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# Comparative efficacy of three 2′-fluoropyrimidine nucleosides and 9-(1,3-dihydroxy-2-propoxymethyl)guanine (BW B759U) against pseudorabies and equine rhinopneumonitis virus infection in vitro and in laboratory animals

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**Summary**

The three 2′-fluoropyrimidine nucleosides 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine (FIAC), 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodouracil (FIAU), and 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-methyluracil (FMAU), showed high activity in $RK_{13}$ monolayers against equine rhinopneumonitis virus, (EHV-1, $IC_{50}$ range 0.02–0.18 μM), Aujeszky's disease virus (SHV-1, pseudorabies, $IC_{50}$ range 0.25–7 μM) and infectious bovine rhinotracheitis virus (1BR, BHV-1, $IC_{50}$ range 0.1–3 μM). The activity of these compounds was compared with 9-(1,3-dihydroxy-2-propoxymethyl)guanine (BW B759U, DHPG) in two laboratory animal disease models: EHV-1-induced hepatitis in hamsters and SHV-1-induced encephalitis in mice. All the compounds, provided from 3 to 5 h pre-infection for 5 days, were effective in preventing EHV-1 mortality (at 3–5 mg/kg per day) and in significantly reducing SHV-1 mortality (at 60 mg/kg per day). While FIAU had the greatest activity in vitro, FMAU tended to be more potent in vivo. The reasons for these differences between relative in vitro and in vivo activities are briefly discussed.

antiviral chemotherapy; EHV-1; SHV-1; nucleoside analogues; disease models; veterinary

## Introduction

The three 2′-fluoropyrimidine nucleosides evaluated herein: FIAC (1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine), its deamination product, FIAU (1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodouracil), and its thymine analogue, FMAU (1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-methyluracil), together with the acyclic nucleoside analogue and acyclovir congener, BW B759U (9-(1,3-dihydroxy-2-propoxymethyl)guanine), also known as DHPG, BIOLF-62 or 2′-NDG, have variously shown potent activity, both in cell culture and in animal models, against the herpes viruses of man: herpes simplex virus (HSV) types 1 and 2 [2,10,14,18,24], cytomegalovirus [1,4,7,11,20,21], Epstein-Barr and varicella-zoster viruses [2]. While FIAC and FMAU were shown to be active in vitro against oncogenic turkey herpes virus, Marek's disease virus (MDV) [17], there do not appear to be any other reports of the activity of the fluoronucleosides against viruses of veterinary importance. On the other hand, BW B759U has shown activity in vitro against equid herpesvirus 1 (EHV-1, equine rhinopneumonitis, equine abortion), equine coital exanthema virus (EHV-3), suid herpesvirus 1 (SHV-1, pseudorabies virus, Aujeszky's disease virus) and feline rhinotracheitis virus (FHV-1) [23], and in vivo, in laboratory animal models, high efficacy was demonstrated against EHV-1 and some activity against SHV-1 [16].

Preliminary in vitro studies with the fluoronucleosides indicated high activity against both EHV-1 and SHV-1, and it was considered of interest to evaluate these compounds in vivo. This report presents data, therefore, on the efficacy of FIAC, FMAU and FIAU, in comparison with BW B759U, in two small animal disease models: EHV-1 infection in Syrian hamsters and SHV-1 infection in mice. Tissue culture studies are also reported.

## Materials and Methods

*Compounds*

BW B759U was synthesised and provided by L. Beauchamp, Burroughs Wellcome Co. Ltd., U.S.A, while FIAC, FMAU, and FIAU were the kind gifts of Dr. Colin McLaren, Bristol-Myers Co., Syracuse, NY, U.S.A. Compounds were dissolved in tissue culture medium for in vitro work, and in sterile distilled water for animal studies.

*In vitro studies*

The 50% inhibitory concentrations ($IC_{50}$) of the compounds were obtained by the method of plaque reduction. Rabbit kidney ($RK_{13}$) monolayers in triplicate 60mm dishes were infected with 100–200 plaque-forming units (PFU) of virus in 0.1 $cm^3$ phosphate buffered saline and allowed to adsorb for 1 h before removal and overlay with a mixture of equal parts of double strength maintenance medium and 1% agarose incorporating the drug in doubling dilutions at 5 concentrations. Monolayers were incubated in 5% $CO_2$/air at 37°C and fixed and stained 3 (SHV-

1) or 4 (EHV-1) days later. The $IC_{50}$ values were obtained by linear regression from the dose-response lines obtained by plotting the percent control PFU against $\log_{10}$ compound concentration.

