Antiviral Research 14 (1990) 99–108
Elsevier

AVR 00429

Comparison of antiviral efficacies of 1-β-D-arabinofuranosyl-*E*-5-(2-bromovinyl)uracil (brovavir) and acyclovir against herpes simplex virus type 1 infections in mice

Haruhiko Machida, Takao Ikeda and Noriyuki Ashida

Biology Laboratory, Yamasa Shoyu Co. Ltd., Choshi, Japan

(Received 16 February 1990; accepted 13 April 1990)

Summary

1-β-D-Arabinofuranosyl-*E*-5-(2-bromovinyl)uracil (brovavir) and acyclovir were compared for their antiviral effects against herpes simplex virus type 1 (HSV-1) model infections in mice. Both drugs were not toxic to mice when they were administered orally by the same schedule used for therapeutic experiments. Brovavir was less toxic than acyclovir when injected by the intraperitoneal (i.p.) route. Marked efficacies of brovavir by either oral or i.p. administration were demonstrated in both experimental encephalitis and i.p. infection with HSV-1 WT-51 strain. Treatment with brovavir at a dose of 15 or 25 mg/kg twice daily resulted in increasing both survival rate and mean survival time of the infected mice. On the contrary, acyclovir showed only marginal effect against the experimental encephalitis. Survival rates of mice treated with brovavir were higher than those treated with acyclovir at corresponding doses with statistical significance. The superiority of brovavir was also found in the intracerebral infection with strain VR-3, a highly virulent strain for mice. Brovavir, but not acyclovir, at a dose of 200 mg/kg reduced the mortality. Acyclovir, however, were significantly effective in reducing mortality of systemically infected mice by both oral and i.p. administrations. The effective dose of acyclovir was lower than that of brovavir against i.p. infection with strain WT-51. Differences in mortality of strain VR-3-infected mice were statistically significant between acyclovir- and brovavir-treated groups.

Brovavir; Acyclovir; Encephalitis; Model infection

Correspondence to: H. Machida, Biology Laboratory, R & D Division, Yamasa Shoyu Co. Ltd., 10-1 Araoicho 2-chome, Choshi-shi, Japan 288.

Introduction

1-β-D-Arabinofuranosyl-*E*-5-(2-bromovinyl)uracil (brovavir) is one of the most promising antiherpes agents being developed, particularly for the treatment of varicella-zoster virus infections (Machida, 1986; Machida et al., 1981). We previously showed in vivo antiviral activity of brovavir in mice infected intracerebrally (i.c.) with herpes simplex virus type 1 (HSV-1) VR-3 strain (Machida et al., 1985; Machida and Sakata, 1984). The potencies of brovavir shown in these papers were somewhat lower than those reported by Reefschlaeger et al. (1986). With respect to the efficacies of acyclovir against i.c. infection with HSV-1, we found no therapeutic effect of acyclovir treatment (Machida et al., 1985), in contrast to the observations by Cho and Feng (1980) and Park et al. (1979). One of the reasons for such discrepancies in the results may be due to differences in virus strains used for infection. We, indeed, have shown moderate effects of brovavir against infections with HSV-1 VR-3 strain, highly virulent for mice (Machida and Sakata, 1984) and marked effects against HSV-1 WT-51 strain infections (Machida and Takezawa, 1990). The purpose of this paper is to directly compare antiherpesviral potencies of brovavir and acyclovir in two mouse model infections, experimental encephalitis and systemic infection, using strains of HSV-1 having different virulence for mice.

Materials and Methods

Mice

Four-week-old, random-bred, Swiss albino ICR male mice, (Jcl:ICR or CD-1 strain) were purchased from Clea Japan, Inc. or Charles River Japan, Inc. There were no strain differences in susceptibility to HSV-1 infection and efficacies of antiviral drugs between these two strains. The mice were maintained for 1 to 2 days in our animal laboratory prior to experimental use. The body weight of mice was 19 to 23 g when the experiments were initiated.

