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INHIBITION OF SIMIAN VARICELLA VIRUS INFECTION OF AFRICAN GREEN MONKEYS BY (*E*)-5-(2-BROMOVINYL)-2′-DEOXYURIDINE (BVDU)

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Simian varicella virus infection of the African green monkey was inhibited by (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU). Treatment at 10 mg/kg/day by oral, intramuscular or intravenous administration prevented the development of viremia and the appearance of rash, and averted the anorexia normally observed in untreated virus-infected monkeys. BVDU reduced the clinical disease when administered orally at either 15, 10 or 5 mg/kg/day BID, but even at 1 mg/kg/day it produced a slight inhibitory effect on the disease. BVDU given by gavage at 15 mg/kg/day as late as 6 days after virus inoculation was observed to modify the course of the disease. Antiviral efficacy of BVDU in the treatment of simian varicella virus-infected monkeys exceeded that observed in similar experiments with acyclovir, adenine-5′-monophosphate, phosphonoacetate or phosphonoformate. The similarity of simian varicella virus to human varicella zoster virus points to the potential efficacy of BVDU in the treatment of generalized varicella infection in humans.

varicella-zoster virus African green monkeys BVDU simian varicella virus

INTRODUCTION

Varicella-zoster virus (VZV) replication in human fibroblast cultures is inhibited by addition of (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU) to the tissue culture medium [5, 6]. In preliminary experiments, the concentration of BVDU required for in vitro inhibition of VZV was 0.02–0.04 μg/ml [5, 6]. In later and more definitive experiments (ref. 6 and E. De Clercq et al., submitted for publication). BVDU was found to inhibit VZV replication at a concentration of 0.001–0.01 μg/ml. Thus, the sensitivity of VZV to BVDU is similar to that of herpes simplex virus type 1 (HSV-1) (minimal inhibitory dose: 0.008 μg/ml) but significantly higher than that of HSV type 2 (HSV-2) (minimal inhibitory dose: 1–2 μg/ml [2, 4].

Efficacy in vivo was demonstrated with HSV-1 in athymic nude mice inoculated intracutaneously and treated with BVDU as a 1% ointment or as an intraperitoneal injection at 60 mg/kg [2]. HSV-1 keratitis was successfully treated with a BVDU ointment applied 5 times daily at 2 h intervals for 5 days [9]. Studies of the pharmacokinetics of BVDU revealed mean blood levels in mice of 40–100 μg/ml 20 min following subcutaneous injection of 100 mg/kg. Following oral administration to mice, this same dose resulted

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in BVDU levels of 40–60 μg/ml in serum, thus suggesting the feasibility of oral BVDU treatment. Active blood levels were still detectable 320 min after oral administration [3].

The in vitro data of the susceptibility of VZV to BVDU and in vivo data relating adequate serum levels for inhibition of VZV suggested the potential application of BVDU in the treatment of generalized varicella-zoster infection [5, 6]. We have employed an infection of the African green monkey with simian varicella virus (SVV) as a laboratory model for generalized varicella virus infection [1, 10]. The results reported from this study reveal efficacy of BVDU in the treatment of generalized varicella virus infection occurring in African green monkeys inoculated with simian varicella virus.

MATERIALS AND METHODS

Monkeys

African green monkeys (*Cercopithecus aethiops*) were purchased as feral animals from a commercial supplier. All monkeys prior to use were kept in quarantine for a minimum of 90 days. At the conclusion of quarantine, they were moved to isolation facilities in a building for infectious disease studies and baseline data, including assays for antibody to SVV, were collected. Serum neutralization tests showed all monkeys to be free of antibody to SVV before use. Weights of the monkeys ranged from 1.6 to 4.0 kg at the time of virus inoculation. In each separate experiment monkeys of similar weights were used. Additional care was taken to create control and treatment groups of similar mean weights for each experiment.

