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Acyclovir given as prophylaxis against oral ulcers in acute myeloid leukaemia: randomised, double blind, placebo controlled trial

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Abstract

Objectives—To evaluate (a) the prophylactic effect of the antiherpetic drug acyclovir on oral ulcers in patients with acute myeloid leukaemia receiving remission induction chemotherapy and thus (b), indirectly, the role of herpes simplex virus in the aetiology of these ulcers.

Design—Randomised, double blind, placebo controlled trial.

Subjects—74 herpes simplex virus seropositive patients aged 18-84. Thirty seven patients received acyclovir (800 mg by mouth daily) and 37 placebo. The patients were examined daily for 28 days.

Main outcome measures—Occurrence of herpes labialis, intraoral ulcers, and acute necrotising ulcerative gingivitis.

Results—The two populations were comparable in age, sex, type of antineoplastic treatment, and history of herpes labialis. Acute oral infections occurred in 25 of the acyclovir treated patients and 36 of the placebo treated patients (relative risk 0.69 (95% confidence interval 0.55 to 0.87)). This difference was due to a reduction in the incidence of herpes labialis (one case versus eight cases; relative risk 0.13 (0.02 to 0.95)), intraoral ulcers excluding the soft palate (one case versus 13 cases; relative risk 0.08 (0.01 to 0.56)), and acute necrotising ulcerative gingivitis (one case versus eight cases; relative risk 0.13 (0.02 to 0.95)). However, ulcers on the soft palate were diagnosed with similar frequency in the two groups. Isolation of herpes simplex virus type 1 in saliva was reduced from 15 cases in the placebo group to one case in the acyclovir group (relative risk 0.07 (0.01 to 0.48)).

Conclusion—Intraoral ulcers excluding the soft palate are most often due to infection with herpes simplex virus, whereas ulcers on the soft palate have a non-herpetic aetiology. The findings suggest that acute necrotising ulcerative gingivitis may also be

due to herpes simplex virus. Prophylaxis with acyclovir should be considered for patients with acute myeloid leukaemia during remission induction therapy.

Introduction

Acute myeloid leukaemia has remained a serious disease with a three year survival of only 15-20% after chemotherapy.¹ Further intensification of treatment is limited by chemotherapy induced side effects, in particular increased susceptibility to infection. Consequently, improvement in our ability to diagnose, treat, or prevent these complications is essential to allow further intensification of chemotherapy and thus achieve a reduction in the morbidity and mortality among these patients. Acute oral infections are frequent and clinically important in these patients. During feverish episodes they occur with an incidence of 75%, similar to the overall incidence of non-oral infections.² In particular, oral infections are the possible origin of septicaemia in about one third of cases.³ Acute oral infections often present as oral ulcers.⁴ These can be divided into herpes labialis, intraoral ulcers outside the gingival margin, and acute necrotising ulcerative gingivitis.

Herpes labialis is found in about 15% of an unselected group of patients with haematological disorders undergoing one chemotherapeutic treatment cycle.⁴ This is similar to the prevalence in the background population.⁵ Typically, the clinical picture of herpes labialis is comparable to that seen in healthy people, and overall the condition represents neither a diagnostic nor an aetiological problem in patients with haematological disorders. In contrast, intraoral ulcers outside the gingival margin occur in only 3% of healthy people,⁵ whereas the incidence is as high as 30% in haematological patients during a chemotherapeutic treatment cycle.⁴ The aetiology of intraoral ulcers is

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unknown, but we have recently shown a strong association between these ulcers and the occurrence of herpes simplex virus type 1 in saliva and have hypothesised that intraoral ulcers outside the gingival margin may have a different aetiology depending on the intraoral location.⁶ Acute necrotising ulcerative gingivitis is the most severe type (ulcerative) of acute gingivitis. Usually it is seen only in immunocompromised states, and its aetiology has been attributed mainly to spirochaetes, *Bacteroides intermedius*, and fusobacteria.⁷

The aim of this study was to investigate the preventive effect of the antiherpetic drug acyclovir on oral ulcers and thus, indirectly, assess the aetiological role of herpes simplex virus in these ulcers.