*Viruses*

SHV-1 ref. no. 80/14781 Norwich, obtained courtesy Sheila Cartwright (Central Veterinary Laboratory, Weybridge, U.K.) and EHV-1 Pneumabort vaccine strain (batch 96HLO52975) from Fort Dodge Laboratories, Iowa, were used in animal studies. In addition, for in vitro work, a further field isolate of SHV-1 was used as well as the Rac-H (subtype 1) and H-45 (subtype 2) strains of EHV-1, the latter two obtained courtesy J.A. Mumford (Equine Virology Unit, Newmarket, U.K.).

Virus suspensions were prepared from the supernatant fluid of infected monolayers, harvested at 80% cytopathic effect (CPE) and stored in suitable aliquots at −70°C.

*Animals and Infection*

Weanling male WO/CR Syrian hamsters, obtained from Wrights, Essex, U.K., were caged in groups of 5, and infected subcutaneously in the right flank with 0.2 $cm^3$ inoculum containing approx. $10^6$ PFU EHV-1. Hamsters weighed about 60 g at the time of infection. The primary pathological lesion in this model is one of hepatitis, leading to death in 3–6 days post-inoculation.

Outbred MF1 male mice, 20–25 g, were supplied by Olac, Bedfordshire, U.K., and caged in groups of 10. For infection, mice were anaesthetised with Nembutal (sodium pentobarbitone, 60 mg/kg intraperitoneally), laid dorsally and 25 μl inoculum was dropped onto the nares and allowed to be inhaled passively. Each mouse received approx. $10^3$ PFU SHV-1. Characteristic clinical signs develop from 72 h post-infection, and include salivation and pruritis, with rapidly ensuing death from encephalitis. Animals were provided with food and water ad libitum.

*Medication*

Intraperitoneal (ip) treatment was in divided, twice daily doses, 8 h apart, commencing 3 h pre-infection and continuing for 5 days.

Per os (po) treatment was via medicated drinking water, provided ad libitum from 5 h pre-infection for 5 days. The mean dose rates quoted were calculated from group water consumption measured over days −3 to 0 and day 0 group liveweight, and thus represent the initial intake of drug.

Details of the experimental designs are given in Table 2. Three experiments were conducted: a comparison of FIAC, FMAU and BW B759U, and then FIAU and BW B759U, in the EHV-1/hamster model, and a comparison of the three fluoronucleosides in the SHV-1/mouse model.

*Sampling and observations*

Individual liveweights, group water consumption and mortality were recorded at appropriate intervals. Moribund hamsters and mice were killed, and hamsters examined post-mortem to confirm that hepatitis was present. Grossly, affected ham-

ster livers were of lighter colour than normal and had a finely stippled appearance. Small necrotic foci were evident in most cases [6]. Inocula were titrated in $RK_{13}$ monolayers.

*Statistical analyses*

Differences in total mortalities were evaluated using Fisher's exact test, so enabling pairwise comparisons between groups. Since a full factorial design was adopted for the first experiment, mortalities were additionally analysed on a probit scale using the GLIM (generalised linear interactive modelling) statistical package to test for main effects and interactions between these factors. The number of days to death was examined by a log rank method: this examines for each period (day) the discrepancies between the observed group mortalities and those expected, based on the total number of deaths within the period and the number at risk within each group at the start of the period, and pools this information over all days. This analysis was restricted to comparisons between compounds, between doses and between routes, as appropriate. Duncan's multiple comparison test was applied to the group mean liveweight data.

## Results

*Plaque reduction assays*

The range of in vitro activities recorded in $RK_{13}$ cells is given in Table 1. The compounds may be ranked in order of decreasing activity: thus,
versus EHV-1 Subtype 1 FIAU > FMAU = FIAC > BW B759U
versus EHV-1 Subtype 2 FIAU > FMAU > BW B759U > FIAC
versus SHV-1 (2 strains) FIAU > FMAU > FIAC > BW B759U
versus BHV-1 (3 strains) FMAU > FIAU > FIAC >> BW B759U.

