TABLE 1. Patients Undergoing Transcanalicular-Endonasal Semiconductor Diode Laser-Assisted Revision Dacryocystorhinostomy

Patient No.	Age (years)	Gender	Side (R/L)	Cause of Primary Surgery	Procedure of Primary Surgery	Period of Intubation after Primary DCR (weeks)	Time Between Primary and Revision Surgery (days)
1	76	F	L	Dacryocystitis + upper canalicular obstruction	DCR + upper canaliculoplasty	27	191
2	48	F	R	NLDO	DCR	18	338
3	72	M	L	Common canalicular obstruction	DCR + common canaliculoplasty	16	238
4	70	F	R	Dacryocystitis	DCR	16	337
5	76	M	R	Dacryocystitis	DCR	16	154
6	62	M	L	NLDO + common canalicular obstruction	DCR + common canaliculoplasty	16	208
7	58	M	L	Dacryocystitis	DCR	12	152
8	84	F	R	Common canalicular obstruction	DCR + common canaliculoplasty	14	229
9	60	F	R	Common canalicular obstruction	DCR + common canaliculoplasty	14	159
10	60	F	L	Common canalicular obstruction	DCR + common canaliculoplasty	13	156
11	50	M	R	Dacryocystitis	DCR	19	284
12	76	M	L	Trauma	DCR + upper and lower canaliculoplasty	25	267
13	61	F	R	Common and upper canalicular obstruction	DCR + common and upper canaliculoplasty	12	161
14	61	F	L	Common and lower canalicular obstruction	DCR + common and lower canaliculoplasty	11	156
15	61	F	R	Dacryocystitis	DCR	14	194

DCR = dacryocystorhinostomy; L = left; NLDO = nasolacrimal duct obstruction; R = right.

TABLE 2. Patients Undergoing Transcanalicular-Endonasal Semiconductor Diode Laser-Assisted Revision Dacryocystorhinostomy

Patient No.	Functional Success after First Revision	Period of Intubation after Revision (weeks)	Second Revision	Follow-up after Final Revision (months)	Final Size of Rhinostomy (vertical × horizontal, mm)	Area of Rhinostomy (mm^2)	Final Functional Success
1	Success	31	–	54	1.2 × 1.1	4.1	Success
2	Success	16	–	45	2.1 × 1.4	9.2	Success
3	Fail	10	+	42	5.1 × 2.6	41.6	Fail
4	Success	18	–	30	1.5 × 1.6	7.5	Success
5	Success	14	–	47	3.1 × 2.1	20.4	Success
6	Success	15	–	32	2.2 × 2.4	16.6	Success
7	Fail	15	+	16	1.3 × 2.2	9.0	Success
8	Success	14	–	27	3.4 × 3.3	35.2	Success
9	Success	11	–	23	2.5 × 1.1	8.6	Success
10	Success	11	–	23	3.5 × 2.4	26.4	Success
11	Success	13	–	11	4.4 × 2.5	34.5	Success
12	Fail	13	+	9	3.1 × 3.0	29.2	Success
13	Fail	13	–	13	1.5 × 3.0	14.1	Fail
14	Fail	12	–	13	2.5 × 1.7	13.3	Fail
15	Success	18	–	25	3.3 × 1.8	18.7	Success

DCR = dacryocystorhinostomy.

applied to the initially reopened rhinostomy site to avoid inadvertent damage to the canaliculus or common canaliculus (Figure 2, Bottom left).

After removing the laser probe, the lacrimal system was irrigated to confirm the patency of the nasolacrimal system. Finally, a silicone tube was placed in the rhinostomy

in all patients (Figure 2, Top right). All patients were discharged one day after the surgery. The postoperative medications included both topical and oral antibiotics. The antibiotic eye drops were used four times per day for 12 weeks, and oral antibiotics were used for five days.

The postoperative evaluation was done by one of the authors (J.N.). A routine intranasal cleaning and/or debridment was performed one week after the transcanalicular-endonasal DCR. The initial follow-up period was one week, and subsequent visits were at one-month intervals for six months. Lacrimal irrigation was performed at each visit, and the final nasal examination was performed six months after the surgery (Figure 2, Middle right).

The vertical (a) and horizontal (b) diameters of the rhinostomy were measured using a scaled Schirmer paper strip (Showa Yakuhin Kako Co, Ltd, Tokyo, Japan; Figure 2, Bottom right) at the final nasal examination. ImageJ 1.37 image analysis software (National Institutes of Health, Bethesda, Maryland, USA) was used to calculate the vertical and horizontal diameters of the rhinostomy and the scale (1 mm) of the Schirmer paper strip on the digital nasal endoscopic images. Based on the pixel values of the scale adjacent to the rhinostomy, the vertical and horizontal diameters of the rhinostomy were calculated. In addition, the area of the rhinostomy was calculated as described by Linberg and associates.[27] For this, the area of the rhinostomy was calculated as an ellipse, $A = \pi ab$ Additional follow-up data were obtained by recalling the patients.

The removal of the silicone stent was usually done at 12 weeks. The silicone stent was removed in the office by cutting the exposed tubing at the medial canthus and withdrawing it through the nose. After the silicone stent was removed, mucosal healing and lacrimal patency was confirmed by nasolacrimal irrigation with an office nasal endoscope.

A surgical success was defined as the presence of a patent nasolacrimal drainage system on nasolacrimal irrigation without reflux. A functional successful outcome was defined as both the patent nasolacrimal drainage system in nasolacrimal irrigation, and a resolution of symptomatic epiphora and/or mucoid discharge.

• STATISTICAL ANALYSES: Student *t* tests were used to compare the values obtained from the successes and failed groups. Fisher exact probability tests were used to analyze the relationship between the different factors and between both groups. A P value $< .05$ was taken to be significant.

RESULTS

TWO HUNDRED AND SEVEN EXTERNAL DCRS WERE PERformed on 182 patients during the study period. Of these, 15 eyes in 13 patients were judged to have failed, thus making the success rate of our primary external DCR 92.8%. The mean surgical duration of the successful primary external DCR was 40.6 ± 14.6 minutes (± standard deviation), and that of the failed case was 48.2 ± 17.2 minutes. This difference was not significant.

The initial cause for the primary external DCR in the 15 patients with failed primary DCR is shown in Table 1. DCR had been performed in six cases as the primary surgery, and DCR + canaliculoplasty was performed in the other nine cases as the primary surgery (Table 1). The performance of canaliculoplasty as the primary surgery was not significantly related to the success rate of the revision surgery.

Transcanalicular-endonasal DCR procedures were performed on the 15 failed external DCR cases (nine women, six men; mean age, 65.0 ± 10.2 years). In two patients, transcanalicular-endonasal DCR was performed bilaterally. The time between the primary and revision surgery ranged from 152 to 338 days (mean, 214.9 ± 65.4 days; Table 1), and the mean postoperative follow-up period after the revision surgery ranged from nine to 54 months with a mean of 27.3 ± 14.2 months (Table 2). The time between the primary and revision surgery was not significantly related to the success rates of the revision surgery.

There were no intraoperative and postoperative complications such as false passage, orbital hematoma, orbital fat exposure, and diplopia. None of the patients required septoplasty and/or middle turbinectomy. The intraoperative bleeding was minimal, and none of the patients required a nasal pack after the operation.

After the first transcanalicular-endonasal DCR revision surgery, a patency to irrigation was obtained in 12 cases (80%), and a patency was found in the three remaining cases after a second revision surgery (Cases 3, 7, and 12; Table 2). In the three cases requiring a second revision surgery, the initial cause for the DCR was obstruction of the common canaliculus, dacryocystitis, and trauma, respectively (Tables 1 and 2). However, two cases (Cases 13 and 14) had a functional block; that is, epiphora persisted after first revision surgery in spite of patent irrigation. Therefore, functional success rate was 66.7% after first revision surgery (Table 2). The duration of the first revision surgery ranged from eight to 45 minutes with a mean of 20.5 minutes, and the second revision surgery from 12 to 18 minutes with a mean of 15 minutes. The mean duration of all the revision surgeries was 19.6 minutes. The durations of first and second revision surgery were not significantly related to the success rates of the revision surgery.