Patients and methods

Between November 1989 and April 1993 adult patients admitted to our haematological ward were included in a double blind, randomised, placebo controlled trial. The inclusion criteria were (a) newly diagnosed acute myeloid leukaemia, (b) a positive herpes simplex virus antibody test result before treatment, (c) no oral ulcers, and (d) no treatment with acyclovir within the previous seven days. The day when antineoplastic drugs were initiated was defined as day 1 and the patients were examined daily for 28 days. Patients not eligible for the 28 days were subsequently excluded.

Patients were randomised by a computer generated table of random numbers so that equal numbers of patients would receive identical looking tablets of acyclovir or placebo. Acyclovir (400 mg) or the placebo were given twice daily throughout the study period. In order to obtain optimal compliance all tablets were given by nurses. Prophylaxis began on day 1 and continued for 28 days. Patients were examined daily by the same investigator. The blinded treatment was interrupted in the case of herpes labialis or the occurrence of an intraoral ulcer plus isolation of herpes simplex virus and the patient transferred to an open

treatment schedule of acyclovir (1000 mg by mouth daily) for seven days. Informed consent was obtained from the patients and the protocol approved by the local ethics committee.

Diagnostic criteria—Herpes labialis was defined as clusters of vesicles or crusts, or both, adjacent to the vermilion border of the lip and either a history of recurrence or a culture positive for herpes simplex virus type 1. An intraoral ulcer was defined as a mucosal lesion with complete loss of the epithelial layer located outside the gingival margin. Localisation was recorded by using the topographical division of the oral mucosa described by Roed-Petersen and Renstrup.⁸ Acute necrotising ulcerative gingivitis was diagnosed according to the criteria of Pindborg.⁹ Other acute oral infections were diagnosed according to established criteria.⁴

Viral studies—Samples for viral culture were obtained from all patients by having them gargle with 5 ml of tissue culture medium (Eagle's minimum essential medium with 2% fetal calf serum). Sampling was performed on day 1 and thereafter twice a week until day 28. Before inclusion in the study serum samples were examined for herpes simplex virus antibodies by means of an enzyme linked immunosorbent assay (ELISA). The virus isolation procedure was initiated within two hours of sampling and performed essentially as described on monolayers of human embryonic lung fibroblasts grown in 25 cm² tissue culture flasks.⁶ Individual virus isolates were identified as herpes simplex virus and distinguished as type 1 or 2 on the basis of the characteristic appearance of the cytopathic effect. The isolates were confirmed by a type specific ELISA purchased from DAKO (Denmark).

Statistical methods—Non-parametric tests (Fisher's exact test and the Mann-Whitney test)¹⁰ were used and P values less than 0.05 (two tailed) taken as significant. The sizes of effects were reported as relative risks and 95% confidence intervals.¹¹ It was estimated that 45 patients per group would be necessary to detect a minimal difference of 50% in the rate of ulcers between the two groups (two tailed test, risk of type I error 5%, risk of type II error 5%, oral ulcer rate 40-50%, mortality during study around 10%).¹⁰

Results

Ninety patients were randomised (45 in each group) who met the initial eligibility criteria. Sixteen patients were excluded during the study because they died before completing the full 28 days without having developed an episode of herpes labialis or becoming culture positive for herpes simplex virus. These patients were equally divided between the groups (eight in the acyclovir group, eight in the placebo group). No patients dropped out or were excluded for any other reason. Therefore 74 patients were available for analysis of efficacy.

Table I lists the demographic characteristics of the two study groups. There were no differences in age, sex, underlying subtype of acute myeloid leukaemia, type of antineoplastic treatment, or history of herpes labialis. No adverse effects attributable to acyclovir were observed.

