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Efficacy of bromovinyldeoxyuridine in the treatment of herpes simplex virus and varicella-zoster virus eye infections*

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Summary

As has been established in rabbits, (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU) is superior to 5-iodo-2′-deoxyuridine (IDU) in the topical treatment of epithelial HSV-1 (herpes simplex virus type 1) keratitis, and superior to 5-trifluoromethyl-2′-deoxyuridine (TFT) in the topical treatment of deep stromal HSV-1 keratitis and HSV-1 uveitis. BVDU 0.1% eye drops have also proven efficacious in the treatment of patients with dendritic corneal ulcers, geographic corneal ulcers and stromal keratitis, and combined treatment of BVDU 0.1% eye drops with oral BVDU at 375 mg/day for 5 days led to a prompt healing of keratouveitis and skin lesions in patients with ophthalmic herpes zoster.

bromovinyldeoxyuridine; herpetic keratitis; ophthalmic zoster

Introduction

Bromovinyldeoxyuridine [(*E*)-5-(2-bromovinyl)-2′-deoxyuridine, BVDU] is structurally related to the classical antiherpes drugs idoxuridine (5-iodo-2′-deoxyuridine, IDU) and trifluridine (5-trifluoromethyl-2′-deoxyuridine, TFT), in that they are all 5-substituted analogues of 2′-deoxythymidine (dThd), de natural precursor of DNA synthesis.

BVDU is a highly potent and selective antiherpes agent. In cell culture, it exceeds various other antiherpes compounds, i.e., IDU, TFT, foscarnet (phosphonoformate),

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vidarabine (9-β-D-arabinofuranosyladenine, ara-A, Vira-A) and acyclovir [9-(2-hydroxyethoxymethyl)guanine, acycloguanosine] in potency or selectivity, or both [1–3]. As compared to IDU, BVDU proved about 20 times more active against herpes simplex virus type 1 (HSV-1) (strain KOS) and 60 times less toxic (as monitored by the inhibition of 2′-deoxyuridine incorporation into host cell DNA).

BVDU inhibits the replication of HSV-1 [1–3] and varicella-zoster virus (VZV) [4,5] in vitro, at a concentration of 0.002–0.01 μg/ml. To affect normal cell metabolism concentrations up to 50–100 μg/ml are required. The selective antiherpes action of BVDU is primarily dependent on a specific phosphorylation of the compound by the HSV-1- and VZV-encoded dThd kinase [6,7]. Once it has been converted to its 5′-triphosphate form, BVDU competitively inhibits the utilization of dTTP by DNA polymerases; BVDU 5′-triphosphate (BVDUTP) has a greater affinity for the HSV-1 DNA polymerase than for the cellular DNA polymerases α, β and γ [8]. Moreover, BVDUTP can serve as an alternate substrate of DNA polymerase [9] and be incorporated as BVDU 5′-monophosphate into viral DNA [10]. The amount of BVDU incorporated into viral DNA is closely correlated with the extent of virus yield reduction [10]. BVDU is less active against herpes simplex virus type 2 (HSV-2), because the HSV-2-encoded dThd kinase is less efficient in phosphorylating BVDU [7,11]. In particular, the conversion of BVDU 5′-monophosphate to 5′-diphosphate is hampered in HSV-2-infected cells. BVDU is also less effective or ineffective against HSV mutants which are deficient in dThd kinase induction.

In this report we summarize our findings with BVDU in the treatment of experimental and clinical herpes simplex eye diseases and ophthalmic herpes zoster.

Experimental studies

Epithelial keratitis

In a first set of experiments, treatment of HSV-1-infected rabbit eyes with 0.5% BVDU ointment and 0.5% IDU ointment was initiated immediately after keratitis began to develop [12]. The BVDU and IDU ointments were applied 5 times a day for 5 days. Both BVDU and IDU suppressed the development of keratitis, and although 0.5% BVDU ointment was more effective than 0.5% IDU ointment, this difference was not significant. However, in another experiment 0.5% BVDU ointment proved significantly superior to 0.5% IDU ointment in promoting healing of HSV-1 keratitis which was already established at the time treatment was started [12]. In further double-blind randomized trials in rabbits we compared the efficacy of (i) 0.1% and 2.5% BVDU ointments, (ii) 0.1% BVDU, 0.1% IDU and 0.5% IDU ointments, and (iii) 0.1% BVDU and 0.1% IDU eye drops, in the treatment of established HSV-1 epithelial keratitis. These trials revealed that both IDU and BVDU, whether applied as eye drops or ointment, brought about a significant reduction in the severity of keratitis, and that, in this respect, BVDU was superior to IDU [13]. The 2.5% BVDU ointment was somewhat more effective than the 0.1% BVDU ointment but not to a significant extent. As compared to 0.5% IDU ointment, 0.1% BVDU eye ointment caused a significantly greater healing. 0.1% BVDU ointment was superior to 0.1%

