Preparations containing glycyrrhizic acid employed in dermatovenereologic practice. Conclusions of an international multicentre study

Zastosowanie preparatów zawierających wyciąg z Glycyrrhiza glabra w praktyce dermatowenerologicznej. Podsumowanie międzynarodowego, wielośródmokowego badania klinicznego

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Introduction: Epigen® (Laboratorios Cheminova International) represents an up-to-date preparation the development of which resulted from the experience obtained in the field of traditional medicine. Its excellent antiviral properties have been repeatedly proven by many studies. The indications of the employment of Epigen® are as follows: herpes simplex – labialis, genitalis (vulvovaginitis herpetica, balanopostitis herpetica), herpes simplex recidivans, herpes zoster, HPV infections – verrucae, condylomata acuminata.

Material and methods: 55 patients diagnosed with herpes simplex – labialis, genitalis (vulvovaginitis herpetica, balanopostitis herpetica), herpes simplex recidivans, herpes zoster and condylomata acuminata were being observed at six departments of dermatovenereology as part of an international multicentre study. The series of patients consisted of 26 men (with the average age of 38.5) and 29 women (with the average age of 40.5). The youngest patient was a 12-year-old boy with herpes simplex, the oldest patient was a 78-year-old woman with herpes zoster facialis. The most numerous group of patients consisted of individuals with herpes simplex and Herpes simplex recidivans amounting to the total of 24 patients.

Results: 11 relapses were recorded. The tolerability of the preparation Epigen® was very good in all patients, none of the patients had to discontinue the therapy and no adverse effects were recorded. Even patients with disease relapses spontaneously decided to continue with the application of Epigen® after the termination of the study. The application of Epigen® has significantly accelerated the healing process in local manifestations. The application of Epigen® spray or cream in patients with herpetic infections was followed by desiccation of vesicles without crust formation, which significantly reduced the abuse of analgesics. The effect was excellent in minor manifestations of condylomata acuminata. The treatment of more extensive condylomata manifestations requires a combination of Epigen® application and cryotherapy.

Conclusions: Epigen® cream and spray is a clear contribution to the portfolio of topically employed dermatologic agents.

Key words: glycyrrhizic acid, therapy, virus diseases

Streszczenie


Materiał i metody: 55 pacjentów z jednym z rozpoznań: Herpes simplex – labialis, genitalis (vulvovaginitis herpetica, balanopostitis herpetica), Herpes simplex recidivans, Herpes zoster oraz condylomata acuminata było włączonych do badania klinicznego prowadzonego w 6 ośrodkach dermatowenerologicznych na Słowacji i w Czechach. Badanie było zaplanowane jako wielośródmokowe, międzynarodowe. Grupę badanych stanowiło 26 mężczyzn (średnia wieku 38,5 roku) oraz 29 kobiet (średnia wieku 40,5 roku). Najmłodszym pacjentem był 12-letni chłopiec chorujący na opryszczkę zwykłą, najstarsza zaś była 78-letnia pacjentka z półpasecem twarzy. Najliczniejszą grupę (n=24) stanowili pacjenci z opryszczką zwykłą, w tej grupie u wielu z postacią nawrotową.


Wnioski: Epigen®, krem i spray, należy uznać za cenne uzupełnienie możliwości farmakoterapii miejscowej we wskazaniach dermatologicznych.

Słowa kluczowe: wyciąg z Glycyrrhiza glabra, leczenie, choroby wirusowe

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source plant is a member of the pea family. The name of the plant essentially derives from the Greek words – glykys meaning sweet and riza – the cognate of the English word root. 

*Liquiritia* is a later loaned Latin form of the plant’s name. *Glabra* is the name of the species and relates to the sticky glands on the resiny leaves. *Glycyrrhiza glabra* was mentioned on Egyptian papyruses a few centuries B.C. as the drug for the treatment of respiratory tract catarrh. Similarly, it has been used in Chinese medicine for ages due to its considerable anti-inflammatory properties.

*Glycyrrhiza glabra* is used in pharmacy today as well. The contained active substances in the extract of the root drug can be divided into two groups:

- **group I** – saponin-like substances – *Glycyrrhizin*,
- **group II** – flavonoids – liquiritine and isoliquiritine.