Endoscopic examination during the revision surgery revealed a closed rhinostomy with pearl-color scar tissue in all 15 cases. In 13 cases, irrigation revealed a reflux from the opposite canaliculus, and thus, an obstruction was present either in the common canaliculus or in the common canalicular–lacrimal sac junction, or a lacrimal sac–nasal mucosa anastomosis was present. Two cases had

a canalicular obstruction (Cases 1 and 12). Canaliculoplasty was performed on the upper canaliculus in Case 1, and an upper and lower canaliculoplasty was performed in Case 12. In Case 12, a repeat transcanalicular-endonasal DCR was required to obtain a patency of the nasolacrimal system. The canalicular obstruction in the first revision surgery was also not related to the final functional success rate.

In all cases, there was no bony obstruction at the rhinostomy site, and the rhinostomies were easily reopened and enlarged. In four cases (Cases 3, 4, 5, and 8) endoscopic examination during the stent removal showed granulation tissues around the rhinostomy that were removed with the semiconductor diode laser in the office. One of these four cases required a second revision surgery. The existence of the granulation tissue was not significantly related to the failure of the first revision surgery.

The interval between the installation and removal of the stent varied from 10 to 31 weeks after the first revision surgery (mean, 14.9 ± 5.0 weeks) (Table 2), and from 11 to 23 weeks after the second revision (mean, 17.3 ± 6.0 weeks). An accidental loss of a stent occurred in one case, and it occurred before 12 weeks. The duration of intubation in the successful revision group (16.1 ± 5.8 weeks) was not significantly different from those of the failed group (12.6 ± 1.8 weeks) ($P = .216$). The area of the final rhinostomy ranged from 4.1 mm^2 to 41.6 mm^2 (mean, 19.2 ± 11.6 mm^2). There was no significant difference between the area of the success group (18.3 ± 11.0 mm^2) and failed group (23.0 ± 16.1 mm^2) ($P = .550$) after the second revision.

Finally, three patients complained of recurrent epiphora in spite of a patent nasolacrimal system with nasolacrimal irrigation after the second revision (Cases 3, 13, and 14) (Table 2). Of these three cases, two cases had a patent system after one revision, and the other case required two revisions. After the first revision, the overall success rate was 66.7%; however, following secondary revision with the same technique our success rate was 80% (12 of 15 cases).

DISCUSSION

REVISION DCR TYPICALLY REQUIRES A REOPENING OF THE external skin incisions.[8–13,28] The success rate of a repeat external DCR is high, ranging from 83% to 92%,[1,8,9] and the success rate (80%) of our transcanalicular-endonasal DCR was comparable. Our procedures were especially successful in patients with pure dacryocystitis and no canalicular obstructions, although the number of those cases was only six.

Endonasal and transcanalicular revision surgery have two obvious advantages over the external approach: avoidance of a skin incision in an already scarred surgical field,[13,20] and limited surgical trauma. Furthermore, the procedure can be performed under local anesthesia as an outpatient procedure in the office.[3,11,29,30] Regrowth of bone at the rhinostomy site after DCR is very limited or none,[11,31] and soft scar tissue was responsible for all of the failures.[11] Endonasal or transcanalicular revision surgery has been particularly useful in failed external DCR revision in which a wide boneless window had already been created and bone does not need to be removed.[14,28] Our transcanalicular-endonasal DCR procedure also has these advantages.

Because the insertion of the laser fiber is similar to nasolacrimal probing, the transcanalicular approach is familiar to ophthalmologists,[6,14] and it is easier for ophthalmologists to master.[32] Compared to endonasal revision DCR, this approach is safer because the laser energy is directed towards the lacrimal-nasal sac and energy is not directed towards the eye or orbit.[14,22,33] In addition, we know that this approach will reopen the rhinostomy at the obstructed site correctly from inside the canaliculus.

Patel and associates[13] used this approach for revision DCR using a neodymium-doped yttrium-aluminium-garnet (Nd:YAG) laser. They reported a 46% success rate and did not recommend it for revision DCR. In contrast, Woo and associates[14] had an 83% success rate after the first revision surgery and 100% after the second revision surgery. They suggested that the discrepancy in their success rates with that of Patel and associates may be differences in the origin of the nasolacrimal obstruction because cases of DCR caused by trauma, canalicular obstruction, radiation, sinus tumor, Wegener granulomatosis, and Down syndrome have lower surgical success rates.[13,14] Our success rate was similar to that of Woo and associates even though cases of trauma and common canalicular obstruction were included.

The transcanalicular approach usually creates smaller rhinostomies than external and endonasal approach,[21] and this factor is correlated with the low success rate of the primary transcanalicular DCR.[21] Therefore, one reason for our high success rate compared with that of Patel and associates may be the larger endonasal rhinostomy after the transcanalicular approach.

The causes of a failed external DCR were closure of the rhinostomy, an obstruction of the common canaliculus, adhesion between the rhinostomy and middle turbinate, adhesion between the rhinostomy and nasal septum, and formation of granulation tissue.[8–12,20,34] A canalicular obstruction is the most difficult lacrimal drainage obstruction to treat, not only by the primary DCR[17] but also by revision DCR.[13] Woo and associates[14] reported that transcanalicular revision DCR is not useful for failed external DCR resulting from canalicular obstruction. Our results confirmed that canalicular obstruction was the main cause of the primary DCR failure. However, this did not affect the overall success rate of the revision surgery. In addition, the presence of granulation tissue was also not related to the revision DCR failure. These results indicate that transcanalicular-endonasal DCR is useful for revision sur-

gery in cases of the canalicular obstruction and/or the presence of granulation tissue as well as closed rhinostomies.

Endonasal DCR has been accepted for revision lacrimal surgery as well as for primary DCR.[10,11,13,15,16,23] Using the endonasal approach, the rhinostomy can be sufficiently enlarged and properly positioned.[11] However, the success rate of endonasal revision DCR varies considerably, ranging from 0% to 100%.[10,11,13,15–20] Yung and associates[17] reported that the most important step in this procedure was to identify the opening of the common canaliculus, and it was difficult to differentiate the rhinostomy closure and the common canalicular obstruction during endoscopic revision surgery. In addition, Metson[18] reported that failed endoscopic revision surgery resulted from unrecognized canalicular obstructions. Although the transcanalicular insertion of a light pipe can help identify the obstructed site from the illumination,[19] these procedures need additional instruments and the nontapered sharp edge of the tip of the vitreoretinal surgery fiberoptic probe can cause iatrogenic surgical trauma in the canaliculus.[35,36] Therefore, we believe that it may be difficult to reopen the rhinostomy at the obstructed point correctly by only the endonasal approach, and collateral damage of the common and/or canaliculus may be induced. This is probably one of the factors for the wide variation in the success rates of endoscopic revision DCR. Thus, we performed transcanalicular approach prior to endonasal enlargement for the correct reopening of the rhinostomy at the obstructed point.

It is questionable whether a large surgical anastomosis is required to increase the success rate of external DCR. Some authors believe that opening a large rhinostomy is essential,[8,9,37–39] whereas others report that the size of surgical anastomosis is not correlated with surgical success.[12,27] In revision DCR, a correlation between the size of the rhinostomy and success rate has not been investigated. However, scarring fibrosis existed at the edge of the rhinostomy in failed external DCR,[31] and the endonasal enlargement with dissection of scar tissues may be sufficient to increase the probability of remaining patent after the revision surgery.