Virus

The simian varicella virus was isolated from patas monkeys infected in a natural outbreak at this Center [1]. Propagation and assay for plaque-forming units (p.f.u.) of virus have been conducted in Vero cell cultures in Eagle's minimum essential medium (MEM) with 10% fetal or newborn calf serum. The virus inoculum was prepared at the fifth passage in Vero cells originating from infected monkey tissues and stored frozen at -70°C in 35% sorbitol.

Monkey inoculation

Monkeys were infected with a dilution of stock virus which was administered as 1.5 ml transtracheally through the cricoid cartilage and 1.5 ml subcutaneously into the abdominal area. The inoculum was titrated for plaque-forming units of virus in Vero cells at the time of each experiment.

Drug

(*E*)-5-(2-Bromovinyl)-2′-deoxyuridine was provided by Dr. E. De Clercq through the Cooperative Antiviral Testing Group of the National Institute of Allergy and Infectious Disease. The drug was prepared fresh daily for administration in either distilled water or phosphate-buffered saline (PBS). The pH of BVDU was near neutrality.

Antiviral experiments in monkeys

On two occasions prior to virus inoculation, blood was drawn from each of the monkeys for baseline hematology, including a complete blood count and differential count, clinical chemistry and for antibody assay. Clinical chemistry tests included blood urea nitrogen, creatinine, albumin, globulin, total protein, bilirubin, serum glutamic-oxaloacetic transaminase and glutamic-pyruvic transaminase. If all values were within normal limits, virus infection was accomplished by combined intratracheal and subcutaneous inoculation and the virus titer of the inoculum determined. On post-infection days 3, 5, 7, 9 and occasionally on day 11, blood was drawn for hematology, clinical chemistry and for virus assay. Viremia was determined by collection of 3 ml of blood from which the lymphocytes were separated over Ficoll-Hypaque. The lymphocytes were collected, washed twice in RPMI-1640 medium, resuspended in 10 ml of this medium containing 10% newborn calf serum and divided between two 25 cm^2 culture flasks seeded with Vero cells. The cultures were observed microscopically for the development of plaques which were stained, counted and the mean number of plaques in the two flasks recorded. Monkeys were examined daily for appearance of the varicella-form rash and its duration recorded. Food intake was determined as a measure of clinical well being by observing the number of biscuits consumed daily. Six to eight biscuits of Purina High Protein Monkey Chow ® were provided daily to each monkey depending on the size of the monkey. This number of biscuits was observed to be consumed completely by the monkeys prior to virus infection. At the time of clinical disease the number of biscuits eaten decreased. On days 14 and 21, blood was drawn for serum neutralization tests for antibody to SVV. Titers of serum neutralizing antibody were determined in plaque-reduction assays. Two-fold dilutions of heat-inactivated sera were mixed with an equal volume of medium (MEM) containing a dilution of SVV which would provide 100–200 p.f.u. upon plating. The serum–virus mixtures after incubation for 1 h at room temperature were inoculated in duplicate into 60 mm Petri dishes seeded with Vero cells. Following incubation at 37°C in a CO_2 incubator, the cell monolayers were fixed in methanol, stained with a mixture of methylene blue and basic fuchsin and the number of plaques counted. The antibody titer was the maximum dilution of serum which inhibited 80% of the number of plaques developing in virus control cultures which had been similarly treated but without serum. Monkeys dying from infection were given a complete necropsy with histologic examination of involved tissues.

In the first experiment, BVDU was given by gavage to three monkeys at 7.5 mg/kg

BID or 15 mg/kg/day. A second group of three monkeys received BVDU dissolved in the drinking water at 0.25 mg/ml and provided ad lib. Three control monkeys received PBS by gavage. Treatment was initiated 48 h after virus inoculation and continued for 10 days.

In the second experiment, BVDU was given to groups of three monkeys by stomach tube twice daily at doses of 10, 5 and 1 mg/kg/day. Control monkeys received PBS in a similar manner. BVDU administration began 48 h after virus infection and continued for 10 days.