CLINICAL OUTCOME

One or more acute oral infections occurred in 36 of the 37 recipients of placebo as compared with 25 of the 37 recipients of acyclovir (relative risk 0.69; P=0.001) (table II). The difference was due to the smaller occurrence of oral ulcers (intraoral ulcers outside the gingival margin, herpes labialis, acute necrotising ulcerative gingivitis; nine cases in the acyclovir group versus 22 in the placebo group (relative risk 0.41;

TABLE I—Demographic characteristics of active treatment and placebo groups

	Acyclovir group (n=37)	Placebo groups (n=37)
Median age (range) (years)	60.8 (18-84)	59.6 (18-78)
Sex distribution:		
Male	21	20
Female	16	17
Underlying disease (FAB classification):		
Acute myeloid leukaemia, M4 or M5	11	12
Acute myeloid leukaemia, others	26	25
Antineoplastic remission induction treatment:		
Aclarubicin/cytarabioside	35	36
Other regimens	2	1
History of herpes labialis:		
Yes	15	19
No	22	18

TABLE II—Occurrence of oral infections and herpes simplex virus type 1 isolation rates in active treatment and placebo groups

	Acyclovir group (n=37)	Placebo group (n=37)	P value	Relative risk (95% confidence interval)
Acute oral infection (all causes)	25 (68)	36 (97)	0.001	0.69 (0.55 to 0.87)
Acute oral candidosis	22 (59)	26 (70)	0.47	0.85 (0.60 to 1.19)
Oral ulcer (all causes)†	9 (24)	22 (59)	0.004	0.41 (0.22 to 0.77)
Intraoral ulcer outside gingival margin:				
Excluding soft palate	1 (3)	13 (35)	0.0006	0.08 (0.01 to 0.56)
Soft palate	6 (16)	2 (5)	0.26	3.00 (0.65 to 13.91)
Acute necrotising ulcerative gingivitis	1 (3)	8 (22)	0.03	0.13 (0.02 to 0.95)
Herpes labialis	1 (3)	8 (22)	0.03	0.13 (0.02 to 0.95)
Herpes simplex virus type 1 isolation rate	1 (3)	15 (41)	0.0001	0.07 (0.01 to 0.48)

†Including herpes labialis, intraoral ulcers outside gingival margin, and acute necrotising ulcerative gingivitis.

TABLE III—Oral ulcers from both groups: location, time of occurrence, and relation to herpes simplex virus excretion

Location	Total No†	No with herpes simplex virus type 1‡	Day in treatment	
			Median	Range
Intraoral ulcer outside gingival margin:				
Soft palate	8	0	7	4-18
Hard palate	5	3	11	4-18
Alveolar process	3	3	10.5	3-14
Tongue	3	2	6	6-18
Cheek/lip	3	1	6	4-23
Acute necrotising ulcerative gingivitis	9	4	11	3-28
Herpes labialis	9	8	13	3-28

†Some patients had ulcers at more than one location.

‡All isolations except one from patient with herpes labialis were from placebo group.

$P=0.004$)), whereas the occurrence of acute oral candidosis was similar in the two groups (table II).

Within the group of intraoral ulcers, those on the soft palate occurred with a similar incidence in the two groups (table II), whereas the occurrence of intraoral ulcers not located on the soft palate was significantly less in the acyclovir group (one case versus 13 cases; relative risk 0.08 ($P=0.0006$)). Herpes labialis and acute necrotising ulcerative gingivitis were also less frequent in the acyclovir group (one case versus eight cases; relative risk 0.13 ($P=0.03$ for both conditions)).

Ulcers on the soft palate in all cases emerged in a pre-existing erythema, and erythema on the soft palate was diagnosed with similar frequency in the two groups (12 cases in the acyclovir group, nine in the placebo group; $P=0.62$). Erythema on the soft palate emerged earlier than ulcers located elsewhere in the oral cavity (median day 4 versus median day 10; $P=0.045$).

Herpes labialis occurred without concomitant intraoral ulcers or acute necrotising ulcerative gingivitis in one acyclovir recipient and three out of eight placebo recipients. Intraoral ulcers outside the gingival margin were diagnosed without herpes labialis or acute necrotising ulcerative gingivitis in nine of 15 patients in the placebo group and six of seven patients in the acyclovir group. Acute necrotising ulcerative gingivitis was found without coincident herpes labialis or intraoral ulcers in three of nine patients, all of whom were from the placebo group.