Three cases were classified as functional failures in spite of a patent lacrimal system after the final revision (Cases 3, 13, and 14). These patients had persistent epiphora and elevation of the tear meniscus height. Although DCR improved the symptoms caused by the epiphora after the primary functional nasolacrimal obstruction,[40,41] the treatment for persistent epiphora after surgical successful DCR has not been investigated. Tear outflow is believed to be mainly regulated by the lacrimal pump through the canaliculus and the lacrimal sac accompanying blinking.[42,43] Thus, the elastic tissue in the canaliculus plays an important role for this pumping mechanism.[42,43] Because the primary cause for the primary DCR in these three cases included common and/or canalicular obstruction and canaliculoplasty with the diode laser was necessary in both the primary and revision surgery, there may have been damage to the elastic tissue at the canaliculoplasty, resulting in lacrimal pump dysfunction. Conjunctivodacryocystorhinostomy with a Jones tube placement is the simplest and most highly successful treatment in cases in which both canaliculi are absent or obstructed.[44] Therefore, this procedure may be effective for the treatment in functionally failed DCR.

The diode laser can achieve effective tissue dissection with minimal collateral damage external to the target zone, and these features diminish the risk of retrograde damage.[25] During lacrimal surgery, the use of diode laser for mucosal incision results in minimal hemorrhage and improved intraoperative view.[25] In our procedure, the laser power was 3 W, which is too weak to incise bone,[25] and the rhinostomy cannot be enlarged over the primary bony window. Therefore, the rhinostomy was enlarged safely by centering the small reopened rhinostomy after the transcanalicular approach. Furthermore, the dimensions of our laser apparatus were 345 mm × 247 mm × 177 mm, and the weight was 11.7 kg, which is comparable to a typewriter in size and weight.[25,30] This compact size and light weight are also advantageous to the surgeon because the device can be easily transported to other locations.[6] In addition, the diode laser has similar results as the YAG lasers at much lower cost.[5] For these reasons, we used the diode laser in this study. Although further investigation will be needed, the differences of laser characteristics may be a second reason for the discrepancy of the success rate between our study and the other reports.

In summary, transcanalicular-endonasal DCR was performed as the revision surgery for cases of failed external DCR. Although the limitation of our study is the small sample size, this procedure was minimally invasive and was beneficial as the first step in revision surgery after external DCR. Thus, it can be offered to the patients as an alternative revision surgery.

THE AUTHORS INDICATE NO FINANCIAL SUPPORT OR FINANCIAL CONFLICT OF INTEREST. INVOLVED IN CONCEPTION AND design (J.N., Y.O.); analysis, interpretation, and writing the article (J.N.); critical revision and final of the article (Y.O.); data collection and provision of materials, patients, or resources (J.N.); statistical experience, literature search (J.N.); and review and approval of the manuscript (Y.O.). Approval for this study was obtained from the Institutional Review Board of the Ehime University School of Medicine. The procedures used conformed to the tenets of the Declaration of Helsinki.

We thank Professor Duco Hamasaki, Bascom Palmer Eye Institute, Miami, Florida for advice on analyzing the data and for editing this manuscript.

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REPORTING VISUAL ACUITIES

The AJO encourages authors to report the visual acuity in the manuscript using the same nomenclature that was used in gathering the data provided they were recorded in one of the methods listed here. This table of equivalent visual acuities is provided to the readers as an aid to interpret visual acuity findings in familiar units.

Table of Equivalent Visual Acuity Measurements

Snellen Visual Acuities				
4 Meters	6 Meters	20 Feet	Decimal Fraction	LogMAR
4/40	6/60	20/200	0.10	+1.0
4/32	6/48	20/160	0.125	+0.9
4/25	6/38	20/125	0.16	+0.8
4/20	6/30	20/100	0.20	+0.7
4/16	6/24	20/80	0.25	+0.6
4/12.6	6/20	20/63	0.32	+0.5
4/10	6/15	20/50	0.40	+0.4
4/8	6/12	20/40	0.50	+0.3
4/6.3	6/10	20/32	0.63	+0.2
4/5	6/7.5	20/25	0.80	+0.1
4/4	6/6	20/20	1.00	0.0
4/3.2	6/5	20/16	1.25	−0.1
4/2.5	6/3.75	20/12.5	1.60	−0.2
4/2	6/3	20/10	2.00	−0.3

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Seminars in Ophthalmology, 23:235–240, 2008

ISSN: 0882-0538
DOI: 10.1080/08820530802111010

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Corneal Endotheliitis

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ABSTRACT Corneal endotheliitis is an intriguing clinical entity manifested by corneal edema, keratic precipitates, and mild anterior chamber reaction, and can be defined as a spectrum of the disorder in which the corneal endothelium is the primary site of the inflammation. The disease etiology consists of accumulating evidence of various viral infections including herpes simplex virus, varicella zoster virus, and cytomegalovirus. Corneal endotheliitis can be classified clinically into four forms: linear, sectorial, disciform, and diffuse. Antiviral treatment in combination with topical corticosteroids is generally effective to suppress the inflammation; however, irreversible corneal endothelial dysfunction may develop in some cases.

KEYWORDS corneal endotheliitis, corneal edema, keratic precipitate, herpes simplex virus, cytomegalovirus, polymerase chain reaction

1. INTRODUCTION

The corneal endothelium is the innermost layer of the cornea and plays an important role in maintaining the corneal transparency by pumping and barrier function. Thus, the abnormality of the corneal endothelium often results in corneal edema, leading to irreversible decompensation in some cases. Corneal endotheliitis can be defined as a broad range disorder in which corneal endothelium is the primary site of the inflammation[1]. In this regard, allograft reaction in the corneal endothelium after keratoplasty can be included in the corneal endotheliitis; however, this is a well-known concept and is not discussed in this article. Corneal endotheliitis is characterized by corneal edema, keratic precipitates (KPs), and mild anterior chamber reaction. The disease is also characterized by lack of inflammatory changes in the corneal stroma; therefore, secondary impairment of corneal endothelium due to stromal or interstitial keratitis can be ruled out. Many investigators have reported various forms of corneal endotheliitis and thus a number of nomenclatures have been given to this unique clinical entity, including progressive herpetic corneal endotheliitis,[2] herpetic endothelial keratitis,[3] idiopathic corneal endotheliopathy,[4] and sporadic diffuse corneal endotheliitis.[5]

2. ETIOLOGY

2.1 Autoimmune Mechanism

In 1982, Khodadoust and Attarzadeh first described two bilateral cases of corneal endotheliitis that had linear KPs with accompanying peripheral corneal

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edema, being similar to the finding seen in the allograft rejection of the corneal endothelium.[1] Based upon the clinical findings of bilateral and symmetric involvement, a good response to topical corticosteroids, and the presence of inflammatory cells seen in the anterior chamber, they suspected an autoimmune mechanism against corneal endothelium to be the etiology and they categorized the condition, presumed autoimmune corneal endotheliopathy.

When treating patients with corneal endotheliitis, one should remember that the corticosteroid therapy is not always effective. For instance, in 1982, Sugar and Smith reported one patient in whom stromal and epithelial edema along with a line of KPs simulating an endothelial rejection line was developed following uneventful cataract surgery.[6] After both oral and topical corticosteroid therapy, the inflammation was suppressed, but the corneal edema persisted. In 1985, Ohashi and Kinoshita reported a case with similar clinical findings to the case reported by Sugar and Smith and found that topical and intracameral corticosteroid was ineffective and, as a result, the patient developed irreversible bullous keratopathy.[4] The final outcome of these cases raised a question regarding the autoimmune mechanism proposed by Khodadoust and Attarzadeh. As the patient in the former case developed dendritic keratitis seven months later, the possibility of viral infection, especially the association with herpes simplex virus (HSV), was suggested as an alternative etiology of this disease.