In a third experiment, BVDU was administered at 10 mg/kg/day. Groups of three monkeys received divided doses, either intramuscularly, intragastrically or intravenously. PBS was given intravenously to three infected control monkeys. Treatment was initiated 48 h after virus inoculation and was given twice daily for 5 days.

In a final experiment, the effect of delayed treatment was investigated. BVDU was given by gavage twice daily for 5 days at 15 mg/kg/day. Treatment to three monkeys was given on days 2 through 6. A second group received BVDU on days 4 through 8, while a third group received treatment commencing on day 6 and continuing through day 10. Three control monkeys were given PBS by stomach tube from day 2 through day 10.

RESULTS

In the first experiment, nine African green monkeys were infected by administration of 4.9×10^4 p.f.u. of simian varicella virus to each monkey. BVDU treatment was begun 48 h after virus inoculation in an attempt to evaluate the antiviral activity of orally administered BVDU (Table 1). Three infected control monkeys developed clinical disease with appearance of rash accompanied by a period of anorexia. Viremia occurred in all three monkeys with plaques too numerous to count (TNTC) on days 7 and 9 post infection (p.i.). Two of the three control monkeys died – one on day 11 and one on day 13. Of the three monkeys receiving BVDU by stomach tube at 15 mg/kg/day, viremia was essentially eliminated with only one monkey (A343) showing a minimal number of virus plaques from lymphocytes cultivated on day 3. No rash developed in these three monkeys and only a brief period of anorexia occurred in two of the three monkeys. In the three monkeys receiving BVDU in the drinking water, there was apparently a varying acceptance of the drug. BVDU was administered in this manner to provide a more sustained daily dose throughout the period of treatment. Although each of the three monkeys prior to infection consumed 150–200 ml of drinking water daily, after inclusion of BVDU in the drinking water, acceptance varied. However, daily consumption for each monkey was relatively consistent and therefore a mean daily dose was calculated for the 10 days of treatment in this manner. The mean dose consumed varied from a low of 2.3 mg/kg/day for A330 to 9.4 mg/kg/day for A338 and A335 receiving an intermediate dose of 4.8 mg/kg/day. In each of these monkeys rash occurred but was of short duration in the two monkeys at the higher doses. Viremia was reduced in the monkey receiving 9.4 mg/kg/day and was not detectable in each of the treated monkeys at 9 days

TABLE 1

Evaluation of clinical infection in monkeys inoculated with simian varicella virus and treated orally with BVDU

Monkey No.	BVDU treatment (mg/kg/day)	Viremia – mean p.f.u. on days				Clinical disease		Antibody titer 21 days p.i.
		3	5	7	9	Rash (days p.i.)	Anorexia (days p.i.)	
A337	None[a]	0	1	TNTC	TNTC	9–14	9–12	1 : 640
A339	None[a]	3.5	49.5	TNTC	TNTC	7–11 (D)	9–11	Died
A920	None[a]	0	34	TNTC	TNTC	9–13 (D)	10–13	Died
A332	15[b]	0	0	0	0	None	None	1 : 20
A342	15[b]	0	0	0	0	None	10	1 : 10
A343	15[b]	1.5	0	0	0	None	8	1 : 10
A330	2.3[c]	3	22.5	1.5	0	8–14	6–12	1 : 80
A335	4.8[c]	1	74.5	137.5	0	9–10	10–12	1 : 40
A338	9.4[c]	1	3	38	0	9–10	8–10	1 : 20

[a] Received PBS by stomach tube, BID, beginning 48 h p.i.

[b] Administered by stomach tube, BID, beginning 48 h p.i.

[c] Administered ad lib in drinking water; mean of 10 days administration, beginning 48 h p.i.

p.i., although present at this time in the untreated controls. Antibody response was observed to be lower in each of the BVDU-treated monkeys when compared with the single surviving control monkey. Serum transaminase values were increased in the untreated control monkeys but not in either group of BVDU-treated monkeys (Fig. 1).

