Topical Acyclovir for Recurrent Herpes Labialis in Primary Care

Critical appraisal

GRAHAM WORRALL, MB, BS, CCFP

SUMMARY

I reviewed the literature on the treatment of recurrent herpes labialis with topical acyclovir ointment to determine the effectiveness of this treatment for family practice patients. This article discusses the generalizability of the results to family practice. I concluded that the evidence supporting this therapy is weak and that it cannot, in the light of current knowledge, be strongly recommended.

RÉSUMÉ

J'ai révisé la littérature concernant l'utilisation topique de l'acyclovir en onguent pour traiter l'herpès labialis récidivant afin de déterminer l'efficacité de ce traitement chez les patients de pratique familiale. L'article discute la possibilité de généraliser les résultats au contexte de la pratique familiale. J'en conclus que les preuves à l'appui de cette thérapie sont faibles et qu'on ne peut, à la lumière des connaissances actuelles, émettre des recommandations fermes.

Can Fam Physician 1991;37:92-98.

THREE YEARS AGO, A YOUNG teacher came to see me in my office. She had herpes lesions on her lower left lip. She had, with previous attacks, tried various preparations, but had found none of them helpful. She now requested a prescription for acyclovir ointment, which she had heard was very good for her condition.

Since then, I have had several requests for acyclovir ointment from other herpes labialis sufferers, for both initial and repeat attacks. My local colleagues confirm that they are getting similar demands.

The product monograph for acyclovir ointment in the current *Compendium of Pharmaceuticals and Specialists* does not give herpes labialis as an indication.[1] Unhappy with this situation, I decided to assess the evidence for myself.

WHAT I WANTED TO STUDY

Acyclovir

The acyclic nucleoside analogue acyclovir is a substrate specific for herpes virus thymidine kinase. The thymidine kinase in normal human cells does not effectively use acyclovir as a substrate.[2,3] Herpes virus thymidine kinase transforms acyclovir into acyclovir triphosphate which is both an inhibitor of, and a substrate for, herpes virus DNA polymerase. The acyclovir thus inhibits replication of herpes viruses.[4,5] Although the DNA polymerase in the infected human cells can be inhibited by acyclovir triphosphate, this inhibition occurs only at concentrations very much higher than those that inhibit the herpes virus DNA polymerase. Acyclovir is preferentially taken up and selectively converted to its active form by the herpes-infected cells.[3]

Recurrent herpes labialis

Family doctors are very familiar with this common problem of the facial skin. The superficial clear blisters appear on an erythematous base, usually at the mucocutaneous junction of the lips, at the site of the initial infection.[6] The recurrent condition is attributed to the fact that herpes virus remains in the skin or nerves. Yet, although the virus can be found easily in the vesicular fluid during attacks, it has never been demonstrated in the skin between attacks. Various factors, such as fever, upper respiratory tract infections, and ultraviolet light, are thought to trigger the recurrent attacks, but this reaction is extremely variable and un-

Dr Graham Worrall *is District Medical Officer in Glovertown, Nfld.*

predictable even in the same patient, as is the extent and duration of a particular attack.[7,8] The initial clear vesicles rupture, exude a sticky serous or serosanguinous fluid, and form a yellow crust, which usually heals without scarring (unless there is secondary bacterial infection) within 5 to 10 days.

Recommended uses of acyclovir ointment

The only commercially available product is a 5% ointment in a polyethylene glycol base.[1] It is licensed for use in the management of *initial* episodes of genital herpes infections. The use of oral acyclovir for genital herpes is well established,[9-11] and there is also evidence that topical treatment can be efficacious for genital herpes.[12-15] It is also recommended for the management of non–life-threatening cutaneous herpes simplex infections in immunocompromised patients.

The recommended dosage is to apply the ointment four to six times daily for 10 days. A finger cot or rubber glove should be used while applying the ointment to prevent autoinoculation of other body sites or infection of other people.

The product is not at present recommended for use in herpes labialis, especially not recurrent herpes attacks, nor is it recommended for use in an immunocompetent population. In other words, it is not recommended for the otherwise healthy primary care population that is asking us for it. There is, however, nothing to stop physicians from using it if they wish. For this reason I decided to do a critical appraisal of the evidence that acyclovir is helpful for recurrent herpes labialis.

The study question

Is acyclovir ointment, as commercially available at this time, effective in the management of herpes labialis?