IDU ointment, but this difference was not statistically significant. In all these experiments the ointments were applied 5 times a day at 2 h intervals. When IDU and BVDU were applied as a 0.1% ophthalmic solution, one drop every hour 9 times a day, BVDU was significantly more effective than IDU in promoting healing of established HSV-1 keratitis in rabbits [13].

Stromal keratitis

Stromal keratitis was produced by inoculation of HSV-1 into the central cornea of rabbits. In these experiments TFT instead of IDU was used as the reference compound. Both 0.1% and 0.5% BVDU eye drops and 1% TFT eye drops, applied to the eyes from day 1 to day 6 post-infection (p.i.), significantly suppressed the development of deep stromal keratitis. At both concentrations BVDU was significantly better than TFT in suppressing stromal disease. However, if treatment was initiated on day 7 p.i., BVDU and TFT still effected a significant healing as compared with placebo, but, under these conditions, BVDU was not better than TFT [14].

Keratouveitis

BVDU and TFT have also been compared for their efficacy in the treatment of keratouveitis produced by inoculation of HSV-1 into the anterior chamber of rabbit eyes [15]. In this model keratitis developed as the consequence of endothelium damage by the virus. Treatment with 0.5% BVDU eye drops and 1% TFT eye drops, from day 1 to day 7 p.i., significantly suppressed the development of keratitis. Again, the effect of BVDU was significantly better than that of TFT. Similarly, 1% TFT and 0.5% BVDU eye drops promoted the healing of iritis, and, in this respect, 0.5% BVDU eye drops proved significantly more efficacious than 1% TFT eye drops.

We also attempted to treat HSV-1 iritis in rabbits with oral BVDU administered at 10 mg/kg/day and 100 mg/kg/day for 4 days. Both dosage regimens were equally effective in reducing the severity of iritis. If betamethasone was administered concurrently by subconjunctival injection, there was no synergistic effect with BVDU on the severity of iritis, although betamethasone initially caused a reduction in the iritis scores [15].

Clinical studies

Our initial studies have shown that BVDU is a safe and effective compound for the topical treatment of herpes simplex virus keratitis in patients [16,17]. We shall now describe our further observations during a 15 month follow-up period (Tables 1–5). In addition, we will also review the results obtained with oral BVDU in the treatment of ophthalmic herpes zoster [18] (Table 6).

Dendritic keratitis

BVDU (as 0.1% eye drops) was administered 9 times a day at 1-h intervals to 48 patients who presented with dendritic keratitis (Table 1). About half of them (28 patients: Table 2) had not healed following treatment with other antiviral compounds

TABLE I

Follow-up of herpes simplex keratitis during an average of 15 months

Keratitis	No. of patients	Average healing time on BVDU treatment (days)	Complications[a]	Recurrences[a]
Dendritic ulcers	48[b]	7.9	Corticosteroid dependence (5) Dry eye (3) Bullous keratopathy (2) Lower canaliculitis (1)	After 6 months (2) After 5 and 15 months (1)
Geographic ulcers	15	12.2	Corticosteroid dependence (3) Bullous keratopathy (2) Aseptic epithelium defect (1) Dry eye (1)	After 4 months (1) After 8 months (1)
Stromal	18[c]	39.8	Corticosteroid dependence (10) Dry eye (2) BVDU allergy (1)	After 5 weeks (1) After 6 days dendritic ulcer (1) After 1 month severe iritis (1)

[a] No. of cases in parentheses.
[b] 2 patients were lost to follow-up.
[c] 1 patient lost to follow-up.