VIROLOGICAL OUTCOME

Herpes simplex virus type 1 was isolated from 15 placebo recipients but from only one acyclovir recipient (relative risk 0.07; $P=0.0001$). Isolation of herpes simplex virus type 1 without a concomitantly demonstrable ulcer occurred in only one patient. As to the location of the ulcers (table III), herpes simplex virus type 1 was not found in relation to ulcers on the soft palate. A strong association between location and isolation of herpes simplex virus type 1 was found in herpes labialis, acute necrotising ulcerative gingivitis, and intraoral ulcers on the alveolar process, hard palate, and tongue.

Discussion

It has been established that prophylactic use of acyclovir in patients with acute leukaemia undergoing either remission induction therapy¹²⁻¹⁴ or bone marrow transplantation^{12 15-18} can reduce or prevent herpes labialis and herpes simplex virus culture positive intraoral ulcers. This study confirms that herpes labialis and excretion of herpes simplex virus type 1 in saliva can be prevented by oral acyclovir in patients with acute myeloid leukaemia during remission induction therapy.

Our study differs from other studies by examining the preventive effect of acyclovir on oral ulcers, irrespective of herpes simplex virus culture. By contrast, other workers have evaluated the effect of

acyclovir only on herpes simplex virus type 1 culture positive ulcers.¹²⁻¹⁸ This distinction is important in two ways. Firstly, only about two thirds of all intraoral ulcers are herpes simplex virus culture positive⁶ and, secondly, cultivation of herpes simplex virus type 1 from the surface of an ulcer does not prove a viral aetiology of the ulcer. Cultures from the surface of an ulcer might represent contaminating virus from an inapparent virus excretion in the oral cavity or throat without any aetiological association with the ulcer. A preventive effect of acyclovir, on the other hand, represents indirect proof of a herpetic aetiology.

In our placebo group one or more acute oral infections occurred in 36 of the 37 patients. This incidence is higher than in an unselected group of patients with haematological conditions but similar to what we found previously in patients with acute myeloid leukaemia.¹⁹ Our study shows that the daily use of 800 mg acyclovir by mouth reduces the rate of oral infections. The effect of acyclovir, however, was due entirely to an effect on herpes labialis and oral ulcers in all regions but the soft palate. Consequently, at least a majority of these ulcers are caused by herpes simplex virus type 1, and the study confirms our earlier findings of a strong association between intraoral ulcers at certain locations and the presence of herpes simplex virus type 1 in saliva.⁶

DIFFERENT AETIOLOGY

As to the palate, these ulcers—in contrast with other intraoral ulcers outside the gingival margin—all emerged secondary to erythema. The findings of a similar incidence of erythema in the two patient groups and the fact that palatal erythema occurred earlier in the induction treatment than ulcers in other regions and that herpes simplex virus type 1 was never isolated in patients with these ulcers all suggest a different aetiology and pathogenesis of ulcers on the soft palate. We have previously suggested that such lesions might have a non-virological aetiology, being secondary to a xerostomia induced increase in the salivary concentration of oral bacteria and fungi.¹⁹

Some ulcer types were found concomitantly. This might reflect either a different aetiology or a multifocal nature of the ulcers. As an example, acute necrotising ulcerative gingivitis occurred without other concomitant ulcer types in only one third of the patients. However, acute necrotising ulcerative gingivitis was significantly more frequent in our placebo group. This indicates that it may be caused by herpes simplex virus type 1, a finding that has not, to our knowledge, been reported before. However, a possible viral aetiology of acute necrotising ulcerative gingivitis accords with our finding of the alveolar process as a major region for intraoral herpes infection. A viral aetiology of acute necrotising ulcerative gingivitis might also explain why the incidence of this condition was not influenced by mechanical plaque removal or chemical plaque control, or both, in patients with acute myeloid leukaemia.²⁰

