAH) (Valtreks™, 500 mg, No. 10) [6], so the cost of the course of valacyclovir therapy for herpes zoster can be up to $ 50 (~ 1250 UAH). Valacyclovir treatment of cytomegalovirus infection is longer (90 days or more) and requires the use of 2000 mg (4 tablets) 4 times a day. The cost of the monthly course increases to $ 520 (~ 13,000 UAH) and higher [16, 22]. Ganciclovir exhibiting the highest efficiency in different types of herpes infection is the drug of choice

for treating cytomegalovirus infection [31]. This drug is in the highest price range, and it is reflected in the cost for the course of treatment (Table 2). At the Ukrainian market the injectable form of the drug dominates (Ganciclovir-Farmeks – LLC "Farmeks Group", Ukraine; Cymevene, company "F.Hoffmann-La Roche Ltd", Switzerland), but there is also an oral form (Valcyte 450 mg, No. 60), the price of 1 package reaches $ 650. For the treatment of cytomegalovirus infection the drug is used in the dose of 900 mg (2 tablets) for 21 days (~ 1 pack). Famciclovir (Famvir, "Novartis Pharmaceutica SA", Switzerland) reveals significant efficiency, but the price range of the drug and the need for treatment of herpes zoster in the dose of 1500 mg (one tablet three times a day) for 7 days raise the cost of treatment up to more than 100 $ (~ 4000 USD) and higher [22].

It is shown that guanosine derivatives exhibit predominantly the antiviral activity, and it requires additional therapies, the use of antioxidants (vitamins E and C) and, if necessary – NSAIDs [3]. The base of modern immunotherapy of herpesvirus infections is drugs of interferon and immunoglobulins. The purpose of such treatment, except for certain indications, corresponds to a high level of evidence. Immunotherapy can not substitute antiviral chemotherapy, but addition of immunotherapeutic drugs can improve the treatment efficacy, reduce the course of treatment and prevent induction of resistance to acyclic guanosine analogues. However, such polypharmacy complicates the treatment of herpes virus infections and often requires involvement of the medical staff, significantly increases the financial costs of treatment [4]. For example, the cost of human recombinant interferon alfa-2a depending on the dosage form, the dose and the manufacturer is in the range from $ 7 to $ 95 (from 180 to 2400 USD) per a pack, and human recombinant interferon alfa-2b – 5-34 5 $ (130 to 870 UAH). Hence, the cost of treatment of herpes zoster with the domestic acyclovir taking into account the daily use of human recombinant alpha-2b interferon (Introferobion PJSC «Pharmstandart-Biolik») according to the scheme of 1 mln of IU intramuscularly, and 2 mln of IU subcutaneously into several points around the affected area with duration up to 7 days increases the treatment costs compared with acyclovir monotherapy by more than 3 times.

Today drugs with the multivector activity (direct antiviral, immunomodulating, interferon-stimulating, antioxidant, apoptosis-modulating, etc.) against herpes virus infection are of considerable interest. Proteflazid® possesses these pharmacodynamic properties; its distinctive feature is its natural origin providing tropism to the human body and a high safety profile, therefore, this drug can be prescribed in pregnancy and lactation, as well as for children from birth. In addition, Proteflazid® takes the medium sized niche among other antiherpetic drugs – the weighted average retail price of the drug, as for March 2016, is about $ 11 (274 UAH) [6]. Due to the range of its pharmacodynamic effects Proteflazid® allows to exclude antioxidants, immunomodulators from the antiherpetic therapy scheme, or to adjust their use, and it can significantly reduce the cost per a course of treatment. For example, the cost of treatment of acute herpes using Proteflazid® drug averages $ 11 (from 288 to 330 UAH) per a month, it is significantly lower than the cost of treatment by other drugs. It should be noted that when using the drug as a therapeutic and preventive (antirelapse) agent for one month only one bottle is enough; it is not only economically feasible for the user, but also increases its compliance for treatment.

CONCLUSIONS

1. The accumulated clinical experience with the original Ukrainian drug Proteflazid® (drops) as an effective and safe antiviral drug based on economic expediency are weighty justification in favour of its choice among other antiherpetic drugs.