TABLE 2

Analysis of data on patients clinically resistant to other antiviral drugs

Keratitis	Antiviral agent used before	No. of patients[a]	Average healing time on BVDU therapy (days)
Dendritic keratitis	IDU	21	8.8[b]
	TFT	7 (2 patients also resistant to IDU)	9.1[b]
	Vira-A	1 (also resistant to IDU)	5
Geographic ulcers	IDU	10	10.4
	TFT	4 (2 patients also resistant to IDU)	13
	Vira-A	3 (also resistant to IDU)	11.3
Stromal keratitis	IDU	11	35.6[b]
	TFT	5 (3 patients also resistant to IDU)	37.4
	Vira-A	0	

[a] Patients clinically resistant to more than one antiviral drug were counted separately for each drug.
[b] 1 patient lost to follow-up.

(IDU, TFT or Vira-A) for at least 10 days. In this group, 33 patients had associated stromal disease, and 12 had keratic precipitates. Sixteen patients were using topical corticosteroids together with the antiviral medication. Two patients were taking oral prednisolone after a kidney transplantation. Two patients were lost to follow-up. The remaining patients healed within an average period of 7.9 days (Table 1). Upon BVDU treatment the patients which were clinically resistant to IDU, TFT and Vira-A healed within 8.8, 9.1 and 5 days, respectively (Table 2). In all patients concurrent topical corticosteroid therapy was terminated when BVDU treatment was begun. Corticosteroids were given again only if the associated stromal disease worsened. Of the 46 patients followed up for 15 months, 5 patients developed corticosteroid dependence. Other complications observed were bullous keratopathy (2 patients), dry eye (3 patients) and canaliculitis (1 patient) (Table 1).

In 35 patients the duration of the acute keratitis episode before BVDU therapy was started was 1 month or less (average 10.9 days), and in these patients the average healing time on BVDU therapy was 7.8 days (Table 3). Of the 11 patients with disease continuing for more than 1 month but less than 1 year (average: 2.9 months), the average healing time on BVDU therapy was 19 days. The remaining patient who had had recurrent dendritic keratitis episodes for 1.5 years, without actually becoming free of symptoms, showed resolution of his disease in 12 days (Table 3). Dendritic keratitis recurred in 2 patients after 6 months and in one patient twice after 5 and 15 months (in total 3 out of 47 patients (6%)). Prior to BVDU treatment, 20 patients (43%) had experienced recurrences (Table 3). The recurrences responded to BVDU treatment as swiftly as the initial episodes.

TABLE 3

Topical BVDU treatment in patients with dendritic corneal ulcers

Treatment regimen: BVDU 0.1% eye drops 5–9 × per day, up to 3 weeks

Number of patients: 48 (2 lost to follow-up)

Number of patients with *clinical resistance to IDU, TFT and/or Vira-A*: 29

Average *duration of symptoms* before BVDU treatment *versus healing time* on BVDU therapy:

Duration of symptoms		Average healing time	No. of patients
Total period	Average		
< 1 month	10.9 days	7.8 days	35
1 month–1 year	2.9 months	19 days	11
> 1 year	1.5 years	12 days	1

Recurrences before BVDU treatment: 20 patients (43%)

Recurrences after BVDU treatment: 3 patients (6%)

Geographic corneal ulcers

A total number of 15 patients presented with geographic corneal ulcers (Table 1). Associated stromal keratitis was present in all patients, and 8 patients had keratic precipitates. Except for 3 patients, all others had been using other antiviral drugs (IDU, TFT or Vira-A) when they first presented in the clinic (Table 2). Eight patients were also using topical corticosteroids. BVDU treatment (0.1% eye drops) caused healing of the geographic corneal ulcers within an average period of 12.2 days (Table 1). Patients which were clinically resistant to IDU, TFT or Vira-A healed within 10.4, 13 and 11.3 days, respectively, after BVDU treatment was begun (Table 2). Of the 15 patients, three became corticosteroid dependent, one patient developed an aseptic epithelium defect and bullous keratopathy appeared in two other patients. Dry eye was seen in one case (Table 1).

In 9 of the 15 patients with geographic corneal ulcers the duration of the acute episode prior to BVDU treatment was 1 month or less (average: 14.2 days), and in these patients the average healing time on BVDU therapy was 11.5 days (Table 4). In the remaining 6 patients the duration of the acute episode was 1 month or more (average: 5.7 months), and in these patients the healing time averaged 13.2 days (Table 4). In 2 of the 15 patients (13%) the keratitis recurred, in one patient after 4 months and in the other patient after 8 months. Prior to BVDU treatment, 6 patients (40%) had experienced recurrences (Table 4).