A distinction must be made between the terms efficacious and effective. An efficacious treatment is one that has been shown to work well in a clearly defined but sometimes artificial situation; an effective treatment is one that has been shown to work in the real world.[16] In this case, an effective treatment would be cheap, be easily available, be free from side effects, be easy to use, be acceptable to patients, and produce desirable clinical effects, such as a noticeable difference in appearance, discomfort, or duration of herpes lesions.

METHODS

The criteria used in selecting studies to assess are based both on validity (is the study true?) and generalizability (is the study relevant to my patients?).[17,18]

Evaluating the studies

1. Were the study patients randomized? If the study claims to be a randomized trial, was the method of randomization described?
2. How were the patients selected? From what population base did they come? Was this population typical for the disease? How closely does this population resemble my patients?
3. How well was the treatment defined? (How easily could the reader reproduce it?) Was the treatment appropriate? (Was it safe, affordable, and feasible for most patients?)
4. Was the outcome assessment of treatment complete, objective, and well defined? For example, how were pain, erythema, itching, size, and degree of vesiculation measured?
5. Was the study blinded? Did the physicians prescribing the treatment know which treatment was being used? Did the patient know? Was the outcome assessed by the same physician who prescribed the treatment, or by another blinded physician? How much did the outcome assessment depend on patient opinion?
6. Was follow up complete? Were all patients who entered the study accounted for at its conclusion?
7. Was compliance measured? With a treatment that might have to be applied up to six times daily, was there any attempt to measure how frequently patients used the ointment?
8. Were there any measures of the complications of treatment?
9. How were the study results analyzed? Are the statistical methods described? Was an estimate made of the power of the study (the probability of finding a

small difference between treatment and placebo) and the effect of the sample size on the power of the study?

Criteria related to validity are randomization, the method of randomization, similarity, treatment definition, treatment blinding, outcome definition, completeness, compliance, statistical methods, and power. Generalizability is addressed by representiveness, treatment definition, treatment appropriateness, outcome definition, compliance, and complications.

Article selection

The search was restricted to articles in English and French. A computerized MEDLINE search was done of *Index Medicus* since 1980. The Index of Medical Reviews was checked since 1980; the reference sections of all review articles were checked. All major infectious diseases texts in the Health Sciences Library, St John's, Nfld, were checked for references to herpes labialis. These methods turned up 13 clinical studies, dating from May 1982 to June 1989,[19-31] and nine review articles, dating from May 1983 to August 1988.[32-40] I then searched the Science Citation Index manually, using the most recent study[31] as the cited work.

After excluding trials on animals or on immunocompromised patients, trials that used oral acyclovir and acyclovir ointment in a strength or a formulation very different from that available commercially, and articles in foreign languages, only six papers remained to be evaluated.[19,27-31] All these papers described randomized controlled trials (RCTs). No RCTs were found in foreign journals.

RESULTS

Spruance et al

A group of physicians[30] in the United States tested 227 patients who had recurrent herpes labialis: the average duration of their complaint was 20 years. The patients' ages ranged from 18 to 65 years; the mean age was not given; 65% of them were women, and none was pregnant. Randomization was by random numbers, and the code was held by an independent group (the National Institute of Allergy and Infectious Diseases), which did not break the code until after the last patient had entered the study.

Patients were told to use 0.6 cm of ointment on their lesions four times daily for 5 days. They were given either 5% acyclovir in polyethylene glycol or plain polyethylene glycol as a placebo. The day of the first visit was day 0; patients returned to the clinic for observation on days 1 and 2, and then on alternate days until the lesions were healed. There was no measure of patient compliance with treatment.

The pain, size, and stage of the herpes labialis lesions were recorded by the clinic physicians, the same doctors who prescribed the treatment. Patients were not asked their subjective feelings, but were asked to mention any possible complications.

The study was double blind, and 208 of the 227 study patients (91.6%) were accounted for. The methods of statistical analysis were clearly described and included multiple stepwise regression to allow for potential influence of several pretreatment variables on the outcome.

No significant clinical benefit, measured in terms of duration, painfulness, or size of lesion, was found in the patients who used acyclovir ointment rather than placebo. The large sample size meant that this study had the power to detect a small difference between treatment and placebo groups, but the study failed to show any such difference clinically.

At day 1 the median titer of virus from the acyclovir-treated patients was significantly lower than from the lesions of placebo-treated patients.

