TREATMENT OF FIRST-ATTACK GENITAL HERPES—ACYCLOVIR VERSUS INOSINE PRANOBEX

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Summary 77 patients with a first attack of genital herpes were entered into a double-blind trial to compare the efficacy of acyclovir with that of inosine pranobex. 24 patients received acyclovir alone, 25 inosine pranobex, and 28 both drugs. Patients treated with acyclovir or both drugs healed more quickly and had a shorter duration of viral shedding than those treated with inosine pranobex. The time to first recurrence and frequency of subsequent recurrences were similar in the three treatment groups. Acyclovir is the treatment of choice for patients with a first attack of genital herpes.

Introduction

FIRST-ATTACK genital herpes is a severe illness lasting two to three weeks, characterised by genital pain and dysuria and often accompanied by systemic symptoms including malaise, fever, and headaches.[1] Until lately little could be done to treat such patients, but two drugs, acyclovir and inosine pranobex, have now been reported to be effective in the management of primary genital herpes.

Acyclovir is a specific antiherpetic drug which acts by competing with viral thymidine kinase and also inhibits DNA polymerase.[2,3] In a series of clinical trials the oral preparation decreased the duration of viral shedding and symptoms and reduced the time to healing in patients with a first attack of genital herpes.[4-6] Unfortunately, the drug does not seem to prevent subsequent recurrences or reduce their frequency.

Inosine pranobex is an immunomodulator whose action depends upon stimulation of the body's own immune mechanism. It is not a specific antiviral agent, yet clinical studies have suggested that the drug might reduce the duration of viral shedding and the time to healing in patients with first-attack genital herpes.[7,8]

We report here a double-blind trial designed to compare the efficacy of these two drugs in patients with first-attack genital herpes.

Patients and Methods

Patient Selection

Patients with a first attack of genital herpes presenting within five days of onset to the departments of genitourinary medicine at the Middlesex Hospital, London, or the Royal Hallamshire Hospital, Sheffield, were offered the opportunity to participate in the study. Informed consent was obtained from all patients. Exclusion criteria (including: patients under 16 years; females not using adequate contraception; patients unable to attend at the required intervals; and those who had used any antiviral drugs in the preceding 2 weeks) were identical to those in previous studies.[9,10] Also excluded were patients with a history of gout, hyperuricaemia, or immunodepression. Since a high proportion of men attending the Middlesex Hospital clinic were homosexual, with a high attendant prevalence of HIV infection, all men from this centre were excluded.

Treatment

Patients were randomly allocated to three treatment groups: one group received active acyclovir and "dummy" inosine pranobex; one received active inosine pranobex and dummy acyclovir; and the third received both active acyclovir and active inosine pranobex. This last group was investigated to see if the two treatments complemented each other in any way.

The dosage of acyclovir was 200 mg four times daily and of inosine pranobex, 1 g four times daily. Treatment was for seven days.

Clinical Evaluation, Virology, and Safety Tests

Patients were assessed at entry and three times a week until complete healing occurred. Thereafter, patients reattended (or were contacted by telephone) monthly for the next six months and during the first recurrence. At each visit the clinical status of patients was recorded on a standardised schedule.

TABLE I—DEMOGRAPHIC CHARACTERISTICS OF 77 PATIENTS WITH FIRST-ATTACK GENITAL HERPES TREATED WITH ACYCLOVIR, INOSINE PRANOBEX, OR BOTH

—	Acyclovir (n=24)	Inosine pranobex (n=28)	Both (n=25)
Age (yr)*	25·5 (7·02)	23·3 (4·9)	24·3 (7·9)
Duration of symptoms at entry (days)*	4·3 (1·4)	3·9 (1·3)	4·6 (3·3)
Duration of signs at entry (days)*	3 4 (1·8)	3·2 (1·5)	2·9 (1·3)
Women/men	21/3	24/4	21/4
London/Sheffield	11/13	12/16	13/12
External lesions	24 *(100%)*	28 *(100%)*	25 *(100%)*
Internal lesions	15 *(62·5%)*	14 *(50%)*	11 *(44%)*
Type I	9 *(37%)*	13 *(46%)*	12 *(48%)*
Type II	11 *(46%)*	12 *(43%)*	10 *(40%)*
Not typed	4 *(17%)*	3 *(11%)*	3 *(12%)*
Primary/initial	13 *(54%)*	18 *(67%)*	16 *(24%)*

*Mean (SD).

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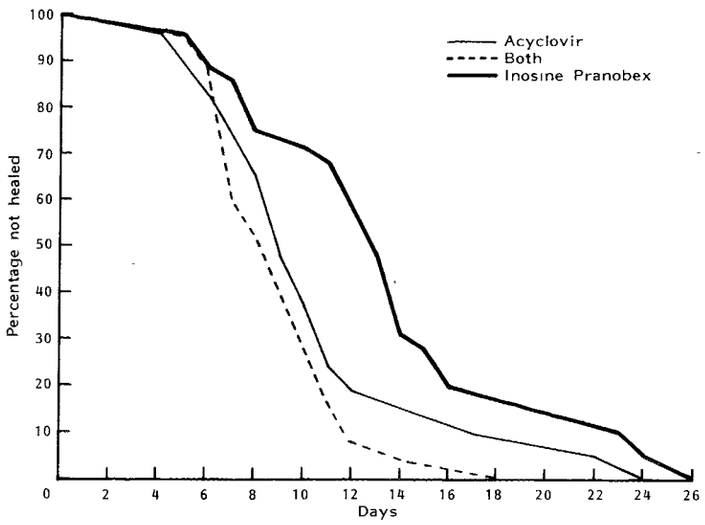

Fig 1—Time to healing for all lesions in the three treatment groups.