When the dose of BVDU was varied from 10, 5 to 1 mg/kg/day given by stomach tube twice daily, a dose response was observed. Treatment was begun at 48 h after administration of 1.3×10^4 p.f.u. of simian varicella virus and was continued for 10 days (Table 2). The control monkeys developed infection with rash, anorexia and viremia. One of the three control monkeys died on day 13 with generalized varicella infection observed at necropsy. Antibody response in the two surviving monkeys was 1 : 320 and 1 : 640, respectively. Two of the three monkeys receiving BVDU at 10 mg/kg/day did not

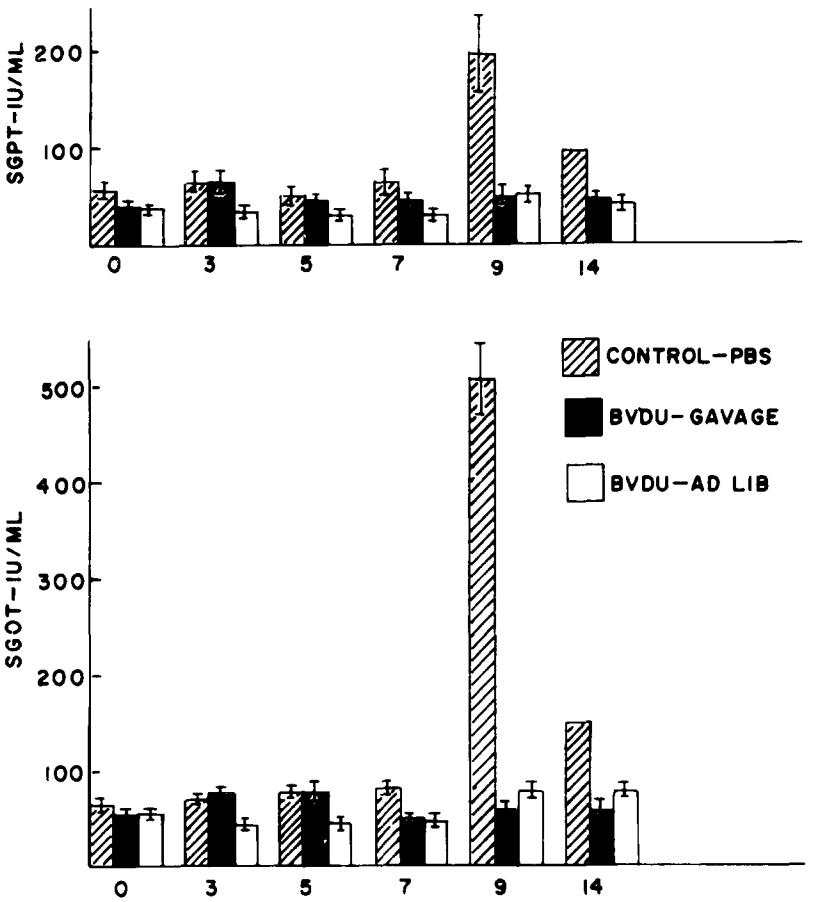

Fig. 1. Serum transaminase values on African green monkeys infected with simian varicella virus bled on days 0, 3, 5, 7, 9 and 14 days after virus inoculation. Treatment began 48 h after virus with control monkeys receiving PBS by gavage, BVDU gavage monkeys received BVDU at 7.5 mg/kg twice daily for 10 days, and BVDU ad lib received BVDU in the drinking water at 0.25 mg/ml.

TABLE 2

Evaluation of clinical infection in monkeys with simian varicella virus and treated with varying doses of BVDU