Viruses

HSV-1 strains VR-3 and WT-51 grown on human embryonic lung (HEL) cells were used. Strain VR-3, a laboratory-stock strain, was provided by Dr. S. Yamazaki, National Institute of Health of Japan, and propagated through HEL cells. Strain WT-51, a recent clinical isolate from a patient with herpes keratitis, was supplied by Dr T. Kurimura, Research Institute for Microbial Diseases of Osaka University, and propagated only once or twice after isolation. Strain VR-3 shows high virulence for mice. Its LD_{50} values were 0.5 and 430 plaque forming units (pfu) by i.c. and intraperitoneal (i.p.) inoculation routes, respectively. Strain WT-51 exhibits moderate virulence. Its LD_{50} values were 8 and 1700 pfu by i.c. and i.p. inoculation routes, respectively. There were no differences in the susceptibilities to brovavir and acyclovir between the two strains. The 50% plaque reduction doses for strains

VR-3 and WT-51 of brovavir were 0.021 and 0.020 μg/ml, respectively, while those of acyclovir 0.105 and 0.093 μg/ml, respectively, when assayed on HEL cells.

Inoculation of HSV-1

Groups of about 20 mice were infected i.c. without anesthetization with 10 μl of virus suspension containing either 19 LD_{50} of strain WT-51 or 6 LD_{50} of strain VR-3 to induce experimental encephalitis. For i.p. infections, 100 μl of virus suspension containing either 90 LD_{50} of strain WT-51 or 23 LD_{50} of strain VR-3 were inoculated. Usually, 90 to 100% and 85 to 100% of mice in placebo-treated control group died by these i.c. and i.p. infections, respectively.

Drug treatment and evaluation of efficacy

The drugs were dissolved in saline or suspended in saline containing 0.5% carboxymethylcellulose (Nakarai Chemicals Ltd., viscosity; 1.94 cps) and administered to mice in a volume of 1 ml/10 g body weight to the infected mice either orally or i.p. twice daily for 5 to 9 days beginning 4 h post infection. Mice in control groups received saline instead of drug. The infected mice were observed twice daily for 21 days for paralysis and death. The differences in mean survival times and survival rates between control and drug-treated groups were evaluated by Student's t test and χ-square test with Yates' correction, respectively. Only animals that died on or before day 21 were included in calculation of mean survival times.

Results

Drug toxicity for mice

Brovavir exhibited little toxicity for mice upon single administrations irrespective of the route of administration (Machida et al., 1985). Brovavir and acyclovir were tested for their toxicity for mice in the same treatment schedule used for therapeutic experiments. Both drugs were tolerable to uninfected mice at an oral dose as high as 400 mg/kg twice daily for 7 days. For i.p. administration, however, acyclovir exhibited more toxic than brovavir. No animals died in a group receiving brovavir i.p. twice daily at a dose as high as 800 mg/kg without body weight loss, while two out of 10 mice receiving 200 mg of acyclovir per kg died on day 2 and day 3. The maximum tolerated dose of acyclovir for uninfected mice was 100 mg/kg by the i.p. route, although body weight loss was a side effect.

Effects on experimental encephalitis

The therapeutic effect of oral treatment with brovavir on experimental encephalitis caused by infection with strain WT-51 was compared with that of acyclovir (Table 1). Treatment with brovavir at doses of 25 mg/kg or higher twice daily was

TABLE 1
Effects of oral treatments with brovavir and acyclovir on experimental encephalitis in mice infected with HSV-1 WT-51 strain

Expt.	Treatment[a]		Survivors per total		Mean survival time of mice that died (days ± standard error)	
	Drug	Dose (mg/kg)				
1	None (control)	0	0/24		6.00 ± 0.28	
	Brovavir	10	3/22		6.57 ± 0.55	$P<0.05$[b] ($P<0.05$)[c]
	Brovavir	50	13/21	$P<0.001$[d] ($P<0.05$)[e]	11.00 ± 0.93	$P<0.001$[b] ($P<0.001$)[c]
	Acyclovir	10	3/22		5.68 ± 0.33	
	Acyclovir	50	5/21	$P<0.05$[d]	5.88 ± 0.27	
2	None (control)	0	2/21		5.42 ± 0.32	
	Brovavir	25	15/22	$P<0.001$[d] ($P<0.001$)[e]	8.86 ± 1.22	$P<0.01$[b] ($P<0.01$)[c]
	Brovavir	100	19/22	$P<0.001$[d] ($P<0.001$)[e]	12.33 ± 2.33	$P<0.001$[b] ($P<0.001$)[c]
	Acyclovir	25	1/21		6.05 ± 0.37	
	Acyclovir	100	1/22		7.00 ± 0.38	$P<0.01$[b]

[a]Mice were treated with brovavir or acyclovir twice daily for 5 days in expt. 1 or for 7 days in expt. 2. Mice in control group received saline.
[b]Significance in difference from the saline-treated control (Student's *t*-test).
[c]Significance in difference from acyclovir-treated group at the same dose (Student's *t*-test).
[d]Significance in difference from the saline-treated control (χ^2 analysis with Yates' correction).
[e]Significance in difference from acyclovir-treated group at the same dose (χ^2 analysis with Yates' correction).