Stromal keratitis

A total number of 18 patients of stromal disease were submitted to topical BVDU therapy (0.1% eye drops) (Table 1). These patients did not have any epithelial ulcers. Except for 4 patients, all others had been using either IDU or TFT at the time they

TABLE 4

Topical BVDU treatment in patients with geographic corneal ulcers

Treatment regimen: BVDU 0.1% eye drops 5–9 × per day, up to 3 weeks

Number of patients: 15

Number of patients with *clinical resistance to IDU, TFT and/or Vira-A*: 12

Average *duration of symptoms* before BVDU treatment *versus healing time* on BVDU therapy:

Duration of symptoms		Average healing time	No. of patients
Total period	Average		
< 1 month	14.2 days	11.5 days	9
> 1 month	5.7 months	13.2 days	6

Recurrences before BVDU treatment: 6 patients (40%)

Recurrences after BVDU treatment: 2 patients (13%)

were switched to BVDU eye drops. With one exception, all of them were also using topical corticosteroids. In all patients corticosteroid therapy was initially stopped and not begun again unless the stromal disease deteriorated. One patient was lost to follow-up. Stromal keratitis became quiescent within an average period of 39.8 days (Table 1). Upon BVDU treatment, the patients who were clinically resistant to IDU or TFT healed within 35.6 and 37.4 days, respectively (Table 2). Ten patients became corticosteroid dependent. Two of them had associated dry eye and one developed contact allergy to BVDU eye drops (Table 1).

In 7 of the 18 patients stromal keratitis had begun 1 month or less (average: 16.7 days) prior to BVDU treatment, and in these patients healing occurred within an average time of 49 days (Table 5). In a further 7 patients the duration of stromal keratitis prior to BVDU treatment was more than 1 month but less than 1 year (average: 3.4 months), and in these patients the healing time averaged 34.8 days. In the remaining 4 patients the stromal disease had persisted for an average of 3.9 years. These patients showed a marked improvement within 22.5 days of BVDU treatment (Table 5). In one of the latter patients the lesions resolved within 16 days of treatment, after the patient had been suffering from stromal disease for 8 years. In one patient stromal keratitis recurred 5 weeks after all medication was terminated. Another patient developed a dendritic ulcer 6 days after terminating therapy. Severe iritis occurred in a third patient 1 month after the stromal disease had healed. Thus, 3 out of 18 patients (17%) showed recurrences after BVDU treatment. This is in marked contrast with the frequency of recurrences before BVDU treatment: 13 patients (72%) (Table 5). All the recurrences, whether epithelial keratitis, stromal keratitis, or iritis, were successfully treated with topical BVDU.

TABLE 5

Topical BVDU treatment in patients with stromal keratitis

Treatment regimen: BVDU 0.1% eye drops 5–9 × per day, up to 6 months

Number of patients: 18 (1 lost to follow-up)

Number of patients with *clinical resistance to IDU and/or TFT*: 13

Average *duration of symptoms* before BVDU treatment *versus healing time* on BVDU therapy:

Duration of symptoms		Average healing time	No. of patients
Total period	Average		
< 1 month	16.7 days	49 days	7
1 month–1 year	3.4 months	34.8 days	7
> 1 year	3.9 years	22.5 days	4

Recurrences before BVDU treatment: 13 patients (72%)

Recurrences after BVDU treatment: 3 patients (17%)

Ophthalmic herpes zoster

Oral BVDU had proved efficacious in the treatment of severe herpes zoster in cancer patients [19]. A similar oral BVDU treatment regimen (3 × 125 mg BVDU per day, for 5 days) combined with 0.1% BVDU eye drops is also efficacious in the management of ophthalmic zoster [18].