Monkey No.	BVDU treatment[a] (mg/kg/day)	Viremia – mean p.f.u. on days					Clinical disease		Antibody titer 21 days p.i.
		3	5	7	9	11	Rash (days p.i.)	Anorexia (days p.i.)	
B024	None,	49	41.5	347	686	47.5	9–13 (D)	6–11	Died
B023	PBS, i.g.	31.5	93	206	45.4	8.5	7–14	6–11	1 : 640
B022		2	36	623	48.5	21.5	10–14	6–11	1 : 320
B021	10 i.g., BID	2.5	5	0	0	0	none	6–11	1 : 20
B020		4	9	2.5	0	1	11–14	6–10	1 : 320
B019		0	4	1.5	0	0	none	none	1 : 80
B018	5 i.g., BID	2	12	4	0	0	none	none	1 : 40
B017		77	109	TNTC	Died		7– 8	6– 8 (D)	Died
B016		0	4.5	0	0	0	none	6– 7	1 : 40
B015	1 i.g., BID	2	21.5	31.5	7	1.5	9–14	10–11	1 : 160
B014		0	24.5	32.5	0	0	8–14	7–11	1 : 160
B013		2	24.5	44	1.5	1	7–14	None	1 : 320

[a] Treatment began 48 h p.i. and continued for 5 days.

have a typical rash and one of the three was not anorexic. A minimal viremia occurred in each of the three monkeys. Antibody response was inhibited in two monkeys while one monkey (B020), which developed rash, had an antibody titer of 1 : 320. When BVDU was administered at 5 mg/kg/day, only one monkey developed a marked infection. Viremia occurred early, at day 3, and the plaques cultured from the lymphocytes on day 7 were too numerous to count. The monkey died 8 days after virus inoculation with generalized varicella confirmed at necropsy. The two remaining monkeys in this group had no rash, only a limited viremia, and their food consumption was affected minimally or not at all. Antibody response was reduced when compared with the untreated infected control monkeys. The three monkeys which received BVDU at 1.0 mg/kg/day became infected with development of rash and viremia. The viremia was less than that observed in the untreated monkeys but continued through day 9 and 11 in two of the three monkeys. Food consumption was slightly decreased in one monkey but not in the other. Antibody titers in each of the three monkeys were not inhibited at this dose. Transaminase values were increased in the untreated monkeys and in the monkeys receiving BVDU at 1 mg/kg (Fig. 2).

The antiviral effectiveness of BVDU against simian varicella virus infection was independent of the route of administration of the drug (Table 3). Twelve monkeys were infected by inoculation with 1.6×10^4 p.f.u. of virus. Groups of three monkeys received BVDU treatment at 10 mg/kg/day by intramuscular (i.m.), intragastric (i.g.) or intravenous (i.v.) administration twice daily for 5 days beginning 48 h after virus inoculation. The three untreated control monkeys became infected with appearance of viremia, development of rash and two of the monkeys were anorexic. Recovery from infection was followed by appreciable titers of serum-neutralizing antibody. None of the BVDU-treated monkeys in any of the three treatment groups developed rash, and viremia when detected was minimal. Food consumption was variable but, in general, was better than that observed in the untreated monkeys. Antibody titers were lower in the majority of BVDU-treated monkeys. Only monkey number 917, which received BVDU intravenously, developed an antibody titer similar to those in the untreated monkeys.

Finally, the effect of delay of BVDU treatment was investigated. Simian varicella virus at a dose of 8.4×10^3 p.f.u. was given to each of 12 monkeys. BVDU was administered intragastrically twice daily at 15 mg/kg/day. Treatment to groups of three monkeys was begun at 2, 4, or 6 days after virus inoculation and continued in each group for a total of 5 days. The untreated control monkeys received PBS by stomach tube twice daily from 2 to 10 days p.i.

From Table 4 it is clear that each of the three untreated monkeys developed a viremia and varicella-form rash with accompanying anorexia. One monkey died 12 days after virus inoculation with generalized varicella infection. BVDU treatment, even when deferred as late as 6 days after virus inoculation, had an effect on virus infection. Viremia and the appearance of rash were suppressed in each of the treatment groups. It was observed that monkey B031 had a significant viremia on day 5 p.i. BVDU treatment was begun on day 6, and by day 7 an appreciable reduction in circulating virus occurred, suggest-