significantly effective in decreasing the mortality and increasing the mean survival time, and most of the infected mice receiving 100 mg of brovavir per kg survived. In contrast, acyclovir showed only marginal effects. Survival rates of brovavir-treated mice were higher than those of acyclovir-treated mice with statistical significance in comparison of corresponding doses. When mice were infected i.c. with a highly virulent strain, HSV-1 VR-3 strain, efficacies of brovavir were demonstrated by increasing the mean survival time at a dose of 25 or 50 mg/kg twice daily and by increasing both the survival rate and the mean survival time at a dose of 200 mg/kg (Table 2). In this experiment, higher doses of drugs were employed for evaluation of their efficacies than those used against strain WT-51 infections, since a high dose of brovavir was required to demonstrate significant therapeutic effect against HSV-1 VR-3 strain infections (Machida and Sakata, 1984; Machida and Takezawa, 1990). Minimal efficacy of oral treatment with acyclovir was achieved in increasing the mean survival time at a dose of 200 mg/kg. Similar phenomena were observed when drugs were administered i.p. against experimental encephalitis caused by infections with WT-51 and VR-3 strains (Table 3). Intraperitoneal treatment with brovavir at a dose of 50 mg/kg against strain WT-51 infection and that at a dose of 200 mg/kg against strain VR-3 infection resulted in significant increases in both the survival rate and the mean survival time. Acyclovir treatment at 50 mg/kg resulted in only increasing the mean survival time of mice infected with strain WT-51, and

TABLE 2
Effects of oral treatments with brovavir and acyclovir on experimental encephalitis in mice infected with HSV-1 VR-3 strain

Expt.	Treatment[a]		Survivors per total		Mean survival time of mice that died (days ± standard error)	
	Drug	Dose(mg/kg)				
1	None (control)	0	4/21		6.65 ± 0.26	
	Brovavir	25	9/21		9.00 ± 0.84	$P<0.05$[b]
	Brovavir	200	18/21	$P<0.001$[c] ($P<0.01$)[d]	8.00 ± 0.00	$P<0.01$[b]
	Acyclovir	25	7/21		7.14 ± 0.53	
	Acyclovir	200	9/21		7.50 ± 0.42	
2	None (control)	0	0/20		5.25 ± 0.39	
	Brovavir	50	1/20		7.16 ± 0.36	$P<0.01$[b] ($P<0.05$)[e]
	Brovavir	200	6/20	$P<0.05$[c]	7.64 ± 0.43	$P<0.001$[b]
	Acyclovir	50	0/20		5.90 ± 0.38	
	Acyclovir	200	2/21		6.79 ± 0.38	$P<0.01$[b]

[a]Mice were treated with brovavir or acyclovir twice daily for 9 days in expt. 1 or for 7 days in expt. 2. Mice in control group received saline.
[b]Significance in difference from the saline-treated control (Student's *t*-test).
[c]Significance in difference from the saline-treated control (χ^2 analysis with Yates' correction).
[d]Significance in difference from acyclovir-treated group at the same dose (χ^2 analysis with Yates' correction).
[e]Significance in difference from acyclovir-treated group at the same dose (Student's *t*-test).

did not affect survival time of mice infected with strain VR-3. Difference in the mortality of strain WT-51-infected mice treated with brovavir and acyclovir at a dose 50 mg/kg was statistically significant as was in oral treatments. Acyclovir showed toxicity for the infected mice at a dose of 100 mg/kg twice daily. Seven out of the 21 acyclovir-treated mice died on day 2 and day 3 during course of the i.p. treatment probably due to its toxicity.

Effects on systemic infections

Effects of brovavir and acyclovir on systemic (i.p.) infections with HSV-1 were compared. Oral treatment with brovavir was effective against systemic infection with strain WT-51 (Table 4) just as it was against experimental encephalitis. Acyclovir showed marked effects against the systemic infection, in contrast to its lack of effects on experimental encephalitis. Even though both brovavir and acyclovir showed marked efficacies against the systemic infection, oral treatment with acyclovir at doses of 5 and 10 mg/kg significantly reduced the mortality, while the minimum effective dose of brovavir was 15 mg/kg required for statistically significant increase in the survival rate. Brovavir at dose of 5 or 10 mg/kg significantly prolonged the mean survival time, but did not reduce the mortality with statistical significance.