We have now treated a total number of 14 ophthalmic herpes zoster patients with oral and topical BVDU combined (Table 6). New skin lesions ceased to appear within 1–2 days after treatment was started. Crust formation began from the second or third day onwards and the skin eruption healed within an average period of 9.29 days. The neuralgic pain subsided briskly (after 2 days) if treatment was started at an early stage of skin eruption. Keratitis subsided within an average time of 10.7 days. Conjunctivitis resolved within 8–12 days. Lower canaliculitis was seen in 2 patients. One patient developed keratitis with internal rectus palsy after 20 days. Complete resolution took place within 1 month upon topical treatment with 0.5% BVDU eye drops. Many of the patients with ophthalmic zoster had associated systemic disease, i.e., hyperthyroidism, hypothyroidism, asthma, myocardial infarction, diabetes mellitus or fatty liver. BVDU therapy was perfectly well tolerated by these patients.

Toxicity

No toxic side effects were noted upon either topical or oral BVDU treatment. Sometimes patients complained of transient stinging upon BVDU instillation into the eye. Only one patient developed a local allergic reaction which could be attributed to topical BVDU therapy. Even when applied as 0.5% eye drops 9 times a day at 1 h intervals, BVDU did not retard the regeneration of rabbit corneal epithelium [20].

TABLE 6

Oral BVDU treatment of patients with ophthalmic zoster

Treatment regimen: oral BVDU at 375 mg/day for 5 days, combined with BVDU 0.1% eye drops

Number of patients: 14

Average *duration of symptoms* before BVDU treatment: 5.5 days

Average *healing time* on BVDU therapy:
- cessation of new lesion formation: within 1–2 days
- crust formation of skin lesions: within 2–3 days
- complete healing of skin lesions: within 6–12 days
- resolution of keratitis: within 8–12 days
- resolution of conjunctivitis: within 8–12 days

Duration of *neuralgia* on BVDU therapy: variable (2 days–4 weeks)

Neither were pathological alterations detected in the cornea by electron microscopy [20].

Following oral BVDU administration, several parameters of toxicity were followed, i.e., whole blood cell counts, blood platelets, urea, creatinine, electrolytes and liver enzymes (SGPT, SGOT and γGT), but none of these parameters was affected by the medication. Hence, BVDU can be considered a safe drug when used topically, i.e., as 0.1% or 0.5% eye drops, or systemically, i.e., orally at 375 mg per day for 5 days.

Conclusion

When administered to rabbits as either eye ointment or as eye drops (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU) is superior to 5-iodo-2′-deoxyuridine (IDU) both in suppressing the development of herpes simplex virus type 1 (HSV-1) keratitis, and in promoting the healing of established epithelium disease. When applied as 0.1% or 0.5% eye drops, BVDU is also superior to 5-trifluoromethyl-2′-deoxyuridine (TFT) 1% eye drops in suppressing deep stromal HSV-1 keratitis, if treatment is started 1 day post-infection. However, if treatment of stromal disease is started on day 7 post-infection, BVDU and TFT are equally effective. BVDU is again significantly more effective than TFT in the treatment of HSV-1 keratouveitis (produced by inoculation of the virus into the anterior chamber of the eye). Oral administration of BVDU to rabbits at 10 mg/kg/day or 100 mg/kg/day also promotes healing of keratouveitis. However, if oral BVDU treatment at 10 mg/kg/day is associated with subconjunctival betamethasone injection, it does not perform better than if given alone.

When 0.1% BVDU eye drops were administered 9 times a day, at hourly intervals during the day only, to patients with dendritic corneal ulcers, it resulted in healing of epithelium disease in an average time of 7.9 days. When submitted to the same treatment regimen, geographic corneal ulcers healed in an average time of 12.2 days

and stromal keratitis in an average time of 39.8 days. Patients clinically resistant to IDU, TFT or Vira-A (Vidarabine, 9-β-D-arabinofuranosyladenine) responded promptly to topical BVDU therapy. Recurrences in the late follow-up period were again treated successfully with BVDU. Whether BVDU treatment effectively reduces the rate of recurrences will only be known after these patients have been followed for at least 2 years. Treatment of ophthalmic herpes zoster with oral BVDU at 375 mg/day (divided over 3 doses) combined with topical 0.1% BVDU eye drops led to a prompt healing of the skin lesions and keratouveitis.

No toxic side effects were observed in either rabbits or humans upon topical or oral administration of BVDU, except for drug allergy in one patient upon topical application of BVDU. Furthermore, BVDU did not retard the regeneration of corneal epithelium (in rabbits with central corneal erosions).

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