*EHV-1/hamsters*

Mortality data are given in Table 2. FIAC, FMAU, FIAU and BW B759U all prevented any virus-induced mortality when provided in drinking water from 5 h

TABLE 1

In vitro activities ($IC_{50}$ values, μM, in $RK_{13}$ cells) of BWB759U, FIAC, FMAU and FIAU against viruses of veterinary importance

| Virus/strain | Compound | | | |
|---|---|---|---|---|
| | BW B759U | FIAC | FMAU | FIAU |
| EHV-1 Rac-H | ≤0.39 | 0.09 | 0.09 | 0.02 |
| EHV-1 H-45 | 0.09 | 0.18 | 0.08 | ≤0.015 |
| SHV-1 Norwich | 35.6 | 4.2 | 0.6 | 0.25 |
| SHV-1 UK | ≤50.0 | 7.7 | 0.7 | 0.25 |
| BHV-1 Oxford | 126 | 3.0 | 0.44 | 0.67 |
| BHV-1 78/4242 | 30.0 | 1.4 | 0.11 | 0.27 |
| BHV-1 78/3883 | 37.0 | 1.1 | 0.20 | 0.38 |

TABLE 2

Mortality in EHV-1 infected hamsters

| Compound | Route/dose (mg/kg per day) | Mortality (%)[a] | Mean day of death | No. in Group | Liveweight change (%, days 0 to 4)[b] |
|---|---|---|---|---|---|
| *Experiment 1* | | | | | |
| FIAC | po 3 | 0[a] | | 5 | + 16.5[a] |
| FIAC | po 0.6 | 80[b] | 5.3 | 5 | − 3.6[bcde] |
| FIAC | po 0.12 | 100[b] | 3.8 | 5 | − 6.7[cde] |
| FIAC | ip 3 | 80[b] | 5.3 | 5 | − 0.9[bcde] |
| FIAC | ip 0.6 | 80[b] | 4.3 | 5 | − 7.1[cde] |
| FIAC | ip 0.12 | 40[ab] | 4.0 | 5 | − 4.4[bcde] |
| FMAU | po 3 | 0[a] | | 5 | + 11.1[ab] |
| FMAU | po 0.6 | 0[a] | | 5 | + 6.5[abc] |
| FMAU | po 0.12 | 100[b] | 5.4 | 5 | − 3.1[bcde] |
| FMAU | ip 3 | 20[a] | 6.0 | 5 | + 6.2[abc] |
| FMAU | ip 0.6 | 0[a] | | 5 | + 2.3[abcd] |
| FMAU | ip 0.12 | 80[b] | 4.3 | 5 | − 8.1[cde] |
| BWB759U | po 3 | 0[a] | | 5 | + 1.3[abcd] |
| BWB759U | po 0.6 | 60[b] | 5.7 | 5 | − 3.1[bcde] |
| BWB759U | po 0.12 | 40[ab] | 3.0 | 5 | + 5.4[de] |
| BWB759U | ip 3 | 20[a] | 4.0 | 5 | + 1.0[abcd] |
| BWB759U | ip 0.6 | 40[ab] | 5.5 | 5 | − 3.6[bcde] |
| BWB759U | ip 0.12 | 20[a] | 6.0 | 5 | − 10.6[e] |
| | UNTREATED/ INFECTED | 100[b] | 4.4 | 5 | − 10.3[de] |
| | UNTREATED/ UNINFECTED | 0[a] | | 5 | + 10.1[ab] |
| *Experiment 2* | | | | | |
| FIAU | po 5 | 0[a] | | 5 | + 9.1[ab] |
| FIAU | ip 5 | 80[b] | 4.5 | 5 | − 8.3[cde] |
| FIAU | po 1 | 60[b] | 5.3 | 5 | + 2.6[abcd] |
| FIAU | ip 1 | 80[b] | 3.0 | 5 | − 8.0[cde] |
| BWB759U | po 1 | 60[b] | 4.7 | 5 | − 8.1[cde] |
| | UNTREATED/ INFECTED | 100[b] | 4.4 | 5 | − 8.1[de] |
| | UNTREATED/ UNINFECTED | | | 5 | + 11.9[ab] |