Raborn and colleagues

This study[19] was done by staff of the Department of Dentistry at the University of Alberta Hospitals. Sixty patients completed the trial, which followed each of them through two attacks of herpes labialis. All were white patients older than 18 years. There were 42 women who were not pregnant and 18 men. All the patients had recurrent herpes labialis and had previously been volunteers in a study of oral acyclovir on herpes labialis. The method of randomization was not described, but the trial was double blind.

The active ointment used was 5% acyclovir in polyethylene glycol. Patients were instructed to apply this ointment, or the placebo polyethylene glycol ointment, to the lesions and surrounding skin at intervals of 2 hours for 10 days. There was no recorded measurement of patient compliance. Patient lesions were assessed daily at the clinic for 5 days and then on alternate days until healing had occurred.

At each visit, pain from the herpes lesions was assessed, together with the number, type, size, and location of all lesions. All patients kept a home diary to record their evaluations of these parameters twice daily.

There is no information on whether the assessment was done by the person prescribing treatment. The trial was completed by all 60 eligible patients. The methods of statistical analysis are not clearly described, but appear to be comparison of means.

No significant differences were found between the acyclovir-treated and the placebo groups for the main outcome objectives of duration of pain, time to loss of crust, and time to complete healing. The evaluation of a total of 120 episodes of herpes labialis gives the study power to detect a true difference as small as, for example, 1 day in total healing time. But no such differences were detected.

Fiddian and Ivanyi

This study[28] was conducted by a physician on the staff of the pharmaceutical company that makes the acyclovir ointment. It was done on 13 patients in southern England, who experienced 31 episodes of recurrent herpes labialis. The patients were all attending a dental hospital; there were eight females and five males. The method of randomization is not given.

Patients were instructed to start the 5% acyclovir in polyethylene ointment (or placebo ointment) as soon as possible after the onset of prodromal symptoms and to apply the ointment five times daily for 5 days. They were assessed at the clinic on alternate days. There was no measure of compliance with treatment.

The presence of pain and itching and the size, stage, and site of the lesion were recorded at each visit until complete healing had taken place. Patients did not keep a record, nor did the authors state whether the person assessing the lesions was also responsible for treatment. The trial is described as double blind.

The methods of analysis are described and seem appropriate for the small numbers (for example, Fisher's exact test was used to compare the proportions of patients in whom lesions aborted). No confidence limits are given.

The times from onset of symptoms to crust formation and to complete healing were both found to be significantly shorter for episodes treated with acyclovir ointment than for those treated with placebo; mean time to crust formation dropped from 4 to 3 days, and mean time to complete healing was reduced from 8 to 6 days. There was no significant difference in the number of lesions that were aborted.

Fiddian and colleagues

From questionnaires sent to 4500 employees of the British Petroleum Company, a physician and a research assistant working for the company that makes the proprietary acyclovir ointment selected 90 patients with recurrent herpes labialis.[29] Three were youths, The remaining 87 patients were randomly allocated to receive treatment by a method of randomization that is not detailed.

The acyclovir was administered in the form of a 5% cream, rather than an ointment; the paper does not make it clear what base was used for the cream, although it was likely propylene glycol. Patients were instructed to use the cream as soon as possible after symptoms started and to apply it five times daily for 5 days. Patients were assessed daily until healing occurred. There was no measure of compliance.

At each visit, symptoms of itching, pain, or burning were recorded; the stage, size, and site of the lesion were also noted. It was not stated whether the assessor was also the person who prescribed treatment.

Of the 87 eligible patients, only 55 (63%) completed treatment. Some patients were dropped from the study because they started treatment later than recommended, because they did not attend clinic for regular checkups, and because they did not use

the ointment as often as recommended. This is exactly the sort of behavior that family doctors encounter in actual practice. The methods of statistical analysis are described clearly.

The authors claim that the number of first episodes that aborted was significantly higher in the acyclovir group. But only 49 of the 55 patients are accounted for; if the missing six patients are analyzed as successes for placebo (the worst-case scenario), the result is no longer significant. Times to crust formation were reduced from 2 to 1 day by active treatment, and time to complete healing was reduced from 6 to 4 days; again, however, some patients are missing from the analysis.

Van Vloten, Swart, and Pot

Academic physicians working in a department of dermatology of a university hospital in Holland[27] studied 36 patients with recurrent herpes. Few details on the patients are given. The method of randomization is not given, but a third party kept the code, which was not broken until after the last patient had entered the study.