2.2 Evidence for HSV Infection

In support of the above hypothesis, Robin, Steigner, and Kaufman, in 1985, first isolated HSV from the aqueous humor of the patient with progressive corneal endotheliitis and detected herpes simplex virus (HSV) type 1 antigen in the cells obtained from the anterior chamber using fluorescein-tagged antibodies.[2] Later in 1991, Ohashi and his associates demonstrated HSV-DNA in the aqueous humor of the patients with acute corneal endotheliitis using polymerase chain reaction (PCR).[7] The presence of HSV was also documented in the trabeculum of an eye with corneal endotheliitis confirmed by either PCR or immunohistochemical examination.[8,9] These lines of evidence strongly indicate that HSV can infect corneal endothelium and trabecular network, leading to varying degrees of corneal endothelial dysfunction or increased intraocular pressure. Association of HSV with the etiology of corneal endotheliitis is further supported by the favorable clinical response to topical and systemic acyclovir treatment.[10]

2.3 Cytomegalovirus Corneal Endotheliitis

Nonetheless, ophthalmologists have often encountered patients who are suffering from corneal endotheliitis and whose aqueous humor is negative for HSV and VZV DNA, and do not respond well to intensive acyclovir treatment. In the past, these patients have been diagnosed as "idiopathic corneal endotheliitis." Recently, Koizumi et al. reported one case of corneal endotheliitis in which the DNA of cytomegalovirus (CMV) was demonstrated in the aqueous humor.[11] Shortly after, Chee et al. reported 12 eyes of 10 patients of corneal endotheliitis in whom CMV DNA were detected in the aqueous humor.[12] Almost during the same period, Koizumi and Suzuki independently described 8 cases of corneal endotheliitis of CMV origin confirmed by PCR.[13] The patients were all immunocompetent, and systemic and topical ganciclovir was effective to relieve the symptoms of the disease. Shiraishi et al., using confocal microscopy, observed the endothelial lesion of one patient with CMV corneal endotheliitis and found the owl's eye pattern in the corneal endothelium consisting of a large, intranuclear inclusion body, a hallmark finding of CMV infection (Figure 1).[14,15] These facts

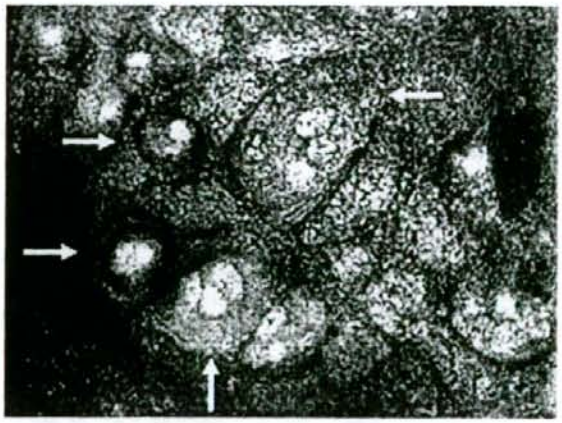

FIGURE 1 In vivo confocal microscopic finding of cytomegalovirus corneal endotheliitis. A group of large cells whose nuclei have a high reflection area surrounded by a halo of low reflection, resembling an owl's eye pathology, was observed in the corneal endothelium of the patient. (Reprinted from Shiraishi et al.[14] with permission of the American Academy of Ophthalmology.)

strongly suggest that CMV is an important pathogen of corneal endotheliitis.

2.4 Corneal Endotheliitis of Other Viral Origin

In addition to HSV and CMV, other viruses can be listed as a causative pathogen of corneal endotheliitis. Maudgal et al. demonstrated numerous herpes virus particles in the corneal endothelium by electron microscopy in a varicella zoster patient who developed peripheral corneal edema.[16] In one case, the patient diagnosis of corneal endotheliitis was associated with mumps infection,[17] and in the other case a vesicular virus was isolated from the aqueous humor of the patient with bilateral corneal endotheliitis.[18]

2.5 The Involvement of ACAID

Although the virus proliferates in the corneal endothelium, the ambiguity of the mild inflammatory response remains. To investigate the cause of such a mild inflammatory response, considering the pathogenesis of corneal endotheliitis one should remember the fact that the anterior chamber is a unique immune-privileged site, governed by anterior chamber-associated immune deviation (ACAID) proposed by Streilein and his associates.[19–22] Generally, delayed-type hypersensitivity (DTH) induces a high degree of immunogenic inflammation in which interferon-γ is a principal effector cytokine; however, in ACAID, DTH is profoundly suppressed, whereas the humoral immune response is intact or even enhanced.

Zheng, Ohashi and their associates established a rabbit model of herpetic corneal endotheliitis by inducing ACAID against HSV and suggested that ACAID might play an important role in the pathogenetic mechanism.[23] First, they induced ACAID by repeated immunization with inactivated HSV into the anterior chamber. When live HSV was inoculated intracamerally, focal corneal edema associated with KPs was formed in the corneal endothelium with minimum anterior chamber reaction, close resemblance to the clinical feature of corneal endotheliitis in humans.

The presumptive mechanism of corneal endotheliitis might function as follows: Every time the virus that has established a latent infection becomes intermittently reactivated,[24,25] a varied dose of virus is shed into the anterior chamber. Repeated shedding of virus particles leads to the induction of ACAID against viral antigens and infection occurs when the pre-existing antibodies are incapable of neutralizing the reactivated virus. Under the suppression of cell-mediated immunity, the virus was presumably able to proliferate efficiently in the corneal endothelium.

2.6 Possible ACAID-related Diseases

In general, the patients with iridocyclitis have KPs at the lower third portion of the posterior corneal surface. Despite this rule, there are some inflammatory anterior segment diseases characterized by scattering KPs and mild anterior chamber reaction such as Fuchs heterochromic iridocyclitis and Posner-Schlossman syndrome. According to the PCR, HSV or rubella virus DNA was detected in the aqueous humor of the patients with Fuchs heterochromic iridocyclitis,[26,27] while HSV-DNA was demonstrated in the aqueous humor of those with Posner-Schlossman syndrome.[28] Together with corneal endotheliitis, especially of linear form, these three diseases share common clinical manifestations as shown in Table 1. Thus, we

TABLE 1 Anterior chamber-associated immune deviation (ACAID)-related syndrome

	Corneal endotheliitis	Fuchs heterochromic iridocyclitis	Posner-Schlossman syndrome
Laterality	unilateral>>bilateral	unilateral	unilateral
Recurrence	+	+	+
Characteristics of KPs	rejection line- or coin-shaped	scattered	scattered
Elevated intraocular pressure	+	+	+
Anterior chamber reaction	mild	mild	mild
Etiologic agents	HSV/VZV/CMV/mumps	Rubella/HSV	HSV
Speculated infection site	Corneal endothelium	Iris?	Trabeculum

KPs, keratic precipitates; HSV, herpes simplex virus; VZV, varicella zoster virus; CMV, cytomegalovirus

propose a new disease category named ACAID-related syndrome.

3. CLINICAL MANIFESTATION

The clinical features of corneal endotheliitis consist of keratic precipitates (KPs), corneal edema without any inflammatory signs in the stroma and mild anterior chamber reaction. According to the review by Liesegang as well as by Holland and Schwartz, corneal endotheliitis can be classified into four forms: linear, sectorial, disciform, and diffuse, based on the distribution of the KP and configuration of the overlying stromal and epithelial edema.[29,30]

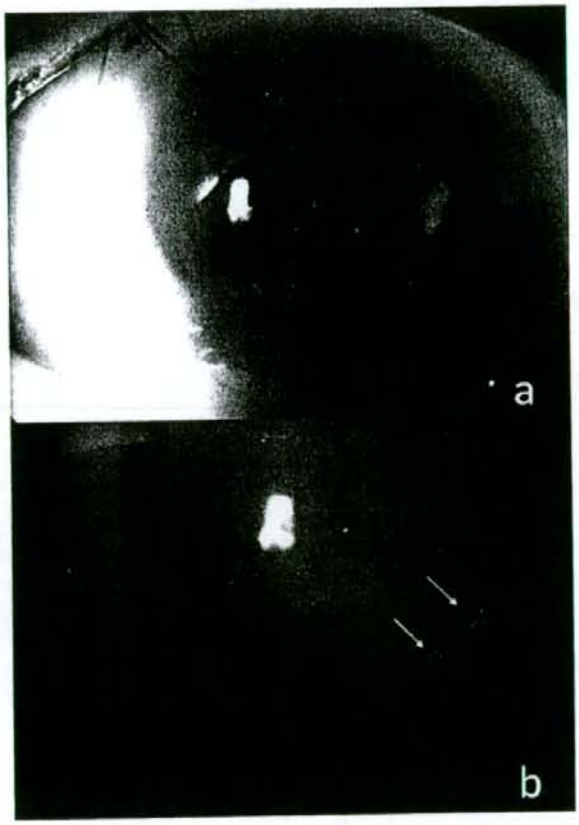

FIGURE 2 Clinical manifestations of linear corneal endotheliitis. (a) Linear corneal endotheliitis, characterized by the appearance of peripheral corneal edema and a line of keratic precipitates (KPs) on the corneal endothelium that progresses centrally. (b) Coin lesion in CMV corneal endotheliitis, the specific arrangement of the KPs in a coin-shaped pattern. (These figures were published in Koizumi et al.,[13] © Elsevier.)

