preceding three months. A preparation of 5% acyclovir in modified aqueous cream (containing 40% propylene glycol) or cream alone was applied twice daily to all areas where herpes lesions occurred. Patients received 16 weeks of each treatment consecutively in random order and they were assessed at monthly intervals for the frequency of herpes simplex lesions or erythema multiforme and for compliance.

Eighteen patients entered the trial but two failed to complete it. Five patients had had herpes simplex lesions alone and 11 had had lesions followed by erythema multiforme. Twelve of the patients had had herpes lesions in the orofacial area and four had had lesions in the genital area or buttocks. Subtyping of the herpes virus was not carried out. For the entire group of patients, the mean number of episodes of herpes virus infection and erythema multiforme occurring with each treatment were compared with Wilcoxon's signed rank test. The proportion of patients having episodes of herpes infection and erythema multiforme with each treatment were compared with Fisher's exact test. These tests were performed on patients receiving placebo first, on those receiving acyclovir first, and on all the patients combined.

There was no significant difference between the mean number of episodes or the proportion of patients having episodes of viral reactivation or of erythema multiforme during acyclovir or placebo treatment (table). The results were not influenced by the order in which acyclovir or placebo was

Comparison of number of herpes simplex virus lesions and episodes of erythema multiforme occurring during acyclovir and placebo treatment

	Placebo	Acyclovir
<i>All patients</i>		
Mean number of episodes*:		
herpes virus infection	3.3	3.7
erythema multiforme	1.2	1.1
Proportion of patients with episodes:		
herpes virus infection	10/16	14/16
erythema multiforme	5/11	8/11
<i>Placebo followed by acyclovir</i>		
Mean number of episodes:		
herpes virus infection	3.7	3.8
erythema multiforme	2.2	1.6
Proportion of patients with episodes:		
herpes virus infection	5/9	9/9
erythema multiforme	4/6	5/5
<i>Acyclovir followed by placebo</i>		
Mean number of episodes:		
herpes virus infection	2.7	3.6
erythema multiforme	0.3	0.5
Proportion of patients with episodes:		
herpes virus infection	5/7	5/7
erythema multiforme	1/6	3/6

*Mean number of episodes per patient in 16 weeks.

given. Episodes of reactivation of herpes virus did not correlate with recorded failure of compliance. No adverse reactions were recorded during the trial despite the application of the cream for 32 weeks, of which 16 were with acyclovir.

Comment

After the early apparent success of acyclovir in one patient the failure of this trial to show that topical prophylactic acyclovir can prevent attacks of herpes virus infection and erythema multiforme is disappointing. Topical treatment was chosen for this trial as we thought that it was likely to offer the safest form of continuous prophylaxis. In the early treatment of herpes labialis acyclovir cream was shown significantly to shorten the duration of lesions and, when the treatment was started before vesicles developed, to increase the number of lesions aborting.² In a study in initial and recurrent genital herpes acyclovir cream significantly shortened the healing of all lesions (Kinghorn GR, *et al*, unpublished observations). In studies of the use of 5% acyclovir ointment in primary genital herpes virus infection Corey *et al* showed that symptoms were less severe and virus shedding was curtailed but that the appearance of new lesions was not prevented and there was little effect on recurrent disease.³

The failure of topical acyclovir to prevent herpes simplex virus lesions suggests that concentrations of acyclovir were inadequate at the site of virus replication either because of inadequate penetration or because of insufficiently frequent application. At least one patient observed the development of "escape" lesions outside the treatment area. This was not specifically assessed during the trial and, as with compliance, their occurrence may have been more frequent. The development of mutants of herpes virus resistant to acyclovir is a further possibility which has not yet been tested.

The successful use of intravenous acyclovir in preventing herpes virus infections in immunocompromised patients⁴ would support the observation that maintenance of adequate tissue levels of the drug is

important. With this in mind we are investigating the use of oral acyclovir to achieve better suppression of the formation of lesions and, we hope as well, the more serious erythema multiforme.

