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Treatment of Primary Acute Genital Herpes in Guinea Pigs by Intraperitoneal Administration of Fluoropyrimidines†

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FIAC [1-(2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-iodocytosine], FIAU [1-(2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-iodouracil], and FMAU [1-(2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-methyluracil] were evaluated for their efficacies in the treatment of genital infections with herpes simplex virus type 2 in guinea pigs. Intraperitoneal administration of these drugs in daily doses of 100 mg/kg of body weight initiated 24 h after virus inoculation and repeated 2 successive days thereafter inhibited development of genital lesions and reduced shedding of virus without evoking untoward reactions. In a comparative study with this 3-day dosage schedule, the efficacy of daily doses of 50 mg of FMAU per kg was greater than that of the same doses of FIAC and FIAU, in that order; all these were more effective than daily doses of 50, 100, or 200 mg of acyclovir or of 500 mg of phosphonoformic acid per kg. These differences in efficacy were enhanced when treatment was delayed for 2 to 3 days after inoculation.

FIAC [1-(2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-iodocytosine], FIAU [1-(2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-iodouracil], and FMAU [1-(2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-methyluracil] inhibit herpes simplex type 1 (HSV-1) and HSV-2 replication in cell culture (20; J. J. Fox, 185th Am. Chem. Soc. Natl. Meet., Seattle, Wash., 1983). FIAC and FMAU are equally active against HSV-1 and HSV-2 strains and have about the same potency as acyclovir (ACV) when assayed in rabbit kidney cells (2, 17). FIAU and FMAU are more active than ACV in the treatment of HSV encephalitis in mice (13). Topical application of FIAC and FMAU is also effective in the treatment of ocular infections in rabbits (17, 18).

Previous studies have shown that guinea pigs inoculated intravaginally with HSV-2 develop lesions of the external genitalia which follow a clinical course similar to that of herpes infections in human females; furthermore, this experimental infection may be used to evaluate the efficacy of various antiviral agents (8, 14, 16). Effective ACV and phosphonoformic acid (PFA) treatment of genital herpes in guinea pigs is well documented (1, 4, 6, 10). This model has also been used to show the potential of prophylactic therapy with a lipid amine (22), minimal effect of treatment with adenine arabinoside and several of its analogs (12), and failure of treatment with 2-deoxy-D-glucose (5, 15). This paper describes the effectiveness of treatment of genital HSV-2 infection with FIAC, FIAU, and FMAU after intraperitoneal administration and compares their activities with those of ACV and PFA.

MATERIALS AND METHODS

Virus. The HSV-2 strain (1868) used was originally isolated from a patient with a penile lesion. It was identified as HSV-2 by its ability to replicate equally well in chicken embryo and guinea pig embryo cells (11), by its insensitivity to inhibition by bromovinyldeoxyuridine (9), by its inability to induce an HSV-1-specific enzyme (21), and by neutralization with HSV-2-specific antisera.

Cell culture and virus assay. Primary guinea pig embryo cells were prepared from 30- to 40-day-old Hartley guinea pig embryos (Camm Research Institute, Wayne, N.J.) as described previously (11). Cells were grown in Eagle minimal essential medium containing Hank balanced salt solution and 10% heat-inactivated newborn donor calf serum. Confluent monolayers were maintained with minimal essential medium containing Earle balanced salt solution and 2% newborn donor calf serum.

Infectivity titers were determined by plaque formation in guinea pig embryo cells in multiwell panels. Three wells were used per dilution. After adsorption of virus for 1 h, monolayers were overlaid with 0.5% methylcellulose in minimal essential medium. After 4 days of incubation at 36°C in a 5% CO_2 incubator, the monolayers were stained, plaques were enumerated, and virus titers were calculated.

Inoculation of guinea pigs. Young, adult female Hartley guinea pigs (Camm Research Institute, Wayne, N.J.) weighing ca. 250 g each were anesthetized with sodium pentobarbital and inoculated intravaginally with $10^{4.5}$ to $10^{5.0}$ PFU of HSV-2. In each separate experiment, six animals in each drug group and in the control group were inoculated. The virus inoculum (0.1 ml) was delivered into the vagina with a tuberculin syringe without a needle. The vagina was then plugged with soluble Gelfoam (The UpJohn Co., Kalamazoo, Mich.) surgical pads. The animals were examined for clinical manifestations of genital infection, and the severity of clinical illness was scored as follows: 0, no sign or symptoms of illness; 1, vaginal erythema; 1 or 2 lesions; 2, 3 to 10 lesions; 3, 11 to 20 lesions; 4, 21 lesions through confluent; 5, loss of bladder control or paralysis; −1, beginning of healing (drying and crusting of lesions). This scoring system has been used in previous reports by our laboratory (6, 10, 22) and is comparable to those used in other studies (8, 14).