3.1 Linear Corneal Endotheliitis

The linear form of corneal endotheliitis is manifested by peripherally located, sectorial corneal edema and a line of KPs in the corneal endothelium that resembles a rejection line and progresses centrifugally[31] (Figure 2a). This form is probably most dangerous as the loss of corneal endothelial cells is rapid and numerous. A line of KPs is formed at the boundary of corneal edema, and a satellite lesion consisting of KPs arranged in a coin-shaped pattern can be seen beyond the line of KPs.[11,13,32] Ciliary injection is not remarkable and the anterior chamber reaction is minimum. Frequently, the patient exhibits an intermittent episode of increased intraocular pressure similar to Posner-Schlossman syndrome.[4,31,33] Linear corneal endotheliitis generally appears unilaterally,[34] and can occur after the penetrating keratoplasty[32] or cataract surgery.[6,33,35] Etiologic agents in linear corneal endotheliitis include HSV and CMV. Especially, the arrangement of KPs in a coin-shaped pattern would be a specific manifestation of CMV-related corneal endotheliitis[11,13,32] (Figure 2b).

3.2 Sectorial Corneal Endotheliitis

In 1984, Sutcliffe et al. reported four cases of idiopathic acute corneal endotheliitis, which exhibited sectorial corneal edema with disseminated KPs[36] (Figure 3a). Although the location of the edema is similar to the linear form, the lesion is generally resolved without the progressive linear pattern of KPs and profound loss of corneal endothelial cells. A similar case was reported by Kuljaca et al.[37] This may be a mild form of linear corneal endotheliitis in which the virus less actively proliferates in the corneal endothelium.

3.3 Disciform Corneal Endotheliitis

Disciform corneal endotheliitis, the most common manifestation of the corneal endotheliitis, forms a round or disc-shaped stromal edema in central or paracentral region of the cornea (Figure 3b). The edema in disciform corneal endotheliitis shows a strikingly focal pattern with a definite boundary between affected and unaffected area. There are numerous KPs on the corneal endothelium inside the corneal edema. Because of the severity of the corneal edema, it is sometimes difficult to directly observe the KPs. A mild-to-moderate iritis accompanies disciform corneal endotheliitis with occasional elevation of intraocular pressure. Etiology of

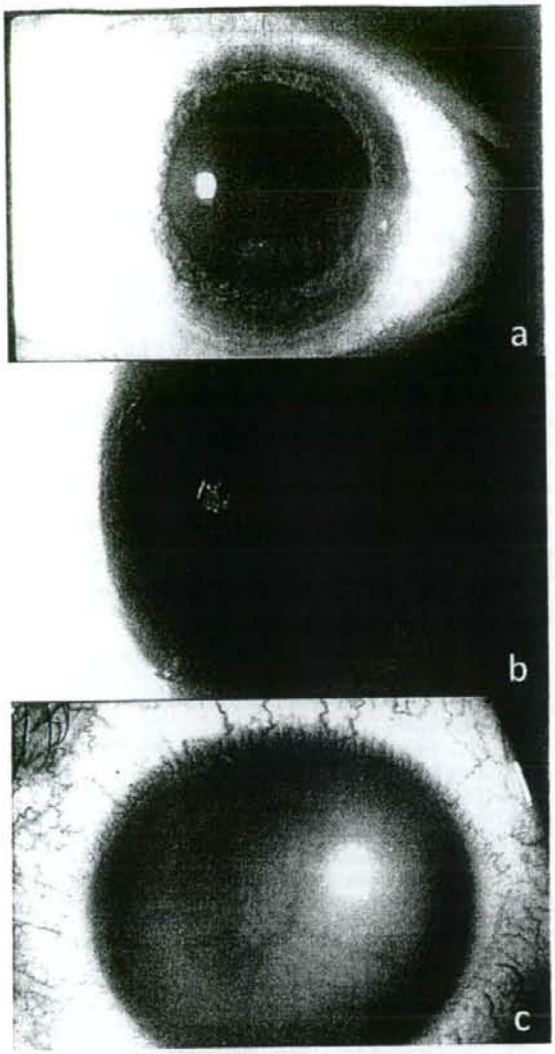

FIGURE 3 Clinical manifestations of corneal endotheliitis. (a) Sectorial corneal endotheliitis, a sectorial corneal edema in paracentral portion associated with KPs. (b) Disciform corneal endotheliitis, a focal corneal edema in the central cornea. (c) Diffuse corneal endotheliitis, an edema of the entire cornea. (Courtesy of Dr. Yuko Nakagawa, Tokushima Eye Clinic, Tokyo, Japan.)

disciform corneal endotheliitis might be associated with HSV and VZV because the disease frequently occurs following a documented episode of infectious epithelial keratitis by these two agents.[36] The loss of corneal endothelial cells is not prominent in this form.

3.4 Diffuse Corneal Endotheliitis

Diffuse corneal endotheliitis is relatively rare, and usually occurs in association of systemic infection such as by the mumps virus. The patient exhibits the edema of the entire cornea along with fine KPs scattering within the lesion (Figure 3c). The edema spontaneously resolves within a couple of weeks with decreased corneal endothelial cell density to a varied degree. Little is known about the pathogenesis of this form; however, it is likely that the virus enters the anterior chamber hematogeneously based upon the viremia.

4. DIAGNOSIS AND TREATMENT

The diagnosis of corneal endotheliitis is mainly based on the characteristic clinical findings described above. Strictly speaking, isolation of the virus from the corneal endothelium is necessary; however, it is ethically difficult to collect the specimen directly except from a corneal button at the time of the keratoplasty. Along with biomicroscopic observation, PCR is useful to detect etiologic agents in the aqueous humor as the volume of the specimen is limited.[38] Generally, the aqueous humor is free from any pathogens as far as the sensitivity of the custom PCR is concerned; therefore, the positive result obtained by PCR is almost reliable. In this regard, the real-time PCR might be useful to distinguish between etiologic and bystander virus and to estimate the efficacy of the treatment.[39] In vivo confocal microscopy is sometimes valuable in detecting the corneal endothelial pathology such as pseudoguttata or owl's eye as previously described.[14]

In the treatment of corneal endotheliitis, systemic and topical antiviral treatment with topical corticosteroids is a rational strategy. Systemic (5 mg/Kg/three times/day for 2 weeks) and topical acyclovir (5 times a day) is indicated against corneal endotheliitis associated with HSV,[10,40] while systemic (5 mg/Kg/twice/day for 2 weeks). Topical ganciclovir (0.5% eye drop solution, 8 times/day) is necessary against those associated with CMV.[13,14,32] When myelosuppression or pancytopenia occurs in the use of systemic ganciclovir, the treatment should be discontinued. We sometimes experience that CMV corneal endotheliitis recurs soon after discontinuation of systemic ganciclovir.