As to other possible benefits of preventing infections with herpes simplex virus, Hann *et al* reported a reduction in the number of days with fever in a group of patients having bone marrow transplantation,¹² and Lönnqvist *et al* found a reduction in the number of bacteraemias in patients receiving chemotherapy.¹⁴ On the other hand, Wade *et al* failed to find any influence of acyclovir prophylaxis on the onset and duration of fever.¹⁷

We conclude on the basis of the effect of the acyclovir prophylaxis that oral ulcers have different aetiologies according to their location and that the prophylactic use of oral acyclovir 800 mg daily reduces the incidence of acute oral infections in all regions except the soft palate. This indicates that a substantial

Key messages

- This study examined the putative herpetic aetiology of oral ulcers indirectly by recording the possible preventive effect of the antiherpetic drug acyclovir
- Oral ulcers were found in more than half of patients with acute myeloid leukaemia during remission induction therapy
- The incidence of herpes labialis, intraoral ulcers outside the soft palate, and acute necrotising ulcerative gingivitis was greatly reduced by prophylaxis with oral acyclovir (800 mg by mouth daily) during remission induction therapy
- Intraoral ulcers on the soft palate were not associated with herpes virus infection

proportion of these ulcers in herpes simplex virus seropositive patients have a herpetic aetiology. Acyclovir prophylaxis must therefore be considered for all herpes simplex virus seropositive patients with acute myeloid leukaemia during remission induction therapy. A possible role of primary herpetic oral infections in the aetiology of oral ulcers in these patients could not be evaluated in this study because herpes simplex virus seropositivity was among the inclusion criteria. Further studies are needed to investigate whether the reduction in the rate of intraoral ulcers also results in lower rates of fever and systemic infection in these patients and to evaluate whether the use of saliva substitutes might decrease the occurrence of ulcers on the soft palate.

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Jaundice in babies: implications for community screening for biliary atresia

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Although prompt referral of babies with biliary atresia ensures early surgery and improves outcome,¹ late referral persists in the United Kingdom, leading to calls for systematic screening of babies with neonatal jaundice persisting beyond 14 days.² This would entail reviewing the baby, establishing whether the stool is pigmented, testing urine for bilirubin, and measuring blood concentrations of conjugated and unconjugated bilirubin.^{2,3} To evaluate the feasibility of systematic screening, we ascertained the prevalence of (a) jaundice in babies aged 2, 4, and 6 weeks, and (b) dark urine or pale stools as reported by the parents or a health visitor. We also established how often stools or urine of jaundiced babies were noted by health visitors at their first visit to gauge the effect on workload.

Subjects, methods, and results

In Solihull Health District health visitors examine all babies between 12 and 14 days of age. We recorded jaundice at this primary visit for convenience of clinical practice. Over six months the health visitors noted

name, date of birth, date of examination, method of feeding, and presence of clinical jaundice (defined as yellow skin pigmentation). If jaundice was present they noted the colour of the eyes, stools, and urine and whether the colour of stools and urine was based on their observation or a parental report. Further reports were submitted at 4 and 6 weeks if the babies were still jaundiced. The study excluded babies still in hospital but included those who had moved into the district in

Detection of jaundice by health visitors at primary visit and when babies were aged 4 and 6 weeks. Values are numbers of babies unless stated otherwise

	Primary visit (12-14 days)	4 Weeks	6 Weeks
Proportion (%) of babies with reports	985/1170 (84)	140/175 (80)	22/31 (71)
No of babies with clinical jaundice	175	31	7
Prevalence of jaundice per 100 live births (%)	15	2.6	0.6
<i>Factors associated with clinical jaundice</i>			
Colour of sclera:			
Yellow	78	—	—
White	79		
Not recorded	18		
Feeding pattern:			
Breast	101	27	6
Bottle	62	4	1
Mixed	7		
Not known	5		
Sex:			
Male	112	23	7
Female	63	8	
Proportion male	0.64	0.74	1
(95% confidence interval)	(0.57 to 0.71)	(0.58 to 0.89)	