2. According to the results of the evaluation of the course of treatment of herpes-induced diseases it is expedient to use Proteflazid® (drops) with the therapeutic and preventive purposes since it allows the patient to reduce the cost of treatment and achieve the optimal clinical and economic effect.

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ПРОТЕФЛАЗИД®: КЛІНІКО-ЕКОНОМІЧНЕ ОБГРУНТУВАННЯ ЗАСТОСУВАННЯ У ТЕРАПІЇ ГЕРПЕТИЧНОЇ ІНФЕКЦІЇ

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Ключові слова: герпетична інфекція; противірусні препарати; ациклічні нуклеозиди; Протефлазид®; клінічна ефективність; вартість лікування

Епідеміологічні дані свідчать про значне поширення і сталість високої динаміки зростання захворюваності на герпесвірусну інфекцію, що обумовлено різноманітністю форм вірусу і шляхів його передачі, високою контагіозністю, довічною персистенцією вірусу в організмі інфікованих і недостатньою ефективністю існуючих методів лікування. Основною групою противірусних препаратів, які традиційно застосовуються для етіотропного лікування герпетичної інфекції, є ациклічні похідні гуанозину, серед недоліків яких відзначаються формування

резистентності при тривалому застосуванні, необхідність залучення імунотерапії, а також висока вартість лікування. Огляд літературних даних з клінічного досвіду застосування оригінального вітчизняного препарату Протефлазид® (краплі) при лікуванні вірусних інфекцій, у тому числі спричинених HHV, свідчить на користь його ефективності та безпеки. При проведенні порівняльної оцінки вартості курсового лікування герпесіндукованих захворювань із застосуванням противірусних препаратів показана економічно обгрунтована доцільність використання Протефлазиду® (краплі) з лікувальною метою і для підтримуючої терапії. Протефлазид® займає середньовартісну нішу серед інших антигерпетичних препаратів, крім того, завдяки різноспрямованості дії відносно герпесвірусної інфекції (пряма противірусна, імунокоригувальна, інтерферонстимулювальна, антиоксидантна, апоптозмодулювальна тощо) застосування препарату забезпечує зменшення потреби в супутній імунотерапії і дозволяє істотно знизити вартість витрат на курс лікування.

ПРОТЕФЛАЗИД®: КЛИНИКО-ЭКОНОМИЧЕСКОЕ ОБОСНОВАНИЕ ПРИМЕНЕНИЯ В ТЕРАПИИ ГЕРПЕТИЧЕСКОЙ ИНФЕКЦИИ

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Ключевые слова: герпетическая инфекция; противовирусные препараты; ациклические нуклеозиды; Протефлазид®; клиническая эффективность; стоимость лечения

Эпидемиологические данные свидетельствуют о широком распространении и устойчиво высокой динамике роста заболеваемости герпесвирусной инфекцией, что обусловлено разнообразием форм вируса и путей его передачи, высокой контагиозностью, пожизненной персистенцией вируса в организме инфицированных и недостаточной эффективностью существующих методов лечения. Основной группой противовирусных препаратов, традиционно применяемых для этиотропного лечения герпетической инфекции, являются ациклические производные гуанозина, среди недостатков которых отмечаются формирование резистентности при длительном применении, необходимость подключения иммунотерапии, а также высокая стоимость лечения. Обзор литературных данных по клиническому опыту применения оригинального отечественного препарата Протефлазид® (капли) при лечении вирусных инфекций, в том числе вызванных HHV, свидетельствует в пользу его эффективности и безопасности. При сравнительной оценке стоимости курсового лечения герпесиндуцированных заболеваний с применением противовирусных препаратов показана экономическая целесообразность использования Протефлазида® с лечебной целью и для поддерживающей терапии. Протефлазид® занимает среднестоимостную нишу среди других антигерпетических препаратов, кроме того, благодаря многовекторности действия в отношении герпесвирусной инфекции (прямое противовирусное, иммунокорригирующее, интерферон-стимулирующее, антиоксидантное, апоптозмодулирующее и др.) применение препарата обеспечивает снижение потребности в сопутствующей иммунотерапии и позволяет существенно снизить стоимость затрат на курс лечения.

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