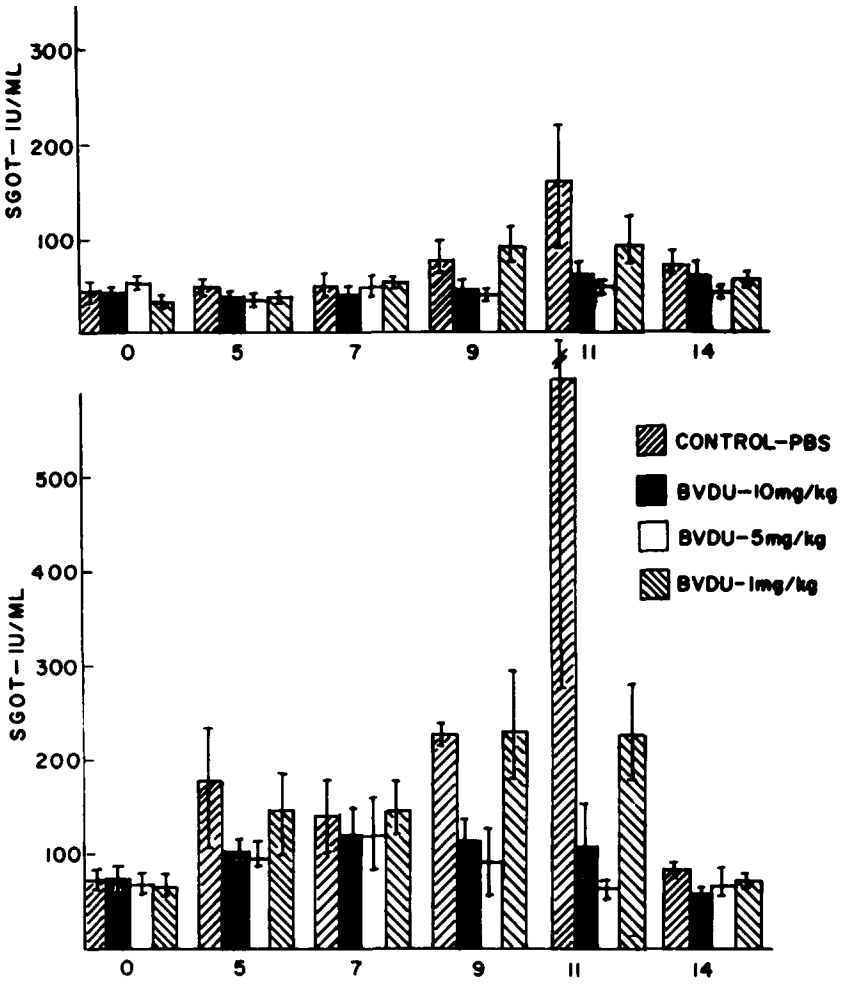

Fig. 2. Serum transaminase values on African green monkeys infected with simian varicalla virus bled on days 0, 5, 7, 9, 11 and 14 days after virus inoculation. Treatment at the indicated doses given by gavage began 48 h after virus inoculation and continued for 10 days.

ing inhibition of the viremia presumably as a consequence of BVDU treatment. Antibody response in the BVDU-treated monkeys was lower than that observed in the untreated control monkeys.

DISCUSSION

(*E*)-5-(2-Bromovinyl)-2′-deoxyuridine administered to African green monkeys following inoculation with simian varicella virus inhibited the development of clinical disease. Antiviral activity occurred following oral, intramuscular or intravenous BVDU treatment.

TABLE 3

Evaluation of clinical infection in monkeys inoculated with simian varicella virus and treated i.v., i.m. or i.g. with BVDU