5. CONCLUSION

Corneal endotheliitis is characterized by corneal edema of various locations, the presence of KPs that are consistent with corneal edema, and the mild anterior chamber reaction. Although the disease is not so common, misdiagnosis and treatment can lead to significant

damage in the corneal endothelium. It is assumed that this disease occurs through ACAID based upon clinical and basic experimental findings. The route by which the virus enters the eye to infect the corneal endothelium, or the persistence of the virus in the ocular tissue, is unknown. Further investigations are needed to elucidate the pathogenesis precisely, leading to more accurate diagnosis and proper treatment.

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J Infect Chemother (2008) 14:204–207
DOI 10.1007/s10156-008-0612-5

ORIGINAL ARTICLE

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Ocular distribution of intravenously administered micafungin in rabbits

Received: November 1, 2007 / Accepted: March 13, 2008

Abstract The ocular distribution of micafungin (MCFG), which has antifungal activity against *Candida* and *Aspergillus* species, was followed after the systemic administration of MCFG in rabbits. After MCFG (10 mg/kg) plus fluconazole (FLCZ; 10 mg/kg) was administered intravenously, the rabbits were killed, and MCFG and FLCZ concentrations in retina-choroid, vitreous humor, and plasma were determined by high performance liquid chromatography or liquid chromatography/mass spectrometry. The mean concentrations of MCFG in the retina-choroid at 0.25, 0.75, 4, 8, and 24 h after administration were 20.18, 15.97, 13.19, 6.27, and 0.75 μg/g, respectively, and were comparable with the MCFG plasma concentrations. The MCFG concentrations in retina-choroid and plasma exceeded the minimal antifungal inhibitory concentrations for endophthalmitis, although MCFG was not detected in the vitreous humor. These results suggest that the intravenous administration of MCFG is an effective treatment for endogenous fungal endophthalmitis when the causative fungus is localized in the retina and choroid.

Key words Rabbit · Eye · Pharmacokinetics · Micafungin · Fungi · Fluconazole

Introduction

Endogenous fungal endophthalmitis is a sight-threatening infection that occurs when a fungal pathogen spreads to the choroid, retina, and vitreous body of an immunocompromised host or patient undergoing intravenous hyperalimentation. Intravenous antifungal agents such as fluconazole (FLCZ) penetrate eye tissues and are effective against *Candida albicans* in an endophthalmitis rabbit-eye model.[1-3] Thus, they are often used as an adjuvant treatment. However, recently, candidemia and endogenous endophthalmitis caused by fluconazole-resistant *Candida* sp. such as *C. glabrata* or *C. krusei* have been reported.[4-7] Thus, intravenous fluconazole appears to have limited efficacy for endophthalmitis caused by fluconazole-resistant *Candida* sp. and *Aspergillus* sp.

Micafungin (MCFG) is an echinocandin with antifungal activity against *Candida* and *Aspergillus* species.[8,9] MCFG is distributed rapidly and moderately into various tissues including the liver, kidney, and lungs in rats and rabbits,[10,11] whereas MCFG levels are low or undetectable in the brain, cerebrospinal fluid, vitreous humor, and aqueous humor.[10] However, little is known about the ocular distribution of MCFG.

In the present study, we investigated the ocular distribution of MCFG in a rabbit model following the systemic administration of MCFG in combination with FLCZ, the standard therapy for fungal endophthalmitis, and we compared the distribution of these antifungals.

Materials and methods

Materials

MCFG was supplied by Astellas Pharma (Tokyo, Japan), and FLCZ injection was purchased from Pfizer (New York, NY, USA). All other reagents were of the highest purity commercially available.

Animals

Female Japanese white rabbits weighing 2.5 to 2.8 kg (Kitayama Labes, Nagano, Japan) were anesthetized with an intramuscular injection of ketamine (35 mg/kg of body weight) and xylazine (5 mg/kg) for all procedures and were killed with intravenous pentobarbital.

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Animal studies

We investigated the pharmacokinetics of coadministered MCFG and FLCZ and compared the distribution of these antifungals in the same animal. MCFG was dissolved in the FLCZ injection (Pfizer) to a final concentration of 10 mg/ml of each antifungal. Rabbits were treated with 10 mg/kg each of MCFG and FLCZ over a 15-min period by intravenous infusion into an ear vein. Three to seven animals per time point were killed at 0.25, 0.75, 1.25, 2, 4, 8, and 24 h post-administration.

Blood samples were collected from the ear before the animal was killed, and the samples were immediately centrifuged to obtain the plasma. The eyes were enucleated, rinsed in sterile saline, immediately frozen, and stored at −80°C. The frozen eyes were dissected and separated. The retina-choroid and vitreous humor were collected and stored at −80°C.

Measurement of MCFG and FLCZ concentrations in plasma and tissues

The tissues were weighed, suspended in 0.5 ml of phosphate-buffered saline (pH 7.4), and homogenized in a Teflon homogenizer. The concentrations of MCFG in plasma and tissue homogenates were determined by high-performance liquid chromatography (HPLC) as described previously.[11,12] FLCZ concentrations in plasma and tissue homogenates were determined as described previously, by HPLC[13] and by liquid chromatography/mass spectrometry (LC/MS),[14] respectively, with a minor modification. Briefly, for the assay of MCFG, acetonitrile was added to the plasma and tissue homogenates, and the mixture was centrifuged. The supernatant was injected into HPLC equipped with an analytical column (TSK gel ODS-80; 150 mm × 4.6 mm internal diameter [ID]; Tosoh, Tokyo, Japan) and the fluorescence intensity of MCFG was detected. For the assay of FLCZ, the plasma and tissue homogenates were extracted with ethyl acetate. The organic phase was evaporated, and chromatographic analysis of the residue was performed by HPLC with an analytical column (Capcell Pak C18 MG II; 250 mm × 4.6 mm ID; Shiseido, Tokyo, Japan) or by LC/MS in a mass spectrograph equipped with a Shim-Pack VP-ODS column (150 mm × 2 mm ID; Shimadzu, Kyoto, Japan). The area under the concentration-time curve (AUC) was calculated by the linear trapezoidal rule, using the mean concentrations in plasma and tissues.

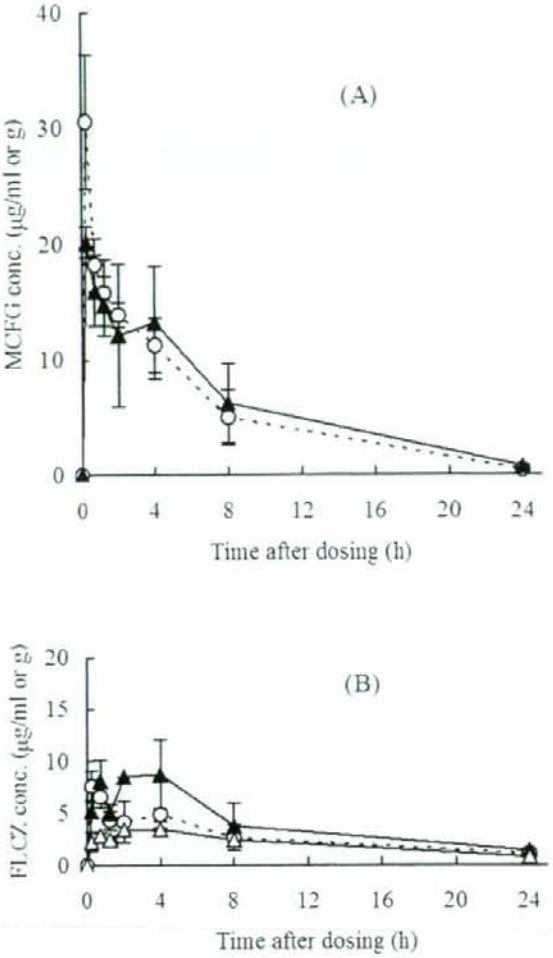

Fig. 1. **A** Micafungin (*MCFG*) and **B** fluconazole (*FLCZ*) concentrations (*conc*.; means ± SD) in plasma (*circles*), retina-choroid (*triangles*), and vitreous humor (*squares*) after an intravenous infusion (15 min) of MCFG (10 mg/kg) and FLCZ (10 mg/kg) to rabbits. The concentration of MCFG (**A**) in vitreous humor is not shown, because MCFG was not detectable in the vitreous humor