Glycyrrhizin is a substance of sour character (a more appropriate name of the substance is *glycyrrhizic acid* – GA) contained in the plant as potassium and calcium salt. The commonly traded glycyrrhizin ammonium salt is used in confectionery.

GA is the representative of substances exhibiting corticometric activity. The drug is best known for its expectorant effect. During WWII, the anti-ulcerous effect of GA on the mucous membrane of the stomach was observed and verified. GA also demonstrates laxative and slightly diuretic properties. In case of prolonged use of the drug, which is not advisable, oedema may occur (1).

During the performance of targeted research activities it has been proven that GA contains an active antiviral group. In 1979 the first study on the antiviral properties of GA was published (2). Other studies and experience developed as the result of its employment in practice followed continuously (3–10). The most numerous and extensive studies *in vitro* were published by Japanese authors in the work from 1988 by Ohtsuki and Iai (11) considered to be the breakthrough in this field.

The knowledge of the best foreign centres was taken advantage of by the Spanish company Laboratorios Cheminova International and became part of their production programme. For the development of the recipe of a topical preparation for the treatment of various virus infections named Epigen® the latest knowledge of scientific research was used. In the development of the preparation the method of molecular activation increasing its biological activity (12) was utilised. The ultimate goal was to present a preparation that would fully meet the attributes of absolute safety and maximum efficacy. The introduction of Epigen® in the market was preceded by elaborated laboratory and clinical studies (13–22). The indication spectrum of Epigen® is as follows: *herpes simplex – labialis, genitalis (vulvovaginitis herpetica, balanopostitis herpetica), herpes simplex recidivans, herpes zoster and HPV infections: verrucae, condylomata acuminata.*

After elaborated multicentre studies had been performed abroad, Czech and Slovak dermatovenereologists were contacted by Laboratorios Cheminova International (Spain) and instructed to perform a study the aim of which would be to verify the effect of Epigen® in patients with virus infections such as *herpes simplex, herpes zoster, herpes progenitalis, condylomata acuminata*, including both the acute as well as relapsing forms in all groups. During the course of performance of the study results were obtained verifying that Epigen® exhibits a significantly positive effect on mucous membrane of the patients affected by bullous diseases of pemphigus and pemphigoid group. The results of the study are now subject of continuous scientific work.

The study was performed at six departments of dermatovenereology in the Slovak and Czech republic from December 2002 till May 2003. Type of study: open, type IV. Post registration observation.

### Material and methods

55 patients with *herpes simplex – labialis, genitalis (vulvovaginitis herpetica, balanopostitis herpetica), herpes simplex recidivans, herpes zoster and condylomata acuminata* were observed at 6 clinics. The representation of single diagnoses is stated in table I.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Herpes simplex labialis</em></td>
<td>26 males (average age of 40.6 year) and 29 females (average age of 36.7 year)</td>
</tr>
<tr>
<td><em>Herpes simplex genitalis</em></td>
<td>12 males and 46 females</td>
</tr>
<tr>
<td><em>Herpes simplex recidivans</em></td>
<td>55 patients</td>
</tr>
<tr>
<td><em>Herpes zoster</em></td>
<td>12 males and 43 females</td>
</tr>
<tr>
<td><em>Condylomata acuminata</em></td>
<td>35 males and 20 females</td>
</tr>
</tbody>
</table>

Exclusion criteria:

- first disease bout,
- disease relapse,
- age: 12–80 years,
- failure of previous therapies with other topical preparations,
- resistance of the local finding to other preparations.

Inclusion criteria:

- pregnancy and lactation,
- patients younger than 12 years,
- bad cooperation between the doctor and the patient,
- patients with polyclonal allergy,
- patients on steroids, immunomodulators, immunosuppressives, topical antiviral agents.

The employed agent: Epigen® cream or spray with effective substance content of 0.1 g in 100 ml of excipient.

Number of applications: 3–5 times a day until the optimisation of the condition, the application duration differs according to single diagnoses from 3 to 60 days.

Application information: provided by the therapist.

Documentation: working protocol.

Photo documentation: 2–3 times in selected patients.
Basic laboratory screening; in every patient, serology PL: in every patient. The evaluation was not subject of the study.

Recommended personal hygiene: Use of non-irritating preparations with no influence on the treatment process.

Other medication: restricted to preparations recommended by other experts and necessary for the health comfort of the patient.