Drug administration. All of the compounds were provided through the Antiviral Substances Program of the National Institute of Allergy and Infectious Diseases, Bethesda, Md. FIAC, FIAU, and FMAU (Bristol-Myers, New York, N.Y.)

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TABLE 1. Treatment of genital herpes in guinea pigs with FIAC, FIAU, and FMAU (100 mg/kg per day for 3 days) intraperitoneally beginning 24 h after virus inoculation

Therapeutic agent	No. of animals with lesions/ no. inoculated	Mean lesion scores (± SD)[a] on day:				Mean reciprocal virus infectivity titer (± SD)[b] on day:			
		3	4	7	10	1[c]	3	4	7
None (control)	10/12	1.0 (1.0)	3.3 (2.2)	4.2 (1.9)	3.5 (1.7)	2.6 (1.0)	2.6 (0.9)	2.4 (0.7)	Neg[d]
FIAC	9/11	0	0.6 (0.8)	0.9 (0.7)	0.3 (0.4)	3.3 (0.3)	2.1 (0.7)	1.3 (0.9)	Neg
FIAU	11/12	0.3 (0.5)	0.9 (1.0)	1.3 (0.9)	1.0 (0.9)	3.0 (1.0)	2.5 (0.8)	1.6 (0.8)	Neg
FMAU	6/12	0	0.3 (0.6)	0.3 (0.6)	0.3 (0.5)	3.5 (0.3)	1.3 (0.2)	Neg	Neg

[a] $P < 0.01$ on each day examined.
[b] Log_{10} PFU per 0.1 ml of vaginal swab suspension.
[c] Vaginal swabs were taken before drug treatment.
[d] Neg, No virus detected.

were dissolved in diluent consisting of 20% propylene glycol, 20% ethanol, and 60% water. ACV sodium (Burroughs Wellcome Co., Research Triangle Park, N.C.) was reconstituted with water, and PFA (Astra Laboratories, Sweden) was dissolved in water to yield a 2.5% solution and diluted in saline. As stated below, appropriate concentrations of each drug were given intraperitoneally, one at 8:00 a.m. and one at 4:00 p.m. every day for 3 consecutive days, beginning 24 to 72 hr after virus inoculation. Controls received diluent containing propylene glycol, ethanol, and water or saline alone. Levels of Na^+, K^+, lactate dehydrogenase, glucose, glutamic oxalacetic transaminase, and glutamic pyruvic transaminase in serum of animals were determined by the hospital chemistry laboratory.

Virus isolation from vaginal swabs. The vagina of each guinea pig was swabbed with premoistened, cotton-tipped, sterile swabs which were then placed in 1 ml of medium containing 10% newborn donor calf serum and 10% dimethyl sulfoxide. All specimens were frozen at −70°C so that serial samples could be assayed at the same time in the same lot of cell cultures. Animals were swabbed on days 3 through 10 after virus inoculation. Swabs for virus infectivity titers were collected only on animals in the first group of experiments (Table 1).

Statistics. Statistical analyses were performed by the Student *t* test. All results were pooled from at least two experiments.

RESULTS

Determination of the 50% effective doses of FIAC, FIAU, and FMAU on HSV replication. Since HSV-2 strain 1868 was used in the animal studies described below, this virus strain was tested in cell cultures to determine the 50% effective doses of FIAC, FIAU, and FMAU on its replication. Different concentrations of the drugs were added to the overlay medium, and the plaque reduction assay method was used with guinea pig embryo cells. The 50% effective doses for HSV-2 strain 1868 were 0.09, 0.12, and 0.06 for FIAC, FIAU, and FMAU, respectively. The 50% effective doses for ACV and PFA were determined in separate studies.

Effect of FIAC, FIAU, and FMAU on genital herpes. FIAC, FIAU, and FMAU at 100 mg/kg of body weight per day for 3 days starting 24 h after virus inoculation had a highly significant effect on the inhibition of genital lesion formation on the days examined (Table 1, $P < 0.01$). Drug-treated animals in which lesions formed had few, and none of the treated animals had a lesion score greater than 2. Infected control animals in which lesions formed each attained a lesion score of at least 4. The FMAU-treated group had the lowest lesion scores, and only half of these animals showed lesions.