Results

The pharmacokinetic profiles of MCFG and FLCZ after intravenous infusion are shown in Fig. 1, and the pharmacokinetic parameters are summarized in Table 1. The MCFG concentrations (mean ± SD) at 0.25, 0.75, 1.25, 2, 4, 8, and 24 h after administration were 20.18 ± 1.34, 15.97 ± 3.06, 14.67 ± 2.54, 12.15 ± 6.18, 13.19 ± 4.89, 6.27 ± 3.44, and 0.75 ± 0.08 μg/g, respectively, in the retina-choroid and 30.59 ± 5.81, 18.22 ± 2.30, 15.81 ± 2.89, 13.89 ± 1.09, 11.26 ± 2.38, 5.00 ± 2.42, and 0.43 ± 0.05 μg/ml, respectively, in the plasma. In addition, the $AUC_{0\text{-}24h}$ values in the retina-choroid and plasma were 150 μg.h/g and 137 μg.h/ml, respectively. These results indicate that MCFG concentrations in the retina-choroid and the plasma were comparable. The MCFG concentrations in the retina-choroid and plasma for up to 8 h after intravenous administration, and the $AUC_{0\text{-}24h}$ value, were higher than those of FLCZ. On the other hand, MCFG was not detectable in the vitreous humor (less than 0.1 μg/ml), whereas FLCZ moderately penetrated the vitreous humor and the retina-choroid.

Table 1. Pharmacokinetic parameters of MCFG and FLCZ in plasma, retina-choroid, and vitreous humor after an intravenous infusion (15 min) of MCFG (10 mg/kg) and FLCZ (10 mg/kg) in rabbits

Drug	Tissue	T_{max} (h)	C_{max} (μg/ml or g)	C_{24h} (μg/ml or g)	$AUC_{0\text{-}t}$ (μg. h/ml or g)
MCFG	Plasma	0.25	30.59 ± 0.05 (100)	0.43 ± 0.05 (100)	137 (100)
	Retina-choroid	0.25	20.18 ± 1.34 (66)	0.75 ± 0.08 (175)	150 (109)
FLCZ	Plasma	0.25	7.61 ± 1.53 (100)	1.10 ± 0.37 (100)	64.4 (100)
	Retina-choroid	4	8.76 ± 3.33 (116)	1.40 ± 0.14 (127)	96.2 (149)
	Vitreous humor	4	3.45 ± 0.19 (46)	0.78 ± 0.13 (71)	49.4 (77)

Values in parentheses are percentages of the values for plasma

Discussion

It is well known that MCFG does not cause clinically significant interactions with coadministered drugs, and that MCFG shows no or only slight inhibition of cytochrome P450 (CYP) activities.[15] In addition, it has been reported that both MCFG and FLCZ have only slight inhibitory effects on multidrug resistance protein 1 (p-glycoprotein) activity.[16] MCFG is metabolized by multiple enzymes, including arylsulfatase, catechol-*O*-methyltransferase, and several types of CYPs, suggesting that MCFG plasma concentrations would not be significantly affected by coadministered drugs.[17] Furthermore, preliminary studies showed that plasma concentrations of coadministered MCFG and FLCZ in rabbits were comparable with the plasma concentrations of each agent when administered alone (data not shown). Therefore, we investigated the pharmacokinetics of coadministered MCFG and FLCZ and compared the distribution of these antifungals in the same animal.

Endogenous fungal endophthalmitis is uncommon, but is more prevalent than endogenous bacterial endophthalmitis. Bloodborne spread of fungi to the eye occurs in endophthalmitis. This disease presents clinically as one or more creamy-white, well-circumscribed lesions of the choroid and retina, often accompanied by inflammatory infiltrates in the vitreous humor. Though the precise route by which fungi spread to the eye is not known, the infection likely begins in the choroid and progresses anteriorly to the retinal layers.[18] In particular, *Aspergillus* spp. grow preferentially along the subretinal pigment epithelium and subretinal space.[19] Thus, antifungal drugs that penetrate the retina and choroid could be effective antifungal therapies during an initial infection of the retina and choroid.

In the present investigation, MCFG concentrations in the retina-choroid after intravenous administration were higher than FLCZ concentrations, and were comparable to MCFG plasma concentrations. The concentrations of MCFG in the retina-choroid and plasma exceeded the minimal inhibitory concentrations (MICs) for fungal pathogens that cause endophthalmitis (MIC_{90} against clinical isolates of *Candida* spp. and *Aspergillus* spp., 0.0313–0.125 μg/ml[8]). However, MCFG was present only at low levels in the vitreous humor, whereas FLCZ penetrated into both the vitreous body and retina-choroid. These results are consistent with a previous report that MCFG is distributed moderately in the lungs, liver, spleen, and kidneys after intravenous administration in rabbits, whereas the compound is present at low or undetectable levels in the aqueous humor and vitreous humor.[10] Therefore, these findings suggest that intravenous administration of MCFG alone could be an effective therapy when fungal pathogens persist in the retina and choroid, whereas systemic MCFG alone may be insufficient, and another agent, such as FLCZ, would be necessary in addition to MCFG, when a fungal pathogen has disseminated into the vitreous body.

Plasma concentrations of MCFG at 1 and 24 h after single intravenous dosing (150 mg) in healthy volunteers were reported to be 14.303 and 3.295 mg/ml, respectively, and the $AUC_{0\text{-}24h}$ was reported to be 150.1 μg.h/ml.[20] In the present study, the MCFG concentrations at 0.25 and 24 h after administration to rabbits (at 10 mg/kg) were 20.18 and 0.75 μg/g in the retina-choroid and 30.59 and 0.43 μg/ml in the plasma, respectively, and the $AUC_{0\text{-}24h}$ values were 150 and 137 μg.h/ml, respectively, indicating that MCFG concentrations in the retina-choroid were comparable with those in the plasma. Because plasma concentrations of 150 mg MCFG in humans are comparable with those observed in the present study, it can be speculated that the intravenous administration of MCFG would be clinically effective for treating fungal pathogens that persist in the retina and choroid.

It is well known that FLCZ, a CYP3A4 inhibitor, increases the plasma concentrations of some drugs, including midazolam.[15,21,22] However, MCFG does not have a clinical impact on or alter the effects of other drugs.[15,17] Therefore, MCFG may be a more useful therapy than FLCZ when a fungal pathogen persists in the retina and choroid.

There are many cases of endogenous fungal endophthalmitis in which the causative fungi cannot be detected. In these cases, antifungal agents must be selected empirically. Because MCFG has high antifungal activity against *Candida* and *Aspergillus* species and has few side effects, MCFG could be used to treat the initial phase of endogenous fungal endophthalmitis.

In conclusion, the results of the present study suggest that intravenous MCFG could be an effective treatment for initial endogenous fungal endophthalmitis when the causative pathogen is localized in the retina and choroid.

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Dacryocystography with nasolacrimal probing under fluoroscopic guidance for treatment of congenital dacryocystocele

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A congenital dacryocystocele is an uncommon variant of congenital nasolacrimal duct obstruction[1] and usually presents as a blue, cystic enlargement of the lacrimal sac just below the medial canthus. [1] It is usually accompanied by epiphora.[1] These findings are seen at birth or develop within the first few weeks of life, and a secondary dacryocystitis frequently develops.[1] It is often complicated by an intranasal cyst, which contributes to airway obstruction.[1-3] The treatment of congenital dacryocystocele is still controversial. We report a case of dacryocystocele in which dacryocystography with nasolacrimal probing under fluoroscopic guidance was effective.