Monkey No.	BVDU treatment[a] (mg/kg/day)	Viremia – mean p.f.u. on days				Clinical disease		Antibody titer 21 days p.i.
		3	5	7	9	Rash (days p.i.)	Anorexia (days p.i.)	
918	None,	2.5	4.5	55	542.5	10–14	none	> 1 : 640
919	(PBS, i.v.)	2	128	353.5	477	9–14	9–14	> 1 : 640
921		2.5	13.8	38.5	42.5	10–14	9–14	1 : 320
907	10 i.m., BID	1	0	0	0	none	none	< 1 : 10
908		0	0	0	0	none	none	1 : 10
909		0	1	0	0	none	9–11	1 : 20
910	10 i.g., BID	3	1.5	0	0	none	9–12	1 : 40
911		0	0	0	0	none	none	1 : 10
912		1	0	0	0	none	none	1 : 10
915	10 i.v., BID	3	2	0	0	none	9	1 : 80
916		0	0	0	0	none	none	1 : 20
917		0	2.5	2.5	0	none	9–13	1 : 320

[a] Treatment began 48 h p.i. and continued for 5 days.

TABLE 4

Evaluation of clinical infection in monkeys inoculated with simian varicella virus and treated by gavage at various intervals of time with BVDU

Monkey No.	BVDU treatment[a] (mg/kg/days)	Viremia – mean p.f.u. on days					Clinical disease		Antibody titer 21 days p.i.
		3	5	7	9	11	Rash (days p.i.)	Anorexia (days p.i.)	
B040	None,	2.5	39	387	40	4	10–14	7–14	1 : 320
B041	PBS i.g.,	1	71.5	43.5	49.5	6	10–14	6–12	1 : 160
B042	days 2–10	1.5	26	213	79	11.5	9–12 (D)	9–12 (D)	Died
B039	15, days 2–6	1	0	0	0	0	none	none	1 : 40
B038		0	0	0	0	0	none	none	1 : 40
B037		0	2.5	0	0	0	none	none	1 : 80
B036	15, days 4–8	3	0	0	0	0	9–11	7– 9	1 : 10
B035		1.5	4.5	1.5	1.5	0	none	6– 8	1 : 40
B034		3	7	0	0	0	none	6–12	1 : 20
B032	15, days 6–10	0	4	0	0	0	9	8–12	1 : 40
B031		2	119.5	7	2.5	0	9–11	8–12	1 : 80
B030		1	31	6	0	0	none	7–11	1 : 80

[a] Treatment given BID at times indicated following virus inoculation.

Simian varicella virus infection of the monkey has been used as an animal model for severe generalized varicella infection of man [1, 12]. The observed effectiveness of BVDU in the monkey model suggests the application of this drug in the treatment of human varicella zoster infection.

Simian varicella virus has been shown to be antigenically similar to VZV [8]. The cultural characteristics of the simian virus including its strict cell association are like those of VZV [1]. In the monkey, natural infection has been shown to have a high morbidity and mortality [12]. The clinical disease, in addition to the vesicular rash, involves a viremia with development of lesions in the lungs, liver, spleen and gastrointestinal tract. Increases in serum transaminases occur concomitantly with systemic disease. The viremia which follows experimental inoculation occurs at about day 3 and persists for approximately one week. Anorexia and elevated transaminase values occur about day 7 and the rash generally erupts by day 9. The rash is present for 4–5 days before desquamating. Serum neutralizing antibody to the simian varicella virus appears by day 14 and reaches a peak titer at about day 21. The site of primary replication of the virus is not known, although the respiratory tract would appear to be the natural route of entry. The consistent appearance of the virus associated with the lymphocytes of the infected monkey which occurs early after virus inoculation and before the appearance of clinical disease suggests a possible role of lymphocytes in early virus replication.

BVDU at daily oral doses of 15 mg/kg reduced or inhibited the virus circulating with the lymphocyte. Delaying BVDU treatment to day 4 or day 6 following virus inoculation, a time when appreciable virus would be lymphocyte-associated and presumably metastatically seeded, limited the course of viremia and the resulting systemic infection. The development of rash was aborted as well as the increase in serum transaminase values indicative of systemic involvement. The reduced titers of serum neutralizing antibody to simian varicella virus which was noted in BVDU-treated monkeys could be interpreted as a reduction of antigenic stimulus as a consequence of lowering the virus load. An immunosuppressive effect of BVDU could also explain the lower antibody titers; however, no evidence for this effect of the drug has been reported.