[a] Mean values showing the same letter are not significantly different using Fisher's exact test ($P<0.05$).
[b] Mean values showing the same letter are not significantly different by Duncan's test ($P<0.05$).

pre-infection at doses of 3, 0.6, 5, and 3 mg/kg per day, respectively ($\bar{x}$ = 9.6, 2d.f., $P<0.05$). Intraperitoneal dosing commencing 3 h pre-infection was less effective in reducing mortality, particularly for FIAC and FIAU. For Expt. 1, there was no dose-related trend in mortality for the ip route ($\bar{x}$ = 0, 1d.f., $P>0.05$), but a marked one for po ($\bar{x}$ = 17.3, 2d.f., $P<0.05$). Similarly, the dose-response relationship was strongest for FMAU ($\bar{x}$ = 13.3, 2d.f., $P<0.05$), whilst for both FIAC and BW B759U, the response at 0.12 mg/kg per day was similar to that at 0.6 mg/kg per day. Regarding mean day of death, significance was demonstrated both for compounds ($\bar{x}$ = 8.03, $P<0.05$) and doses ($\bar{x}$ = 11.05, $P<0.05$) but not for routes ($\bar{x}$

TABLE 3

Cumulative mortality in SHV-1 infected mice (Expt. 3)

| Compound | Route/dose (mg/kg per day) | Day post-infection | | | | | | | | Total[a] % | Mean day of death |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2 | 3am | 3pm | 4am | 4pm | 5 | 6 | 7+ | | |
| FIAC | ip 60 | 0 | 0 | 0 | 1 | 1 | 2 | 4 | 4 | 40[a] | 5.3 |
| FMAU | ip 60 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 10[a] | 7.0 |
| FIAU | ip 60 | 0 | 1 | 3 | 3 | 3 | 5 | 5 | 5 | 50[a] | 3.8 |
| UNTREATED | - - | 0 | 2 | 8 | 10 | | | | | 100[b] | 3.2 |

[a] Mean values showing the same letter are not significantly different using Fishers exact test ($P<0.05$).

= 0.01, $P>0.05$). In contrast, in Expt. 2, significance in respect of days to death was shown for routes ($\bar{x}$ = 5.21, $P<0.05$) but not doses ($\bar{x}$ = 1.56, $P>0.05$).

Liveweight data are included in Table 2. Untreated, infected control hamsters showed an average weight change of –9.2% over days 0 to 4, and the untreated, uninfected controls +11%. Weight changes for the treated hamsters varied from about equal to or greater than the uninfected controls (+9.1 to 16.5% at 3 or 5 mg/kg per day) to around that of the untreated, infected controls. In general, weight gains were greater in the hamsters on oral medication than those receiving ip treatment. The most marked positive weight changes overall were in the FMAU treatment group, as shown by the Duncan's multiple range test.

*SHV-1/mice*

Treatment with either FIAC, FMAU or FIAU at 60 mg/kg per day ip resulted in a significant reduction in mortality and an increase in survival time compared with the untreated controls (see Table 3). FMAU appeared the most effective overall although differences between compounds were not statistically significant.

## Discussion

The high in vitro activities of the three fluoro-arabinofuranosyl nucleoside analogues, FMAU, FIAU and FIAC, against these two herpes viruses of veterinary importance were reflected in vivo by the laboratory animal disease models described herein. All compounds, with therapy commencing pre-infection, were effective in preventing or reducing EHV-1 and SHV-1 induced mortality in hamsters and mice, respectively, compared with the untreated, infected controls. Overall, FMAU performed marginally better than BW B759U in the EHV-1/hamster model. Although the latter compound was not included in Expt. 3, the SHV-1/mouse model, it has proved slightly less effective than FMAU in this disease model, with mortality of 20% at 60 mg/kg per day ip (E.A. Rollinson, unpublished observations). Superior activity of FMAU over BW B759U has been reported also for herpes simplex virus 1 (HSV-1) induced encephalitis, following peripheral inoculation, in mice [11].

