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Herpetic iridocyclitis

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Abstract

Twenty patients with presumptive herpetic iridocyclitis without active corneal inflammation received either topical idoxuridine 0.5% or acyclovir 3% ointment. The uveitis of all ten patients treated with acyclovir resolved within one to eight weeks. Four of ten patients treated with idoxuridine worsened but subsequently responded to topical prednisolone 0.3%. The pathogenesis of herpetic iridocyclitis is discussed with a literature review.

Introduction

Anterior uveitis may occur during the course of a systemic viral illness or in association with viral keratitis (46, 81). Occasionally, iridocyclitis may be the principal manifestation of a viral infection (11, 43). Of the viruses which have been implicated in the etiology of endogenous anterior uveitis (52), *Human Herpesvirus 1* (HHV) is one of the most frequently encountered, being suspected in 1–9% of cases (29, 53, 73).

While cycloplegic and anti-inflammatory medications have been utilized in the treatment of viral uveitis, new antiviral compounds which penetrate to the uveal tract may provide a therapeutic advantage. We report a series of patients with presumptive herpetic iridocyclitis without corneal involvement and compare the efficacy of two antiviral drugs.

Material and methods

Twenty patients with presumptive herpetic iridocyclitis were studied. Dendritic ulceration had previously occurred in the same eye in each patient. Except for a residual corneal opacity keratitis was not present at the onset of iridocyclitis.

The degree of anterior uveitis was quantified (31) by a scoring system (19) of symptoms (blurring, redness, watering, photophobia, and pain) and signs (ciliary injection, corneal edema, KP, flare, cells in aqueous and vitreous, exudate, hypopyon, posterior synechiae, and ptosis). Patients were followed weekly until complete resolution of the iridocyclitis.

Ten patients received topical idoxuridine 0.5% (IDU) ointment four times daily. A subsequent group of ten patients received topical acyclovir 3% (ACV) ointment four times daily. Atropine 1% eyedrops were administered twice daily to all patients. If the severity of the anterior uveitis increased over two consecutive examinations, topical

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prednisolone acetate 0.3% four times daily was added to the regimen.

The results were analyzed by comparing the percentage change in symptom and sign scores. Wilcoxon's rank sum test was used to compare the treatment groups.

Results

Twenty patients were studied, 10 treated with idoxuridine (Table 1) and 10 with acyclovir (Table 2). The patient groups were composed of 6 males and 14 females with an average age of 47 ± 18 years and a history of herpetic eye disease from 3 months to 46 years. Sixteen (80%) of the patients had had more than one episode of ulcerative herpetic keratitis.

Iridocyclitis varied from slight flare and a few cells in the anterior chamber to marked uveitis which obscured iris detail; no patient had a hypopyon or hyphema although erythrocytes were noted suspended in the aqueous in two patients. Intraocular pressure greater than 21 mmHg was present in 9 (45%) and returned to normal within three weeks.

During the first four weeks of therapy acyclovir was statistically better than idoxuridine after 7 and 14 days. The difference did not reach a statistical difference after 21 and 28 days of therapy (Fig. 1).

The treatments were also compared by the time to complete resolution of symptoms and signs of

Table 1. Clinical characteristics of 10 patients treated with IDU.

Age	Sex	Duration of symptoms (days)	Length of therapy (days)	Initial IOP (mmHg)
18	F	3	28	17
20	F	7	10	17
20	F	5	14	27
21	M	8	70*	18
34	M	7	7	19
38	M	7	30*	22
46	F	6	21	16
53	F	14	22*	24
56	F	7	21	24
61	F	7	42*	18

*Topical steroid administered.

Table 2. Clinical characteristics of 10 patients treated with ACV.

Age	Sex	Duration of symptoms (days)	Length of therapy (days)	Initial IOP (mmHg)
36	M	7	17	8
41	F	3	12	12
44	F	7	23	28
52	F	4	35	15
54	F	6	14	35
60	F	4	21	22
63	M	5	21	9
70	F	14	42	26
74	M	10	56	22
75	F	8	14	16

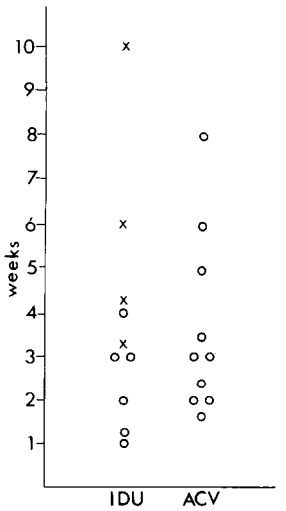

Fig. 1. Comparison of topical idoxuridine (IDU) and acyclovir (ACV) according to weeks to resolution (open circles) of presumptive herpetic iridocyclitis. X indicates topical prednisolone was administered for progressive uveal inflammation.