Although there was no statistical significance in differences between the mortalities of two groups receiving acyclovir and brovavir at the same doses, four more

TABLE 3
Effects of i.p. treatments with brovavir and acyclovir on experimental encephalitis in mice infected with HSV-1

Challenge virus strain	Treatment[a]		Survivors per total		Mean survival time of mice that died (days ± standard error)	
	Drug	Dose(mg/kg)				
WT-51	None (control)	0	0/21		5.19 ± 0.34	
	Brovavir	10	1/21		6.25 ± 0.32	$P<0.05$[b]
	Brovavir	50	16/20	$P<0.001$[c] ($P<0.001$)[d]	9.00 ± 1.63	$P<0.01$[b]
	Acyclovir	10	1/20		5.74 ± 0.32	
	Acyclovir	50	1/20		6.58 ± 0.37	$P<0.05$[b]
VR-3	None (control)	0	2/20		5.94 ± 0.37	
	Brovavir	12.5	6/20		7.07 ± 0.67	
	Brovavir	50	7/20		8.08 ± 0.45	$P<0.01$[b] ($P<0.01$)[e]
	Brovavir	200	11/20	$P<0.01$[c]	8.55 ± 0.73	$P<0.01$[b]
	Acyclovir	12.5	2/20		6.11 ± 0.31	
	Acyclovir	50	4/20		6.31 ± 0.37	

[a]Mice were treated with brovavir or acyclovir twice daily for 9 days for strain WT-51 or for 5 days for strain VR-3 infection. Mice in control group received saline.
[b]Significance in difference from the saline-treated control (Student's *t*-test).
[c]Significance in difference from the saline-treated control (χ^2 analysis with Yates' correction).
[d]Significance in difference from acyclovir-treated group at the same dose (χ^2 analysis with Yates' correction).
[e]Significance in difference from acyclovir-treated group at the same dose (Student's *t*-test).

mice in groups receiving acyclovir survived at doses of 10, 15, and 20 mg/kg than in those treated with brovavir at corresponding doses. Oral treatment with acyclovir was also more effective than that with brovavir against systemic infection with strain VR-3 (data not shown). The survival rate of the infected mice receiving 50 mg/kg of acyclovir was significantly higher than that treated with the same dose of brovavir ($P < 0.05$ by χ^2 analysis with Yates' correction). When drugs were administered i.p., survival rates of strain WT-51-infected mice receiving acyclovir were higher than those treated with brovavir (Table 5) as seen in oral administration of drugs, although there was no statistical significance in the difference between acyclovir- and brovavir-treated groups at corresponding doses, either. Acyclovir showed efficacies more significantly than brovavir against systemic infection with strain VR-3. Differences in mortality of the infected mice were statistically significant between acyclovir- and brovavir-treated groups at the same doses.

Discussion

Both i.p. and i.c. model infections with HSV-1 in mice are often used for evaluation of in vivo efficacy of anti-herpesviral drugs. However, there have been some discrepancies in the results on the efficacies of an antiherpesviral drug reported by different researchers even if the same infection and administration routes were

TABLE 4
Effects of oral treatments with brovavir and acyclovir on i.p. infection with HSV-1 WT-51 strain in mice

Expt.	Treatment[a]		Survivors per total		Mean survival time of mice that died (days ± standard error)	
	Drug	Dose (mg/kg)				
1	None (control)	0	2/20		6.78 ± 0.31	
	Brovavir	5	8/20		8.71 ± 0.79	$P<0.05$[b]
	Brovavir	15	14/20	$P<0.001$[c]	8.83 ± 1.65	
	Brovavir	50	19/20	$P<0.001$[c]	12.00 ± 0.00	
	Acyclovir	5	9/20	$P<0.05$[c]	8.14 ± 1.04	
	Acyclovir	15	19/20	$P<0.001$[c]	10.00 ± 0.00	
	Acyclovir	50	20/20	$P<0.001$[c]		
2	None (control)	0	2/19		5.65 ± 1.17	
	Brovavir	10	8/19		6.73 ± 1.56	$P<0.05$[b]
	Brovavir	20	13/19	$P<0.001$[c]	8.50 ± 1.22	$P<0.001$[b]
	Brovavir	50	18/19	$P<0.001$[c]	10.00 ± 0.00	
	Acyclovir	10	12/19	$P<0.01$[c]	7.71 ± 0.95	$P<0.001$[b]
	Acyclovir	20	17/19	$P<0.001$[c]	8.50 ± 0.00	
	Acyclovir	50	19/19	$P<0.001$[c]		