If lesions were present swabs were taken for viral culture and handled as described before.[9,10] In London, isolates were typed by an immunofluorescence test with monoclonal antibodies,[11] whereas those from Sheffield were typed by a modified ELISA technique.[12] Acute and convalescent sera were tested for herpes antibodies. Patients with a titre of ≤ 1 in 2 in the acute serum were classed as having primary infection.

At entry to the trial blood was taken for a full blood count, measurement of uric acid, and renal-function and liver-function tests. These were repeated on day 8.

Statistical Analysis

The demographic characteristics and the frequency of recurrences were compared by either the chi-square test or the Mann Whitney U test. Differences between groups in healing time, duration of viral shedding, duration of symptoms, and time to the first recurrence were compared by a log rank test.

Results

Patient Demography

88 patients were recruited (39 in London and 49 in Sheffield). 11 were subsequently excluded—8 who were lost to follow-up after the initial visit, 1 who lost her tablets, 1 who proved to have varicella zoster and not herpes simplex virus, and 1 who was virus-negative with no antibody response. Thus the data from 77 patients were analysed: 24 received acyclovir alone, 25 inosine pranobex alone, and 28 both drugs.

At entry, age, proportion of men and women, viral type, antibody status, or duration of signs and symptoms did not differ between the three treatment groups (table I) or between the two centres. No side-effects were noted.

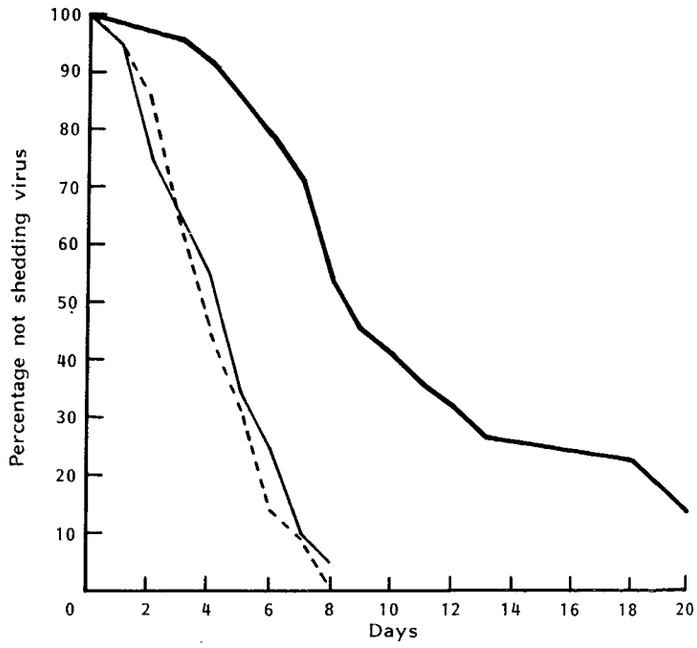

Fig 2—Duration of viral shedding (first day of negative culture) in the three treatment groups.

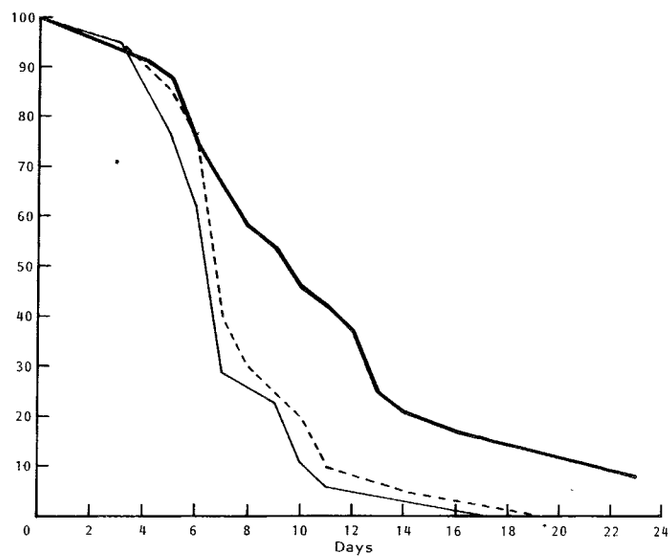

Fig 3—Duration of symptoms in women in the three treatment groups.