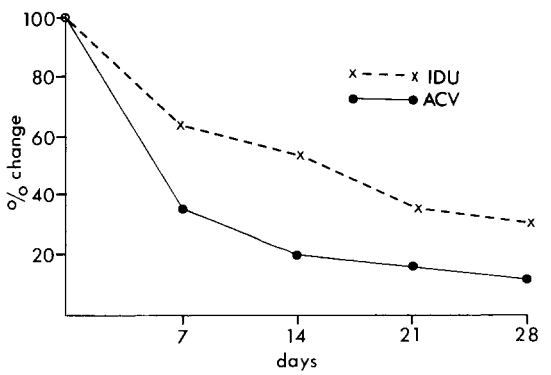

Fig. 2. Percentage change in symptom and sign scores during first 4 weeks of therapy with either idoxuridine (IDU) or acyclovir (ACV).

iridocyclitis (Fig. 2) The uveitis of six patients treated with IDU alone improved and resolved within one to four weeks; the uveitis of four patients receiving IDU worsened but later improved after topical prednisolone. All patients receiving ACV improved within one to eight weeks.

Visual acuity improved in 19 patients; one patient receiving IDU and prednisolone had a decrease from 6/12 to 6/24 due to a grey-white haze of the anterior lens cortex.

Discussion

Uveitis may occur during the course of herpetic eye disease (8, 57, 82). The uvea is usually involved anteriorly in recurrent disease; posterior uveitis may also develop during severe neonatal (54) or recurrent (65) infection. If choroiditis occurs, it tends to become bilateral, possibly as a result of viremia (69, 74) or viral spread within neuroglia via the optic nerves and chiasm (32).

Manifestations of herpetic iridocyclitis

Unilateral anterior uveitis may present in association with recurrent corneal disease or as an isolated phenomenon (14, 44). Although a marked uveitis with hypopyon can occur with ulcerative keratitis (26, 80), it usually consists only of a few cells in the anterior chamber (13). This associated iridocyclitis may be on the basis of a neurological reflex and is usually self-limiting, resolving when the epithelium heals.

A more severe uveal response can be associated with stromal inflammation. Because of the decreased corneal sensation associated with herpetic keratitis, the presence of ocular pain usually signifies an accompanying anterior uveitis. Secondary complications such as ocular hypertension and cataract may ensue, and hyphema has been noted in up to 12% of cases (81); iris atrophy rarely develops during keratouveitis. While there is frequently a poor response to mydriatic agents, they can prevent the formation of anterior and posterior synechiae. Topical anti-inflammatory therapy may be effective; the uveitis usually resolves as the stromal inflammation is controlled.

Occasionally iridocyclitis may be the only manifestation of recurrent herpetic eye disase (23, 24). In 1952 Cavara first reported the isolation of HHV from the aqueous of a series of patients with iridocyclitis without apparent keratitis (10). Usually, however, a presumptive diagnosis is made on the basis of corneal hypesthesia (18) or opacification (5, 26, 75) due to a previous herpetic lesion. HHV can also be suspected as the cause if iridocyclitis follows fever (11, 81), accompanies cutaneous

(28, 85) or genital (25, 77) lesions, precedes or follows dendritic keratitis (2, 3), is associated with an endothelial plaque (1, 55) or presents as a hemorrhagic iritis (4, 7, 38, 47, 48). Anterior uveitis in an eye with other evidence of disease due to HHV should be considered herpetic until another cause is identified (67). Because iridocyclitis indicates recurrent disease, serum antibody titers and the presence of sensitized lymphocytes are not usually diagnostically helpful (16).

Herpetic iridocyclitis usually presents as an acute painful uveits with perilimbal congestion and widely distributed white medium-sized keratic precipitates. Because the endothelium may have been previously damaged stromal edema may occur during an episode of uveal inflammation. Single foci of iris atrophy may occur (45) which can be best visualized with retroillumination. The atrophy typically takes place near the pupillary margin (Fig. 3); permanent dilatation may ensue if the iris sphincter is involved (87) or if the ciliary ganglion is infected (83, 88). The iris may be congested, and Koeppe nodules may rarely develop. Mononuclear and red blood cells are present in the anterior chamber. Synechiae may form (83) although not as readily as during the course of keratouveitis. The disease tends to last for 1 to 8 weeks but may persist for several months.

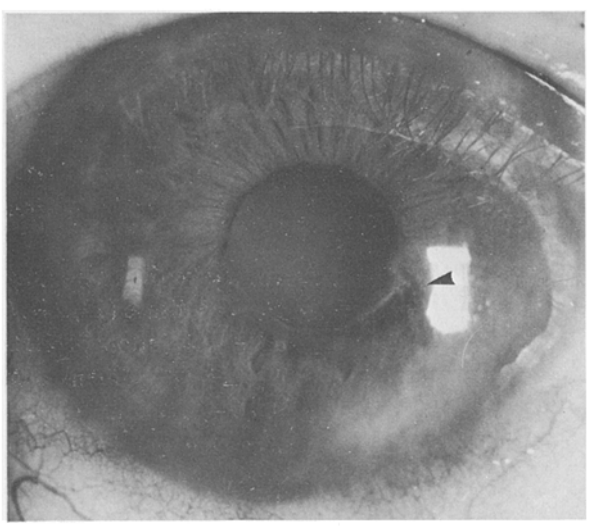

Fig. 3. Single focus of iris atrophy at pupillary margin (arrowhead) following herpetic iridocyclitis.