[a]Mice were treated with brovavir or acyclovir twice daily for 8 days. Mice in control group received saline.
[b]Significance in difference from the saline-treated control (Student's *t*-test).
[c]Significance in difference from the saline-treated control (χ^2 analysis with Yates' correction).

used. For example, some investigators showed significant effects of acyclovir against experimental encephalitis in mice caused by HSV-1 infection (Cho and Feng, 1980; Park et al., 1979; Reefschlaeger et al., 1986), but we observed no therapeutic effect of acyclovir treatment of i.c. infection with HSV-1 VR-3 strain (Machida et al., 1985). We also recently showed that brovavir exhibited significant efficacy against strain WT-51 infections, while it was less effective against strain VR-3 infections, suggesting that the difference in the observed potency of brovavir was related to differences in virulence of the two strains (Machida and Takezawa, 1990). Therefore, antiviral drugs can be compared for their potencies only under the same experimental conditions of challenge virus strain, dose level of challenge virus, and drug treatment schedule as well as infection and administration routes.

In the present study, the potencies of brovavir and acyclovir were directly compared in mouse model infections. Marked effects of brovavir were observed in both experimental encephalitis and systemic infection when mice were inoculated with HSV-1 WT-51 strain. Against HSV-1 VR-3 strain infections, brovavir was also effective, although a much higher dose was required. Only marginal effects of oral and i.p. treatments with acyclovir, in contrast, were achieved against experimental encephalitis. Survival rates of strain WT-51-infected mice treated with brovavir were higher than those receiving acyclovir with statistical significance in comparison of corresponding doses. However, our findings were different from those reported by Park et al. (1979) showing that acyclovir treatment led to a significant increase in the survival rate of mice infected i.c. with HSV-1 Mc Krae strain. Although Reefschlaeger et al. (1986) showed that brovavir led reduction of mortality of mice i.c. infected with HSV-1 strain Kupka with higher

TABLE 5
Effects of i.p. treatments with brovavir and acyclovir on i.p. infection with HSV-1 in mice

Challenge virus strain	Treatment[a]		Survivors per total		Mean survival time of mice that died (days ± standard error)	
	Drug	Dose(mg/kg)				
WT-51	None (control)	0	3/19		6.38 ± 0.40	
	Brovavir	12.5	8/19		7.45 ± 0.37	
	Brovavir	50	11/19	$P<0.05$[b]	7.75 ± 0.53	
	Acyclovir	12.5	13/19	$P<0.01$[b]	7.50 ± 0.92	
	Acyclovir	50	16/19	$P<0.001$[b]	11.67 ± 2.03	$P<0.001$[c] ($P<0.05$)[d]
VR-3	None (control)	0	0/21		6.10 ± 0.24	
	Brovavir	12.5	1/21		7.37 ± 0.33	$P<0.01$[c]
	Brovavir	50	3/21		7.39 ± 0.49	$P<0.05$[c]
	Brovavir	200	12/21	$P<0.001$[b]	8.00 ± 0.87	
	Acyclovir	12.5	7/20	$P<0.05$[b] ($P<0.05$)[e]	8.38 ± 0.46	$P<0.001$[c]
	Acyclovir	50	20/20	$P<0.001$[b] ($P<0.001$)[e]		

[a]Mice were treated with brovavir or acyclovir twice daily for 7 days. Mice in control group received saline.
[b]Significance in difference from the saline-treated control (χ^2 analysis with Yates' correction).
[c]Significance in difference from the saline-treated control (Student's t-test).
[d]Significance in difference from brovavir-treated group at the same dose (Student's t-test).
[e]Significance in difference from brovavir-treated group at the same dose (χ^2 analysis with Yates' correction).

rate than did acyclovir, they also found that effect of brovavir in reducing mortality was comparable to that acyclovir against i.c. infection with HSV-1 strain 64.