When comparing the relative order of activity in vivo and in vitro for these com-

pounds, certain anomalies are apparent. While FIAU had the greatest activity in vitro in $RK_{13}$ cells, FMAU tended to be more potent in vivo in hamsters or mice. FIAC was the least active in $RK_{13}$ cells against EHV-1, subtype 1, but was slightly more active than FIAU in mice against SHV-1. Such differences between in vitro and in vivo potencies have been reported previously for BW B759U, bromovinyldeoxyuridine (BVDU) and acyclovir (ACV) in a murine ear flap model of SHV-1 [8] and in HSV-1 encephalitis in mice [9].

When attempting to explain the relative activities of these compounds in vitro and in vivo, a number of factors should be considered, from the cellular, enzymatic level to the whole animal, pharmacological level. The species from which the cell line used was derived may have a profound effect on the antiviral activity recorded. For example, it has been shown, in the case of activity against Marek's disease virus (MDV), that conversion of FIAC to FIAU, by a deoxycytidine-deaminase enzyme, is an important first step for antiviral action [17]. The lower activity of FIAC compared with FIAU in $RK_{13}$ monolayers reported herein may reflect relatively low levels of the dCyt-deaminase enzyme in this cell line. The lack of activity of FIAC against MDV in chick embryo fibroblasts (CEF) was attributed to the fact that this cell line lacks the dCyt-deaminase enzyme. In chick kidney cell (CKC) cultures, which possess the enzyme, FIAU and FIAC were equally active [17]. Similar arguments regarding enzymes may be applied in vivo.

Because of these variations between cell lines, it is preferable, when making comparisons with the in vivo situation, that the in vitro studies have been undertaken in a cell line homologous with the animal disease model in question. Unfortunately, no data are available on the activities of the 2-fluoronucleosides against EHV-1 in hamster cells and against SHV-1 in murine cells. However, it has been shown that BW B759U was more active (x13) against SHV-1 in mouse embryo fibroblasts than in a hamster cell line (BHK-21) [8], and more active (x20) against EHV-1 in BHK-21 than in $RK_{13}$ cells (E.A. Rollinson, unpublished observations).

BW B759U, FMAU and FIAU are all selectively phosphorylated to the monophosphate by a virus-coded thymidine kinase [3,13]. Subsequent phosphorylation to the triphosphate is achieved via cellular enzymes, and it is the triphosphate which selectively inhibits the viral DNA polymerase and/or becomes incorporated into DNA. Smee and coworkers [22] reported that BW B759U triphosphate breaks down at a slower rate than acyclovir triphosphate when drug is removed from infected cultures. No data are available on the relative degradation rates of the triphosphates of FIAC, FIAU and FMAU, but such differences could have implications for their antiviral effects in vivo following decline of drug concentrations in the blood.

Of possible greater significance in respect of antiviral effect in vivo may be the pharmacokinetic behaviour of the compounds per se. Certainly in mice, following intraperitoneal injection, concentrations of FMAU in brain were some 2–4 times greater than for FIAC [19]. Other studies [10] have shown a similar relationship following oral dosing with FIAC and FMAU in mice and rats. Moreover, FMAU has a longer half-life in the mouse than does FIAC [10] and FIAC is reported to be rapidly metabolised [12,13]. No data have been published on bioavailability of

FIAC or FMAU in hamsters, and there do not appear to be any data on FIAU in mice or hamsters. However, in hamsters, all the compounds were more effective following oral dosing compared with the ip route, probably reflecting that more constant serum concentrations of the drug are maintained with ad libitum medication. In contrast, in the SHV-1/mouse model, oral dosing with BW B759U has always proved less effective than ip (E.A. Rollinson, unpublised observations), corroborating the report that this compound is poorly absorbed from the murine gut [7].

In the absence of a suitable small animal model for IBR (BHV-1) and given the limited supply of drug, the compounds were not assessed for in vivo efficacy against the bovine virus. However, the high in vitro activity of FIAC, FMAU and FIAU against BHV-1 suggests that it would be worthwhile to evaluate them in cattle against rhinotracheitis.

Although a number of antiviral agents has been tested for activity against viruses of domestic animals, none has yet been registered for veterinary use (for review, see ref. 15). There is, nevertheless, a need for effective prophylaxis/therapy of virus disease in farm and companion animals, particularly where vaccines do not exist or do not provide adequate or enduring immunity. The results presented here indicate that the 2′-fluoronucleoside analogues and BW B759U are worthy of further investigation in target species, viz. against rhinopneumonitis in horses and Aujeszky's disease in pigs.

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