Healing Time

The median time to healing in the acyclovir group and the group receiving acyclovir and inosine pranobex was shorter than in the inosine-pranobex group (acyclovir *vs* inosine pranobex $p < 0.05$; both *vs* inosine pranobex $p < 0.001$). By the 11th day 40 (82%) of 49 patients treated with acyclovir

TABLE II—HEALING TIME AND DURATION OF VIRAL SHEDDING AND SYMPTOMS IN THE THREE TREATMENT GROUPS*

—	Acyclovir (n = 24)	Insosine pranobex (n = 28)	Both (n = 25)	Acyclovir *vs* inosine pranobex (p)	Acyclovir *vs* both (p)	Inosine pranobex *vs* both (p)
All Patients						
Healing	9 (4–24)	13 (1–26)	9 (5–18)	<0·05	NS	<0·001
Viral shedding	5 (1–8)	8 (3–20)	4 (1–8)	<0·0005	NS	<0·0005
Dysuria	6 (3–18)	7 (1–21)	7 (1–21)	NS	NS	NS
All symptoms	7 (3–19)	8 (4–23)	7 (3–19)	0 05 >p<0·1	NS	0·05 >p<0·1
Women						
Healing	9·5 (4–24)	13 (1–26)	9 (5–18)	0·05 >p<0·1	NS	<0·005
Viral shedding	5 (1–8)	8 (3–20)	4 (1–8)	<0·005	NS	<0·005
Dysuria	5·5 (3–11)	7·5 (1·21)	6 (3–19)	<0·02	NS	NS
All symptoms	7 (3–19)	9·5 (4–23)	7 (3–19)	<0·05	NS	0·05 >p<0·1

*Median (range). NS, not significant (p > 0·05).

TABLE III—FREQUENCY OF RECURRENCES (PER 28 DAYS OF FOLLOW-UP) IN THE THREE TREATMENT GROUPS BY VIRAL TYPE*

Viral type	Treatment group			
	Acyclovir	Inosine pranobex	Both	All patients
HSV type–I	0·11 (0·13)	0·14 (0·22)	0·21 (0·24)	0·16 (0·2)
HSV type–II	0·49 (0·32)	0·38 (0·51)	0·48 (0·32)	0·45 (0·39)
P value	0·004	0·138	0·044	<0·0005

*Mean (SD).

or both drugs were healed whereas only 8 (32%) of those who received inosine pranobex alone were healed (fig 1).

Duration of Viral Shedding

The duration of virus shedding was longer in patients treated with inosine pranobex than in those in the other two treatment groups ($p < 0·0001$ for both) (fig 2). All patients treated with acyclovir and both drugs were culture-negative by the 8th day whereas 11 (45%) of those treated with inosine pranobex were still shedding virus. 5 (20%) of those treated with inosine pranobex were still culture-positive on the 18th day after entry.

Symptoms

The duration of symptoms did not differ in the three treatment groups. However, a subgroup analysis in the women (who tend to have the most severe symptoms) showed that the duration of dysuria and all symptoms was shorter in those treated with acyclovir than in those treated with inosine pranobex ($p < 0·02$ for dysuria, $p < 0·05$ for all symptoms; fig 3).

Table II summarises the differences in healing time and duration of viral excretion and symptoms in the three treatment groups.

Recurrences

The median time to first recurrence (acyclovir 187·4 days, inosine pranobex 142·5 days, both 132·7 days) and the frequency of recurrences were similar in the three treatment groups (table III). Herpes simplex virus (HSV) type-II infections recurred earlier (median 64 days) than did HSV type-I (median 238·2 days; $p = 0·0015$); HSV type-II infections also recurred more frequently than HSV type-I infections. The differences were irrespective of treatment given (table III).

Discussion

The efficacy of acyclovir in the treatment of first-attack genital herpes has been confirmed in numerous randomised double-blind placebo-controlled trials.[4-6,9,10,13-16] The use of inosine pranobex, on the other hand, has been surrounded by controversy.[17,18] Although several trials have been reported in patients with mucocutaneous herpes,[7,8,19-24] a recent review commented that the "results are difficult to assess because most of the trials are poorly designed or reported".[25] The only randomised double-blind placebo-controlled trial looking exclusively at patients with first-attack genital herpes has not been reported in full.[7] A brief abstract of this trial suggested that inosine pranobex may be beneficial in patients with "primary infections". However, our investigation showed no such benefit. The remainder of the reports were of patients with recurrent genital herpes, labial herpes, or combinations of both.[8,9,19-24]

We believe that our investigation ends the controversy about the use of inosine pranobex in patients with first-attack gential herpes, and we suggest that the drug no longer has a place in its treatment. Indeed its only remaining justified use is in the context of a controlled trial comparing its "suppressive efficacy" with that of acyclovir.[25] Such trials are in progress.

The observation that neither drug had any impact on the time to first recurrence, or the frequency of recurrences, is of particular interest. It is widely reported that acyclovir when used to treat first-attack gential herpes does not reduce the frequency of subsequent recurrences, probably because the virus has already established latency by the time therapy is initiated. Inosine pranobex on the other hand is said to have both antiviral and immunopotentiating properties. Despite these properties the drug has no apparent effect on the establishment of latency or subsequent reactivation, which suggests that in the context of genital herpes the immunostimulating properties of the drug are unimportant.

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