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Effect of thalidomide on orogenital ulceration

Severe recurrent oral and genital ulceration may be difficult to treat, but a recent report suggested that thalidomide may be used in Behçet's syndrome.¹ We report the effect of thalidomide in three patients with severe orogenital ulceration.

Case reports

CASE 1

A 20 year old white woman had an eight year history of recurrent severe mouth and vulval ulcers, which failed to respond to multiple systemic and topical antibiotics and antifungal treatment. Trials of colchicine and cytotoxic drugs were unsuccessful, and only prednisolone in excess of 30 mg daily influenced the disease. Results of investigations were mostly normal except for an increased alkaline phosphatase activity of 332 IU/l (normal 46-190 IU/l). Anticomplementary activity was detected in the serum, suggesting the presence of circulating immune complexes, and the plasma complement degradation product (C₃d) concentration was raised.

She was admitted and, with full informed consent, given thalidomide 200 mg twice daily for five days followed by 100 mg twice daily. Three weeks after admission she was discharged taking thalidomide 200 mg each evening. Improvement continued over the next month: the mouth ulcers healed completely and only one small vulval ulcer remained. The alkaline phosphatase activity also returned to normal. Concern regarding the long term use of thalidomide led to its withdrawal and replacement with clofazimine 200 mg twice daily, though this had previously been ineffective. Over the following 10 weeks the vulval and oral ulcers returned. She was readmitted and given thalidomide 400 mg each evening. The ulcers healed over the next four days, and thalidomide was again withdrawn.

CASE 2

A 29 year old white woman had an eight year history of oral and vaginal ulcers, which were controlled only with high doses of prednisolone. Results of investigations were mostly normal except that the C₃d concentration was increased.

With full informed consent she was admitted and started on thalidomide 200 mg twice daily for five days; the prednisolone dosage was gradually reduced. Within a week ulcers that had been present for up to two months were healing, and she was discharged taking thalidomide 200 mg at night. A month later no ulcers remained and the dose was reduced to 100 mg daily. After a further two weeks she developed more ulcers, which rapidly cleared when the dose was increased to 150 mg daily. She remained free of ulcers for the first time in eight years, and over the next six weeks the dose was reduced to zero. The component degradation product concentration returned to normal. Her condition relapsed one week after thalidomide was stopped but responded to a further short course of treatment.

CASE 3

A 30 year old white man had a four month history of pain and swelling of the wrists, ankles, and knees associated with genital ulcers and sore eyes. A three year history of mouth ulcers, unresponsive to antibiotics and steroid mouth washes, was noted. Tests for syphilis, gonorrhoea, and chlamydial infection yielded negative results. After a 10 month trial of non-steroidal anti-inflammatory agents he was admitted. Results of investigations were normal except that the complement degradation product concentration was raised. With full informed consent he was started on thalidomide 200 mg twice daily for four days and then discharged taking 200 mg at night. The penile and scrotal ulcers healed completely and his oral ulcers improved, although the iritis and arthritis did not.

Comment

Mascaro *et al* reported improvement in six patients with severe recurrent aphthous ulcers when treated with thalidomide,² and recently Saylan and Saltik reported good results in 26 patients with Behçet's syndrome, although iritis and arthritis did not improve. We have confirmed these findings and also that ulcers recur when treatment is withdrawn, although they are not as severe or as frequent as before treatment.

It is important that the possible development of neuropathy and teratogenesis is not forgotten and that informed consent is obtained. With this caveat we believe that thalidomide is a valuable adjunct to the treatment of severe orogenital ulcers.

We thank Dr BR Allen, Dr D Bossingham, and Mr K Gibbin for allowing us to study patients under their care and Miss E Allen for her secretarial help.

¹ Saylan T, Saltik I. Thalidomide in the treatment of Behçet's syndrome. *Arch Dermatol* 1982;**118**:536.