Subjective evaluation of the condition by the patient: grade 1-5 (1 – excellent, 2 – very good, 3 – good, 4 – without changes, 5 – exacerbation, irritation)

Results

The tolerance of Epigen® was very good in all patients and there was no need to discontinue the therapy in any patient.
during the observation period (tab. II). Even after finish of the study in patients with relapses the preparation Epigen® is continuously used. Evaluation of efficacy and tolerance of the preparation in each groups were detailed in table III.

Herpes zoster: it is evident that the application of Epigen® significantly accelerated the healing of topical manifestations. The application of Epigen® spray or cream resulted in the desiccation of vesicular eruptions without crust formation. The abuse of analgesics was reduced significantly (one of the female patients discontinued their use on the third day already). The healing occurred without the formation of scars in extensive manifestations as well. In one case light depigmentation of the affected area occurred in a male patient. Efficacy and tolerance were assessed as excellent by both the doctor and the patients.

Herpes simplex: In most of the patients the application and effects of Epigen® were evaluated as excellent. Nearly all of the patients reported an instant relief sensation – burning pain relief and the sensation of local anaesthesia. The vesicular eruptions rapidly changed into small hemorrhagic crusts and the inflammatory infiltration receded within 72 hours. Most of the patients reported total healing on the fifth day of application. Whereas in men the efficacy and tolerance were evaluated as excellent by the patients as well as the therapist, in women the results were slightly different. In ten patients with herpes simplex labii oris eruptions the effect and tolerance were excellent. Three patients with permanent manifestations on the lips were utilising Epigen® for nearly a month with short breaks. The result of which was the final healing of the symptoms and the lack of relapses for the period of the following two months. In two patients – one with herpes simplex labii oris sup. recidand and the other with herpes simplex reg. glutaealis recid. the healing was slow and the efficacy and tolerance were evaluated as good and comparable with other external agents utilised by the patients in the past. Within the three months of observation the total of 6 patients experienced a relapse of herpes simplex labii oris. After repeated application of Epigen® the lesions were healed within 72 hours.

Herpes progenitalis: Efficacy and tolerance were assessed as excellent by both the doctor and the patients. Similarly to the group of patients with herpes simplex, in all monitored patients there was a rapid change in vesiculation and the inflammatory infiltration receded within 72 hours. Most of the patients reported healing on the fourth or fifth day of application. The patients were in favour mainly of the rapid remission of the subjective symptoms such as burning sensation and algia. The mental wellbeing of the patients improved significantly. There was a relapse in three patients, which was suppresses rapidly by the repeated application of Epigen®. In one of the patients there was no relapse recorded during the period of four months despite the fact that he had suffered from very frequent relapses prior to Epigen® therapy.

Condylomata acuminata: The application of Epigen® on small condylomata (up to 1 mm) had an excellent effect and was well tolerated. The regression of the finding was evident within 7 up to the maximum of 14 days. In the end the lesions were healed. The most significant effect was observed in a married couple. In two female patients with an extraordinarily extended finding the application of Epigen® was prolonged necessarily from 35 to 60 days. Having had the experience with previous aggressive therapies the patients were demanding to be treated with Epigen®. In patients with more extensive condylomata the employment of other form of treatment such as cryotherapy was inevitable. Epigen® exhibited excellent properties in the treatment of residual manifestations. Moreover, patients after cryotherapy reported an analgesic effect of the preparation. No relapses have been recorded.

We have recorded no differences between the application of creme and spray, however, we preferred to use spray on more extensive areas as well as the intimate parts.

In the group of patients with bullous diseases (the preparation was applied to mucous membrane lesions) the excellent anti-inflammatory and immunomodulatory effect of the preparation has been proven in 14 patients (11 female, 3 male, with the average age of 46.07 years). The treatment took 9 to 28 days. In 7 patients total healing occurred (50%). In 4 cases (28.57%) clinical improvement and in 3 probands (21.42%) visible clinical improvement was recorded. The therapy was well tolerated and no adverse effects were recorded. The study verified that the employment of preparations containing glycyrrhetic acid represents a new possibility of topical treatment of the pemphigus and pemphigoid group.

Discussion

Glycyrrhiza glabra is not only one of the starting substances utilised in the food industry (1, 5), bud can be used in pharmacy mainly as root drug – radix liquoritiae and radix Glycyrrhiza glabrae (1) as well. The roots and shoots of the plant are collected ergo dug out after the third vegetation year.