Shedding of virus from the vaginas of infected animals was also affected by drug treatment. Infectivity titers of HSV in the untreated control animals showed a mean titer of 2.4 to

TABLE 2. Intraperitoneal treatment of genital herpes in guinea pigs with FIAC, FIAU, FMAU, ACV, and PFA for 3 days

Therapeutic agent (daily dose [mg/kg])	No. of animals with lesions/ no. inoculated	Time (h) p.i.[a] of start of treatment	Mean lesion score (± SD) on day:			
			3	4	7	10
None (control)	7/7	24	1.7 (0.8)	2.1 (0.4)	5.0 (0.0)	5.0 (0.0)
	7/7	48	1.4 (2.4)	3.6 (2.4)	4.0 (1.9)	3.9 (1.5)
FIAC (50)	12/12	24	0.3 (0.7)	1.4 (0.7)	1.8 (0.6)	1.9 (1.2)
	12/12	48	0.4 (0.7)	2.4 (1.6)	3.0 (1.5)	2.8 (1.3)
FIAU (50)	12/12	24	0.8 (0.8)	1.6 (0.5)	2.9 (1.6)	3.7 (1.7)
	11/12	48	0.3 (0.5)	1.7 (2.1)	1.8 (2.1)	2.3 (1.7)
FMAU (50)	7/11	24	0.1 (0.3)	0.9 (0.8)	0.8 (0.9)	0.7 (0.9)
	9/12	48	0.2 (0.4)	0.6 (0.7)	0.5 (0.7)	0.9 (0.9)
ACV (50)	11/11	24	0.3 (0.5)	1.7 (1.2)	3.7 (1.8)	3.6 (1.9)
	12/12	48	0.9 (0.9)	1.8 (1.1)	3.6 (1.8)	3.9 (1.5)
PFA (500)	11/11	24	0.5 (0.8)	1.6 (0.5)	4.5 (1.2)	4.5 (1.2)
	12/12	48	0.1 (0.3)	3.7 (1.5)	3.7 (1.5)	3.5 (1.6)

[a] p.i., Postinoculation.

2.6; a reduction of virus titers in the three groups of treated animals was evident. In the latter groups, mean titers of 1.3 to 1.6 by day 4 after inoculation of virus (i.e., 1 day after the last drug injections) were noted. No virus was detected in any of the FMAU-treated animals on day 4, although in other experiments in which a smaller dosage was used, virus shedding persisted at least until day 7.

No apparent drug toxicity was observed. Drug-treated animals gained somewhat more weight than compared with sham-treated controls, but the differences were not significant. Concentrations of Na^+, K^+, lactate dehydrogenase, and glucose in the sera of untreated, diluent-treated, and drug-treated animals were all within normal limits, with the exception of slightly elevated serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase levels. These slightly elevated levels in all but untreated guinea pigs are consistent with alcohol intake (contained in the diluent) for 3 days before serum collection (data not shown) but were not noted in ACV- or PFA-treated guinea pigs in separate studies (7, 10). No difference in lesion scores was noted between diluent- and saline-treated animals and controls.

Comparison of FIAC, FIAU, FMAU, and ACV (50 mg) and PFA (500 mg) treatment on genital herpes. Comparison was made between treatment with FIAC, FIAU, and FMAU and ACV (50 mg/kg per day) and PFA (500 mg/kg per day) for 3 consecutive days beginning 24 or 48 h after virus inoculation (Table 2). When the drug treatments were begun either 24 or 48 h after HSV infection, the mean lesion scores of all five groups of drug-treated animals were less than those of the controls. In addition, the mean lesion scores of FIAC-, FIAU-, and FMAU-treated groups were less than those for the groups treated with ACV and PFA; and the mean lesion scores of the FMAU-treated groups were the lowest scores of any group of animals. Mean lesion scores of control animals reached 5.0, and all 14 inoculated animals developed lesions. The scores of FIAC-, FIAU-, and FMAU-treated animals were all significantly less than those of the controls ($P < 0.05$) on each day examined. Although the scores of ACV- and PFA-treated animals were lower than those of the controls on each day, significant differences were approached only early after inoculation (days 3 and 4). ACV and PFA lesion scores peaked at ca. 4, FIAC and FIAU scores at ca. 3, and FMAU scores at 0.9. None of the FMAU-treated animals had a lesion score greater than 2, and only the FMAU-treated group showed a significant reduction in the number of animals with lesions (16 of 23). Beginning on day 4 after inoculation, significant differences were observed among the different treatment groups, whereas on days 7 through 10 the lesion scores of each of the three fluoropyrimidine-treated groups were significantly less than those of the ACV- or PFA-treated animals ($P < 0.05$). In addition, the scores of the FMAU- treated animals were significantly less than those of the FIAC- or the FIAU-treated animals ($P < 0.05$).