² Mascaro JM, Lecha M, Torras H. Thalidomide in the treatment of recurrent necrotic and giant mucocutaneous apthae and aphthosis. *Arch Dermatol* 1979;**115**:636-7.

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Immediate heart rate response to lying down: simple test for cardiac parasympathetic damage in diabetics

Established simple tests of autonomic function based on cardiovascular reflexes include the heart rate responses to the Valsalva manoeuvre, standing up and deep breathing, and the blood pressure responses to standing and sustained handgrip.¹ We have looked at the possible clinical application of the heart rate response to lying down as a further simple test of cardiac parasympathetic damage. Normally when a subject lies down there is a small but consistent immediate rise in heart rate over three or four beats followed by a fall in heart rate to below the standing level over the next 25-30 beats. This rise is abolished by atropine,² thus showing that the early part of the response is mediated by the efferent cardiac vagal pathways.

Subjects, methods, and results

We studied nine younger normal subjects aged 22-32 (mean 26) years and 11 older normal subjects aged 39-65 (mean 50) years. Each of the younger subjects repeated the test five times to assess the reproducibility of the response. In addition, we measured the response in 58 diabetics with a wide range of ages and duration of diabetes: 23 aged 16-60 (mean 36) years with no abnormalities of cardiovascular reflexes (normal CVS); 15 aged 16-59 (mean 42) years with early parasympathetic abnormalities (early PS); 11 aged 19-79 (mean 55) years with definite parasympathetic damage (PS); and nine aged 26-71 (mean 50) years with parasympathetic and additional sympathetic dysfunction (PS+S).¹ We defined subjects with one abnormal heart rate response as early PS, and with abnormalities in at least two of the

Standing to lying heart rate ratios (S:L ratios) in 20 normal subjects and 58 diabetics with different degrees of autonomic damage (see text for definitions of groups).

three heart rate tests as PS. Subjects with additional blood pressure abnormalities were defined as PS+S.

Each subject was asked to stand quietly and then lie down without help while a continuous electrocardiogram was made from 20 beats before to 60 beats after lying down. A marker button was used to indicate the point at which the subject started to lie down. The individual R-R intervals were measured with a ruler from the electrocardiogram and the results expressed as a ratio of the longest R-R interval during the five beats before lying down to the shortest R-R interval during the 10 beats after lying down (standing to lying ratio; S:L ratio).

The figure plots the individual results from the different groups of subjects. There was no difference in mean values obtained from the younger (1.25 (SD 0.15)) and older (1.25 (0.09)) normal subjects. All but one of the diabetics with definite parasympathetic damage (mean 1.07 (SD 0.04)) and all those with additional sympathetic damage (mean 1.07 (0.04)) had ratios that were lower than any of the normal subjects. Of the 15 subjects with early parasympathetic damage, 11 also had abnormal S:L ratios. In addition, half of those with otherwise normal cardiovascular reflexes had ratios lower than the normal subjects. The S:L ratio correlated significantly with the 30:15 lying to standing heart rate ratio within the whole diabetic group ($r=0.40$; $p<0.01$). The test was found to be reproducible in 10 normal subjects, each of whom performed the test five times, coefficients of variation ranging from 3.2% to 10.0% (mean 5.5%).

Comment

We find that as a clinical test the heart rate response to lying down is easy to perform and is repeatable. Older subjects did not have any lower S:L ratios. In diabetics abnormalities were found as expected in those with other evidence of parasympathetic damage, but we also found abnormalities in some diabetics with apparently normal cardiovascular reflexes. This suggests that the standing to lying heart rate response may be a sensitive and useful test of early cardiac parasympathetic disease in diabetics and might be used in conjunction with currently established simple cardiovascular reflex tests.

¹ Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. *Br Med J* 1982;**285**:916-8.

² Bellavere F, Ewing DJ. Autonomic control of the immediate heart rate response to lying down. *Clin Sci* 1982;**62**:57-64.

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