Pathogenesis and treatment

Because uveitis may persist or recur after all corneal inflammation has subsided (14) active viral replication within anterior uvea has been suspected as the cause (11). Free viral particles and intracellular viral antigens within aqueous marcrophages have been identified in cases of herpetic iridocyclitis (41, 64) as well as anti-HHV antibody in the aqueous in a higher titer than a corresponding serum sample (15). While only varicella-zoster virus has been identified within uveal tissue itself (89), HHV has been cultured from aqueous samples of patients with dendritic keratitis (30, 71), keratouveitis (9, 21, 34, 37, 78) and recurrent iridocyclitis (6, 10, 11, 22, 81). Secondary ocular hypertension was frequently present with the culture-positive cases (78).

In addition to cycloplegic agents, as variety of modalities has been used for herpetic uveitis including gamma globulin, smallpox vaccination, antiherpes vaccine (16), vitamins B_{12} and D (12, 72), interferon inducers (35), and cyclo-oxygenase inhibitors (49). Topical corticosteroids have been effective in controlling persistent or recurrent uveitis (39), although their use may prolong the course of the condition (26). Antiviral medications may be useful if they are able to permeate the eye. Because antivirals penetrate the cornea by nonfacilitated diffusion, a drug with biphasic solubility is needed: water-soluble for tear film transport and stromal penetration and lipid-soluble to cross cell membranes (20).

After topical IDU no unmetabolized drug is detected in the anterior chamber, only the inactive metabolites of 2'-deoxyuridine and iodouracil (56). Recurrent iridocyclitis has developed during therapy with topical IDU (34). Similarly, only trace amount of vidarabine (Ara-A) and its active metabolite hypoxanthine arabinoside appear in the aqueous after topical administration (56). Its penetration is enhanced if the epithelium is damaged; improvement was noted in herpetic uveitis within 1 to 4 weeks when patients with epithelial edema were switched from IDU to Ara-A (66). Therapeutic levels of trifluridine (TFT) may appear in the aqueous after topical administration (68, 76); an

active metabolite, 5-carboxy 2'-deoxyuridine, may also appear in experimental animals (56) but not humans (68). Clinically, while topical TFT is effective, the combination of a steroid and TFT may be better (78).

Acyclovir is a new antiviral medication which is effective in the treatment of ulcerative herpetic keratitis (33). As an analogue of 2'-deoxyguanosine it is converted by virus-specified thymidine kinase within HHV-infected cells to the active triphosphate which has much greater activity against virus-specified DNA polymerase than against corresponding host enzymes. In addition, ACV can penetrate the corneoscleral tissues and reach the anterior uvea where the virus may replicate beyond the reach of other antivirals. Applied to human corneas with intact epithelium mean aqueous levels of 1.7 μg/ml of unchanged drug appear which exceed the *in vitro* mean inhibitory concentration of 0.25 μg/ml of clinical HHV isolates (70).

In this study ACV was found to be superior to IDU in controlling presumptive herpetic iridocyclitis. Because six cases treated only with IDU resolved within one to four weeks, it is possible that some cases of herpetic iridocyclitis are self-limited, similar to spontaneously healing cases of dendritic keratitis. The progression which occurred in the remaining IDU-treated cases which subsequently improved with topical steroid suggest that a secondary immunogenic response or Arthus-type vasculitis can also be involved (62). ACV may inhibit the initial uveal viral replication and prevent this progressive inflammation.

Studies in experimental animals have suggested similar mechanisms (86). Anterior uveitis can be produced experimentally by injecting HHV into a rabbit anterior chamber (50, 51, 86), particularly if there has been a previous nonherpetic uveitis (60), and virus can be later re-isolated from the aqueous (84) and iris (55). This model provides a system of assessing the *in vivo* efficacy of antiviral compounds (40). Steroids (17, 36, 42, 58) and other immunosuppressive medications (61) can potentiate this initial uveal viral proliferation but can control the subsequent immune-mediated response. HHV replication appears to occur in primary experimental uveitis and lead to a subsequent immune reaction during secondary uveitis.

Herpetic iridocyclitis may be initiated by viral replication following viral shedding in the anterior uvea. Some cases resolve spontaneously while others progress to a severe and sometimes hemorrhagic iritis by uncontrolled virogenesis, particularly in patients with altered immunity (63, 79), and a subsequent immunogenic response. Acyclovir, an antiviral medication with good intraocular penetration, is effective in the initial control of recurrent herpetic iridocyclitis.

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