The active treatment was 5% acyclovir in a cream of propylene glycol. Cream was applied to the lesions five times daily for 5 days. Patients attended for assessment every 1 or 2 days (the difference is not made clear). Tubes of cream were examined to assess compliance.

Local symptoms were recorded at each visit and the stage of the lesion recorded. The paper does not say who did the assessment; the study was double blind.

Of 36 eligible patients, 30 completed the trial (17 in the treatment group and 13 in the placebo group). The methods of statistical analysis are described very sketchily, but seem to be comparisons of two sample means.

The authors found that mean duration of vesiculation was reduced from 2.7 to 1.8 days in the active treatment group; mean days to crusting were reduced from 2.6 to 2.3; and mean days to complete healing were reduced from 8.3 to 5.7. Once again, if the missing patients are included in a "worst case" intention-to-treat analysis in which it is assumed that all the missing patients did badly, the results are no longer statistically significant.

Raborn and colleagues

This trial[31] was conducted with patients in a university dental clinic. There were 61 patients registered for the trial; all were white. Patients were 18 years or older, not pregnant, and without psychiatric disease. The method of randomization is not stated. Informed consent was obtained from all patients.

The active medication was 5% acyclovir in a modified aqueous cream; it was applied within the first hour of prodromal symptoms, and every 4 hours thereafter during waking hours for 5 days or until the lesion was judged healed by a physician.

Patients were assessed daily for the first 5 days and on alternate days thereafter. Pain was recorded on a subjective scale; the number, type, size, stage, and location of lesions were recorded at each visit. Patients also kept a home diary to record twice daily subjective and objective parameters. The paper does not say whether the assessor was also the prescriber.

Of the 61 eligible patients, 51 completed the trial, and each was followed through two episodes of herpes labialis; the 10 others were accounted for (they did not comply with treatment or were unavailable for follow up). The methods of statistical analysis are clearly described.

A non-significant trend toward accelerated healing in the active treatment group was found in this study. No significant differences could be demonstrated between groups for duration of pain, time until loss of crust, or time to complete healing.

DISCUSSION

Critical analysis is a way of evaluating the effects of study design and study execution on the conclusions of the study. It is perhaps easy to be overcritical, and it is wise to remember that, given the vagaries of human nature and the nature of everyday practice, it is probably impossible to conduct an ideal trial.

Although all six trials are randomized and double blind, there are notable differences between them. They are divided in their opinions: three conclude that treatment of recurrent herpes labialis with topical acyclovir is of no benefit,[19,30,31] and three claim that there is improvement.[27-29]

Could publication bias have affected what has appeared in print about topical acyclovir? A publication bias tends to under-report negative studies; perhaps there were other negative studies in addition to the three that were published and are reviewed here.

The trials with the larger numbers of patients report negative results. It seems that the trials with smaller numbers of patients (13, 30, and 49) report positive results. Why is a treatment effect that is found in a smaller trial not picked up in three larger trials, which would presumably have greater power and be less likely to miss a significant difference between active treatment and placebo groups if one truly exists? Why are the larger and better designed trials the ones with negative results?

None of the trials give confidence limits on their results; this is perhaps understandable, as the studies were mostly out before it became expected practice to give confidence limits as well as *P* values. The important thing to remember about trials with very small numbers of subjects is that the absence of just a few patients in the analysis can seriously distort results.

Most of these trials were carried out in academic centers, such as university dental and dermatology clinics. It is far from certain that the results from such populations are generalizable to the patients of a family doctor. It seems likely that many of these patients suffered from recurrent herpes labialis of above average severity and frequency. The positive-reporting trial at the large company had its patients picked by the investigators, which introduces the possibility of bias. The trial that had not only the largest number of patients but the population most comparable to a family practice population[30] showed negative results. Even in this trial, the patients had suffered from recurrent herpes labialis for an average of 20 years, which is not typical of my family practice patients.

Most of these studies can be criticized for failing to address the question of compliance. When a treatment has to be started early and applied regularly and frequently, compliance is an important issue and can limit the generalization of results to family practice patients. Patients tend to see me a few days after symptoms have developed, and busy people are unlikely to comply with frequent administrations of treatment.

CONCLUSION

There is some evidence that topical acyclovir ointment may be more useful in prophylaxis,[41] but is there good evidence that the ointment is of any use in attacks of recurrent herpes labialis? Although it is a non-fatal, self-limiting condition, it would be nice to offer the distressed patient an effective treatment rather than compassionate reassurance that their condition will be gone by next week.