On the other hand, acyclovir was significantly effective in reducing the mortality of mice systemically infected with either strain WT-51 or strain VR-3. The efficacies of acyclovir seem to be more marked than those of brovavir against these i.p. infections. Especially, superiority of acyclovir to brovavir was found in the efficacy in reducing mortality of strain VR-3-infected mice with statistical significance. Kern et al. (1982, 1986) found that i.p. treatment with acyclovir was effective against fatal i.p. and intranasal infections with herpes simplex virus type 2 (HSV-2), but showed only its marginal effect, if any, against i.c. infections with HSV-1 and HSV-2 in weanling mice. Similarly, Schinazi et al. (1983) failed to demonstrate a therapeutic effect of acyclovir alone against i.c. infection with HSV-2. The reason why acyclovir is markedly effective against i.p. infection, but poorly effective against experimental encephalitis is not known. One possible reason is the organ distribution or affinity to organs characteristic of the drug. Drug delivery to central nervous system organs may play an important role for expression of efficacy against encephalitis.

Since brovavir showed marked effects on experimental encephalitis in contrast to acyclovir, clinical application of brovavir for treatment of encephalitis can be also expected, as well as that for therapy of herpes zoster because of its potent

activities against VZV in vitro (Machida, 1986) and simian varicella infection in monkeys (Soike et al., 1984).

Acknowledgements

We gratefully thank Dr A.K. Field, The Squibb Institute for Medical Research, Princeton, N.J., for giving valuable comments and critical reading of the manuscript.

References

Cho, C.T. and Feng, K.K. (1980) Combined effects of acyloguanosine and humoral antibodies in experimental encephalitis due to *Herpesvirus hominis*. J. Infect. Dis. 142, 451.

Kern, E.R., Richards, J.T., Glasgow, L.A., Overall, Jr., J.C. and De Miranda, P. (1982) Optimal treatment of herpes simplex encephalitis in mice with oral acyclovir. Am. J. Med. 73, 1A, 125–131.

Kern, E.R., Richards, J.T. and Overall, Jr., J.C. (1986) Acyclovir treatment of disseminated herpes simplex virus type 2 infection in weanling mice, alteration of mortality and pathogenesis. Antiviral Res. 6, 189–195.

Machida, H. (1986) Comparison of susceptibilities of varicella-zoster virus and herpes simplex viruses to nucleoside analogs. Antimicrob. Agents Chemother. 29, 524–526.

Machida, H., Abiru, T. and Ikeda, T. (1985) Selective anti-herpesvirus activity of BV-araU, In: J. Ishigami (Ed.), Recent Advances in Chemotherapy, pp. 1959–1960. University of Tokyo Press, Tokyo.

Machida, H. and Sakata, S. (1984) In vitro and in vivo antiviral activity of 1-β-D-arabinofuranosyl-*E*-5-(2-bromovinyl)-uracil (BV-araU) and related compounds. Antiviral Res. 4, 135–141.

Machida, H., Sakata, S., Kuninaka, A. and Yoshino, H. (1981) Antiherpesviral and anticellular effects of 1-β-D-arabinofuranosyl-*E*-5-(2-halogenovinyl)uracils. Antimicrob. Agents Chemother. 20, 47–52.

Machida, H. and Takezawa, J. (1990) Effect of 1-β-D-arabinofuranosyl-*E*-5-(2-bromovinyl)uracil (brovavir) on experimental infections in mice with of herpes simplex virus type 1 strains of different degrees of virulence. Antimicrob. Agents Chemother. 34, in press.

Park, N.-H., Pavan-Langston, D., McLean, S.L. and Albert, D.M. (1979) Therapy of experimental herpes simplex encephalitis with aciclovir in mice. Antimicrob. Agents Chemother. 15, 775–779.

Reefschlaeger, J., Wutzler, P., Thiel, K.-D. and Herrmann, G. (1986) Treatment of experimental herpes simplex virus type 1 encephalitis in mice with (*E*)-5-(2-bromovinyl)- and 5-vinyl-1-β-D-arabinofuranosyluracil: comparison with bromovinyldeoxyuridine and acyclovir. Antiviral Res. 6, 83–93.

Schinazi, R.F., Peters, J., Sokol, M.K. and Nahmias, A.J. (1983) Therapeutic activities of 1-(2-fluoro-2-deoxy-β-D-arabinofuranosyl)-5-iodocytosine and -thymine alone and in combination with acyclovir and vidarabine in mice infected intracerebrally with herpes simplex virus. Antimicrob. Agents Chemother. 24, 95–103.

Soike, K. F., Baskin, G., Cantrell, C. and Gerone, P. (1984) Investigation of antiviral activity of 1-β-D-arabinofuranosylthymine (ara-T) and 1-β-D-arabinofuranosyl-*E*-5-(2-bromovinyl)uracil (BV-ara-U) in monkeys infected with simian varicella virus. Antiviral Res. 4, 245–257.