Similar experiments with simian varicella infection in monkeys have reported minimal antiviral activity of acyclovir administered intravenously [11] and negligible activity of adenine arabinoside-5'-monophosphate given intramuscularly [10]. Phosphonoacetate [7] and phosphonoformate (unpublished data) injected intramuscularly were observed to suppress viremia and clinical disease. However, elevated transaminase levels and dermatitis suggested associated toxicity. The present studies with BVDU which suppressed the development of simian varicella infection by oral treatment as well as by intramuscular or intravenous injection with no toxic manifestations appears to be the most effective antiviral compound employed at this time in this model of generalized varicella infection.

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REFERENCES

1 Allen, W.P., Felsenfeld, A.D., Wolf, R.H. and Smetana, H.F. (1974) Recent studies in the isolation and characterization of Delta herpes virus. Lab. Animal Sci. 24, 222–228.

2 De Clercq, E., Descamps, J., De Somer, P., Barr, P.J., Jones, A.S. and Walker, R.T. (1979) (*E*)-5-(2-Bromovinyl)-2′-deoxyuridine: a potent and selective anti-herpes agent. Proc. Natl. Acad. Sci. U.S.A. 76, 2947–2951.

3 De Clercq, E., Descamps, J., De Somer, P., Barr, P.J., Jones, A.S. and Walker, R.T. (1979) Pharmokinetics of *E*-5-(2-bromovinyl)-2′-deoxyuridine in mice. Antimicrob. Agents Chemother. 16, 234–236.

4 De Clercq, E., Descamps, J., Verhelst, G., Walker, R.T., Jones, A.S., Torrence, P.F. and Shugar, D. (1980) Comparative efficacy of different anti-herpes drugs against different herpes simplex virus strains. J. Infect. Dis. 141, 563–574.

5 De Clercq, E., Descamps, J., Verhelst, G., Jones, A.S. and Walker, R.T. (1980) Antivirial activity of 5′-(2-halogenovinyl)-2′-deoxyuridines. Current Chemotherapy and Infectious Disease, American Society of Microbiology, pp. 1372–1374.

6 De Clercq, E., Degrief, H., Wildiers, J., De Jorge, G., Drochmans, A., Descamps, J. and De Somer, P. (1980) Oral (*E*)-5-(2-bromovinyl)-2′-deoxyuridine in severe herpes zoster. Br. Med. J. 281, 1178.

7 Felsenfeld, A.D., Abee, C.R., Gerone, P.J., Soike, K.F. and Williams, S.R. (1978) Phosphonoacetic acid in the treatment of simian varicella. Antimicrob. Agents Chemother. 14, 331–335.

8 Felsenfeld, A.D. and Schmidt, N.J. (1979) Varicella-zoster virus immunizes patas monkeys against simian varicella-like disease. J. Gen. Virol. 42, 171–178.

9 Maudgal, P.C., De Clercq, E., Descamps, J., Missotten, L., De Somer, P., Busson, R., Vanderhaeghe, H., Verhelst, G., Walker, R.T. and Jones, A.S. (1980) *E*-5-(2-Bromovinyl)-2′-deoxyuridine in the treatment of experimental herpes simplex keratitis. Antimicrob. Agents Chemother. 17, 8–12.

10 Soike, K.F., Felsenfeld, A.D., Gibson, S. and Gerone, P.J. (1980) Ineffectiveness of adenine arabinoside and adenine arabinoside-5′-monophosphate in simian varicella infection. Antimicrob. Agents Chemother. 18, 142–147.

11 Soike, K.F., Felsenfeld, A.D. and Gerone, P.J. (1981) Acyclovir treatment of experimental simian varicella infection of the monkey. Antimicrob. Agents Chemother. 20, 291–297.

12 Wolf, R.H., Smetana, H.F., Allen, W.P. and Felsenfeld, A.D. (1974) Pathology and clinical history of Delta herpesvirus infection in patas monkeys. Lab. Animal Sci. 24, 218–221.