Comparison of FIAC, FIAU, FMAU (50 mg), and ACV (100 or 200 mg) treatment on genital herpes. When the dosage of ACV was doubled to 100 mg/kg per day and treatment was begun 72 h after virus inoculation, neither ACV nor FIAU had any effect on lesion scores (Table 3). Control, ACV, and FIAU scores all peaked at ca. 3.5. On the other hand, in the FIAC and FMAU groups, scores were consistently lower than those of the controls, with maximum scores of 2.2 and 1.3, respectively. None of the FMAU-treated animals had a lesion score greater than 2, although all animals inoculated in these experiments formed a few lesions. An additional, direct comparison between FMAU (50 mg/kg) and ACV (200 mg/kg) treatments begun 72 h after virus inoculation showed that FMAU lesion scores were significantly lower than ACV scores (data not shown).

DISCUSSION

Previous in vitro studies in which FIAC, FIAU, and FMAU were used have shown these compounds to be among the most potent antiherpetic agents yet described (3). Studies with mice and rabbits showed similar results (13, 17). The current work is in agreement with these previous studies and adds genital herpes in guinea pigs to the list of animal models in which these fluoropyrimidine drugs are very effective.

Each of the three fluoropyrimidines significantly reduced lesions scores when given at 100 mg/kg beginning 24 h after virus infection, and each reduced virus shedding from the vagina. In the second set of experiments, 50-mg/kg treatments were begun 24 or 48 h after virus inoculation and compared with ACV and PFA treatment regimens. ACV is a proven, effective antiviral agent and had become a standard for comparison with other antiviral agents. PFA is also an effective antiherpetic drug in both animal and human studies but has not been licensed for release in the United States (10, 19). All of the antiviral treatments begun 24 or 48 h after virus inoculation had an effect on reduction of lesion scores when compared with those of untreated control animals, but the FIAC, FIAU, and FMAU scores were each significantly lower than the ACV or PFA scores. Moreover, the lesion scores of the FMAU-treated animals were significantly less than those of the FIAC- or FIAU-treated groups. When initiation of therapy was delayed until 72 h after virus inoculation, the potency of FMAU at 50 mg/kg became even more apparent. Lesion scores of FMAU-treated animals were significantly less than those of the controls or any other treatment group. FIAC was effective when given 72 h after virus inoculation, whereas FIAU and ACV, even at 100 mg/kg, were ineffective treatments.

TABLE 3. Treatment of genital herpes in guinea pigs with ACV, FIAC, FIAU, and FMAU for 3 days beginning 72 h after virus inoculation

Therapeutic agent	Dose (mg/kg)	No. of animals with lesions/ no. inoculated	Mean lesion scores (± SD) on day:			
			3	4	7	10
None (control)	0	10/11	1.0 (1.0)	1.7 (0.6)	2.3 (1.0)	3.5 (1.6)
ACV	100	10/10	0.7 (0.4)	1.5 (0.8)	2.3 (0.7)	3.6 (1.6)
FIAC	50	11/11	0.9 (0.8)	1.5 (0.7)	1.8 (0.4)	2.2 (1.1)
FIAU	50	11/11	1.3 (0.8)	1.7 (0.5)	2.5 (1.0)	3.1 (1.9)
FMAU	50	11/11	0.9 (0.8)	1.2 (0.8)	1.3 (0.6)	0.4 (0.5)

It was noted that the lesion scores for untreated guinea pigs varied from experiment to experiment. This was due to slight differences of the virus inoculum in each experiment. Since comparisons between drug treatments were made within each experiment in which all animals, including the controls, received the same amount of virus, evaluation of drug activity within each experiment would not be affected.

In an attempt to have a comparable study, all drugs were administered intraperitoneally since topical forms of FIAC, FIAU, and FMAU were not available at the time the present experiments were conducted. However, these results of the comparisons made in this report must be considered only in the context of the study, i.e., on a milligram (of drug)-per-kilogram basis. Among other considerations which vary from drug to drug are tolerability, optimum dosages, timing of administration, and metabolism. Under the narrow conditions imposed in this study, the fluoropyrimidines, particularly FMAU, appeared to be more potent than the other drugs tested. Whether this relative effectiveness is sustained in clinical trials remains to be seen. FIAC is reportedly effective in treating varicella-zoster infections in immunosuppressed patients and was found to be therapeutically superior to adenine arabinoside (J. J. Fox, Am. Chem. Soc. Natl. Meet.). Widespread use of these fluoropyrimidines for genital herpes treatment will not be feasible until therapeutically safe and effective topical cream formulations can be made, as has been done with ACV and PFA. The effect of FIAC, FIAU, and FMAU on herpesvirus latency, if any, remains to be elucidated.

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