Unfortunately, a critical appraisal of the admittedly scanty evidence seems to indicate that the evidence for benefit with treatment by topical acyclovir is weak. Until we have more information, there is no proven useful topical therapy for recurrent herpes labialis. It is well to remember that the acyclovir ointment is rather expensive – the patient will pay about $20 for a 4-g tube.

To settle this question more fully, we need a well-designed, tightly executed, double-blind, randomized study of acyclovir ointment versus placebo conducted in Canada on family practice patients with recurrent herpes labialis. ■

Requests for reprints to: *Dr Graham Worrall, District Medical Officer, Glovertown, NF A0G 2L0*

References

1. Krogh CME, Gillis MC, Bisson R, et al, eds. *Compendium of pharmaceuticals and specialties.* 24th ed. Ottawa, Ont: Canadian Pharmaceutical Association, 1989:1166.
2. Collins P, Bauer DJ. The activity in vitro against herpes virus of 9-(2-hydroxyethoxymethyl) guanine (acycloguanosine), a new antiviral agent. *J Antimicrob Chemother* 1979;5:431-6.
3. Crumpacker CS, Schnipper LE, Zaia JA, Levin MJ. Growth inhibition by acycloguanosine of herpes virus isolated from human infections. *Antimicrob Agents Chemother* 1979;15:642-5.
4. Furman PA, St Clair MH, Fyfe JA, Rideout JL, Keller PM, Elion GB. Inhibition of herpes simplex virus–induced DNA polymerase activity and viral DNA replication by 9-(hydroxyethoxymethyl) guanine and its triphosphate. *J Virol* 1979;32:72-7.
5. Furman PA, McGuirt PV, Keller PM, Fyfe JA, Elion GB. Inhibition by acyclovir of cell growth and DNA synthesis of cells biochemically transformed with herpes virus genetic information. *Virology* 1980;102:420-30.
6. Habif TP. *Clinical dermatology: a color guide to diag-*

nosis and therapy. St Louis, MO: CV Mosby Co, 1985.