The sort that grows in our climate comes from southern Europe and the Near East. The imported sorts come from Spain, Russia and China and differ in the processing form (finishing), peeling as well as in other properties. The highest specific weight of Glycyrrhiza glabra is represented in the Spanish sort. The content of glycyrrhizin (GA), which is highest in the Chinese peeled sort (5.5%) and the Spanish unpeeled sort (8.9%), is responsible for the sweet taste of liquorice and its extract which is 50 times sweeter than beet sugar. Water extract – success – comes predominantly from the Italian drug. What is really interesting is the fact that the drug in powder form is very often fake (1).

Glycyrrhizic acid (Glycyrrhizin, GA) is a substance of glycosidic character. Aglycon is represented by glycyrrhetinic acid (glycyrrhetin). The pentacyclic triterpene acid glucuronide is of dic character. The sugar component is represented by two molecules of glucuronic acid. The following spilt of the sugar component results in the loss of sweet character.

One of the basic properties of GA is the water foaming property and its low haemolytic efficacy. GA causes the inhibition of prostaglandin E2 in the affected tissue and stops the replication of viruses as the result of virus PKinase activity inhibition. The induction of interpherone formation results in the activation of macrophages and potentiating of their phagocytic and bactericidal property. Interphorones exhibit antiviral and anti proliferative effect (10, 13, 15, 17-22).

In the end, it is possible to characterise the effect of GA as:

- anti-ocular,
- anti-inflammatory,
- antiviral (DNA and RNA virus inhibition ability) – varicella zoster, HIV, influenza A, B, herpes simplex, hepatitis.

The main active substance of Epigen® (Laboratorios Chemi nova International Madrid) is the water extract of GA in the amount of 0.1 g in 100 g of vehicle. Laboratory experiments in vitro have proven its inhibitory effect. Animal testing has proven the zero mortality index as well as the minimal ocular and dermal irritation (6, 11, 13, 17, 20).

Numerous clinical studies with Epigen® performed during the last ten years at clinics of dermatovenerology and gynaecology (15, 16, 18, 19, 21, 23) have proven the exceptional activity of the preparation against infections. Epigen® was applied in pregnant women without any problems. Excellent effects have been described in connection with the application in...
the initial phase in which the agent exhibited a 100% efficacy and 90% efficacy in recurrent cases (16, 19, 21, 22).

Promising effects have been recorded in patients with mucous membrane manifestations in pemphigus and pemphigoid group (24). The first case was the female patient with genital lesions of *pemphigus vulgaris*. The application resulted in the amelioration of burning, pain and desiscation of eroded areas. Even more significant effects were recorded in a female patient with *pemphigus chronicus benignus familiaris* (Hailey-Hailey diseases) localised on the loins, the perigenital area and axillae. The results obtained by monitoring the total of 14 patients were subjected of further study published and presented at the EADV congress in Barcelona 2003.

All of the participating subjects confirm that *Epigen®* significantly reduces: oedema, hyperaemia, burning, itching and accelerates the epithelization of eroded areas. The confirmation of the declared properties of *Epigen®* in 46 patients monitored within the framework of this multicentre international study needs to be supported by the evaluation of application properties. The use of *Epigen®* topical highly effective preparation is restricted to external application on mucous membranes and can be assessed as quick and simple. The preparation is registered in the Slovak Republic in both its cream and spray formulation.

**Conclusion**

*Epigen®* (Laboratorios Cheminova International) is a modern preparation developed based on the experience of traditional medicine. Its excellent antiviral properties were proven by means of the presented multicentre study. It represents an alternative treatment agent for a big group of patients with herpes simplex – *labialis*, *genitalis* (vulvovaginitis herpetica, balanopostitis herpetica), herpes simplex recidivans, Herpes zoster, condylomata acuminata, verrucae vulgares. There were extremely interesting effects observed in patients with bullous dermatoses.

The preparation is extremely well tolerated and causes neither irritation nor other adverse effects. The application is simple and comfortable. What is positive about the application is that it can be applied concomitantly with other systemically applied agents as well as other types of mechanic or physical treatment forms.

The results of the multicentre study fully verified the presumed effect of the utilised molecular activation method increasing the biological efficacy of the preparation (12).

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