7. Baker C, Crumpacker CS, Schnipper LE. The natural history of recurrent facial-oral infections with herpes simplex virus. *J Infect Dis* 1978;138: 897-905.
8. Spruance SL, Overall JC, Kern ER, Krueger GG, Pliam V, Miller W. The natural history of recurrent herpes simplex labialis: implications for antiviral therapy. *N Engl J Med* 1977;297:69-75.
9. Bryson YJ, Dillon M, Lovett M. Treatment of first episodes of genital herpes simplex virus infection with oral acyclovir. *N Engl J Med* 1983;308: 916-21.
10. Nilsen AE, Aasen T, Halsos AM, et al. Efficacy of oral acyclovir in the treatment of initial and recurrent genital herpes. *Lancet* 1982;ii:571-3.
11. Salo OP, Lassus A, Hovi T, Fiddian AP. Double blind placebo-controlled trial of oral acyclovir in recurrent genital herpes. *Eur J Sex Transm Dis* 1983;1:95-8.
12. Corey L, Nahmias AJ, Guinan ME, Benedetti JK, Critchlow CW, Holmes KK. A trial of topical acyclovir in genital herpes simplex viral infections. *N Engl J Med* 1983;306:116-9.
13. Thin RN, Nabarro JM, Parker JD, Fiddian AP. Topical Acyclovir in the treatment of initial genital herpes. *Br J Vener Dis* 1983;59:116-9.
14. Corey L, Bendetti JK, Critchlow CW, Remmington MR, Winter CA. Double-blind controlled trial of topical acyclovir in genital herpes simplex infections. *Am J Med* 1983;73:326-34.
15. Reichman RC, Badger GJ, Guinan ME, et al. Topically administered acyclovir in the treatment of recurrent herpes genitalis. A controlled trial. *J Infect Dis* 1983;147:2103-7.
16. Tugwell P, Bennet K, Haynes RB, Sackett DL. The measurement iterative loop: a framework for the critical assessment of the needs, benefits and costs of health interventions. *J Chronic Dis* 1985;35:339-51.
17. Sackett DL, Haynes RB, Tugwell P. *Clinical epidemiology: a basic science for physicians.* Boston, Mass: Little, Brown & Co, 1985:171-97.
18. DerSimion R, Charette LJ, McPeek B, Mostellar F. Reporting on methods in clinical trials. *N Engl J Med* 1982;306:1332-7.
19. Raborn GW, McGaw WT, Grace M, Houle L. Herpes labialis treatment with acyclovir 5 per cent ointment. *Can Dent Assoc J* 1989;55:135-7.
20. Bilenchi R, Simoni S. Therapy of herpes simplex virus infections with acyclovir cream. *Clin Ther* 1968;125:353-8.
21. Vidas I, Rosin-Gorget K. Effect of Zovirax cream in recurrent herpes labialis. *Acta Stomatol Croat* 1987;21:147-53.
22. Raborn GW, McGaw WT, Grace M, Tyrell LD, Samuels SM. Oral acyclovir and herpes labialis: a randomized, double-blind placebo-controlled trial. *J Am Dent Assoc* 1987;115:38-42.
23. Gibson JR, Klaber MR, Harvey SG, Tosti A, Jones D, Yeo JM. Prophylaxis against herpes labialis with acyclovir cream – a placebo controlled study. *Dermatologica* 1986;172:104-7.
24. Shaw M, King M, Best JM, Banatvala JE, Gibson JR, Klaber MR. Failure of acyclovir cream in treatment of recurrent herpes labialis. *Br Med J* [Clin Res] 1985;291(6487):7-9.
25. Whitley RJ, Levin M, Barton N, Hershey BJ, Davis G, Keeney RE. Infections caused by herpes simplex virus in the immunocompromised host: natural history and topical acyclovir therapy. *J Infect Dis* 1984;150:323-9.
26. Spruance SL, Crumpacker CS, Schnipper LE, et al. Early, patient-initiated treatment of herpes labialis with topical 10 per cent acyclovir. *Antimicrob Agents Chemother* 1984;25:533-5.
27. Van Vloten WA, Swart RN, Pot F. Topical acyclovir therapy in patients with recurrent orofacial herpes simplex infections. *J Antimicrob Chemother* 1983;12(suppl B):89-93.
28. Fiddian AP, Ivanyi L. Topical acyclovir in the management of recurrent herpes labialis. *Br J Dermatol* 1983;109:321-6.
29. Fiddian AP, Yeo JM, Stubbings R, Dean D. Successful treatment of herpes labialis with topical acyclovir. *Br Med J* [Clin Res] 1983;286(6379): 1699-701.
30. Spruance SL, Schnipper LE, Overall JC. Treatment of herpes simplex labialis with topical acyclovir in polyethylene glycol. *J Infect Dis* 1982;146:85-90.
31. Raborn GW, McGaw WT, Grace M, Percy J, Samuels S. Herpes labialis treatment with acyclovir modified aqueous cream: a double-blind randomized trial. *Oral Surg Oral Med Oral Pathol* 1989;67:676-9.
32. Spruance SL, McKeough MB. Evaluation of treatments for recurrent herpes simplex in the dorsal cutaneous nerve guinea pig model. *Antiviral Res* 1988;9:295-313.
33. Raborn GW, McGaw WT, Grace M, Percy J. Treatment of herpes labialis with acyclovir: review of three clinical trials. *Am J Med* 1988;85:39-42.
34. Pazin GJ, Harger JH. Management of oral and genital herpes simplex infections: diagnosis and treatment. *Z Hautkr* 1986;61;1629-32.
35. Kinghorn GR. Topical acyclovir in the treatment of recurrent herpes simplex infections. *Scand J Infect Dis Suppl* 1985;47(Suppl):58-62.
36. Straus SE, Seidlin M, Takiff H. Management of mucocutaneous herpes simplex infections. *Drugs* 1984;27:364-72.
37. Balfour HH. Acyclovir and other chemotherapy for herpes virus group infections. *Ann Rev Med* 1984;35:279-91.
38. Yeo JM, Fiddian AP. Acyclovir in the management of herpes labialis. *J Antimicrob Chemother* 1983;12(Suppl B):95-103.
39. Fiddian AP, Yeo JM, Clark AE. Treatment of herpes labialis. *J Infect* 1983;6:41-7.
40. Corey L, Spear PG. Infections with herpes simplex viruses. *N Engl J Med* 1986;314:748-57.
41. Gibson JR, Kleber MR, Harvey SG. Prophylaxis against herpes labialis with acyclovir cream – a placebo-controlled study. *Dermatologica* 1986;172:104-7.