Case Report

A 31-day-old girl was referred with upper airway obstruction and mucopurulent discharge from her left eye since birth. Her neonatologist diagnosed dacryocystitis and treated her with topical antibiotics.

Our initial examination showed a slightly blue nodule just inferior to the left medial canthus, and pressure on the sac produced a reflux of yellowish material through both lacrimal puncta. Tachypnea, snorting respirations, feeding difficulty, and fever were not present. Bacterial culture of the purulent material grew 1+ *Staphylococcus* sp. The results of the examination were consistent with a dacryocystocele with chronic dacryocystitis.

The patient was anesthetized topically with 0.4% oxybuprocain hydrochloride and underwent a nasolacrimal probing with a hollow Bangerter lacrimal cannula (Geuder AG, Heidelberg, Germany) in the office. The cannula had an outer diameter of 0.64 mm and an inner diameter of 0.35 mm; it was attached to a 2.5 mL syringe containing normal saline (Figure 1A). Because the cannula had a side window, and the tip was round and tapered, nasolacrimal irrigation could be combined with careful probing (Figure 1B). A significant resistance was encountered, and the probing failed. She was treated with oral antibiotics for 1 week after the first probing.

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Submitted September 14, 2007.
Revision accepted January 7, 2008.
Published online March 25, 2008.

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J AAPOS 2008;12:299-301.

1091-8531/2008/$35.00 + 0
doi:10.1016/j.jaapos.2008.01.001

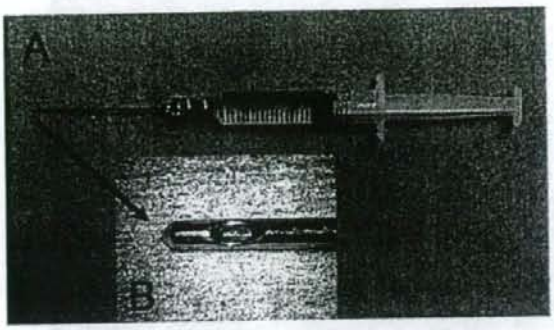

FIG 1. The Bangerter cannula. (A) The hollow probe of Bangerter is attached to a 2.5-mL syringe. (B) The tip of the probe is round and tapered.

Fourteen days later, dacryocystography was performed with the Bangerter cannula attached to a syringe containing 61.2% iopamidol (Iopamiron 300; Nihon Schering K.K., Osaka, Japan), and a digital radiographic system (ADR-1000A; Toshiba Medical Systems, Tokyo, Japan) was used to examine the patency of the lacrimal system. All procedures were performed in the examination room. The probe was inserted into the lacrimal sac through the lower canaliculus, and there was no resistance at the entry of the lacrimal sac. The contrast medium was injected, and the lacrimal sac and nasolacrimal duct were seen to be markedly enlarged. The lower part of the nasolacrimal duct bent medially and extended into the nasal cavity (Figure 2). The inferior turbinate, the lateral nasal wall, and the nasal floor could be identified.

The tip of the probe was inserted into the nasal cavity through the lowest margin of the nasolacrimal duct under fluoroscopic guidance (Figure 2). A soft membranous obstruction was encountered at the distal end of the nasolacrimal duct, that is, at the location of the valve of Hasner. The patency of the lacrimal system was confirmed by nasolacrimal irrigation with the passing of contrast medium.

Her symptoms were completely resolved at the last examination performed 6 months after the second probing.

Discussion

Dacryocystoceles with intranasal cysts may cause an obstruction proximally at the junction of the common canaliculus and the lacrimal sac and distally at the level of valve of Hasner.[1,2,4] The proximal obstruction may be functional, which can be verified by the absence of an anatomic barrier during probing and by reflux of lacrimal sac con-

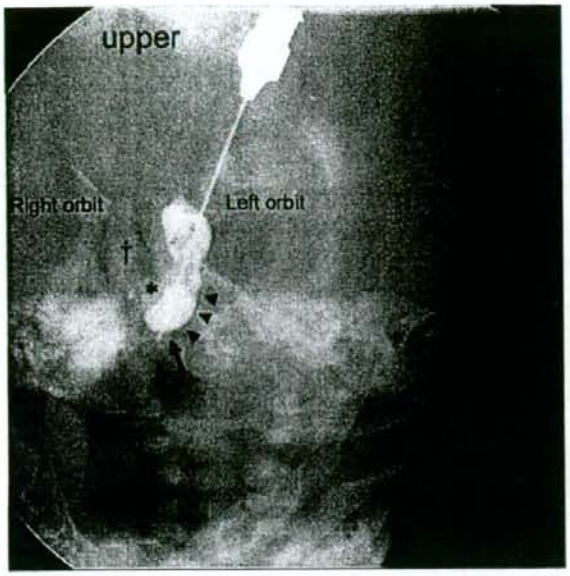

FIG 2. Dacryocystogram showing that the lacrimal sac and nasolacrimal duct are markedly enlarged. The lowest part of the nasolacrimal duct bends medially and extends into the nasal cavity. The tip of the probe was inserted over the lowest edge of the nasolacrimal duct and directed medially. The inferior turbinate (asterisk), nasal septum (dagger), lateral nasal wall (arrowhead), and nasal floor (arrow) can be seen.

tents on digital pressure.[1] Mansour et al[1] reported that 11 of 54 cases (21%) of congenital dacryocystocele had reflux of lacrimal sac material upon digital pressure, while the majority were noncompressible with a firm consistency.

Diagnostic evaluation of a patient with a suspect dacryocystocele may include computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, and nasal endoscopy.[1,5] CT and MRI have proved to be invaluable for an anatomical diagnosis, because they can demonstrate that the dacryocystocele is contiguous with an enlarged nasolacrimal duct, indicating an intranasal cyst. CT and MRI are also helpful in differentiating a dacryocystocele from a medial canthal mass.[1,5]

Intubation dacryocystography is also a useful method to investigate the lacrimal drainage system in infants.[6] This technique can identify the site of obstruction, provide findings that help in planning the appropriate surgical procedures, and is a prognostic guide.[6] In our experience, intubation dacryocystography can be performed under topical anesthesia in the examination room.

The treatment of congenital dacryocystocele is still controversial.[1-3] Several investigators have advocated an initial conservative approach, including intravenous and/or topical antibiotics and lacrimal sac massage.[1,2] However, acute dacryocystitis, cellulitis, and respiratory distress can develop within days or weeks,[2] and such infections at this age can be potentially life threatening due to the risk of sepsis.[7]

Therefore, other investigators have recommended immediate surgical intervention, including a nasolacrimal probing,[1,2] nasolacrimal intubation,[1,8] endoscopic cyst incision or marsupialization,[1,2,7,9] and nasal endoscopy combined with lacrimal probing.[3,5] Nasal endoscopy can confirm the presence of an intranasal cyst.[1-3,5,7] The cyst wall can be extracted and/or excised under direct view.[7,9] However, nasal endoscopic examination requires general anesthesia with an increase in the cost.[7] In Japan, the cost of nasal endoscopic examination is approximately $56 USA; dacryocystography is $9. In addition, the cost of simple probing is approximately $335; nasolacrimal intubation is $163, and nasolacrimal irrigation is $4. The cost of general anesthesia is $890, and topical anesthesia is $2. Therefore the cost of our procedure is approximately $346.

A simple nasolacrimal probing can be performed in the office under topical anesthesia[1,2] and is highly successful in cases that do not have an infection, but not in cases with dacryocystitis or cellulitis.[2] Busse et al[10] reported the presence of a deep bend of the nasolacrimal duct just before it entered the nasal cavity by performing dacryocystography in infants and stated that it was almost impossible to perforate Hasner's membrane with the conventional Bowman probe. Similar anatomical findings in infants were reported by Choi et al.[8] They reported that the failure of simple probing was due to a misdirection of the probe, and a submucosal passing of the probe was seen. They stated that directing the tip medially or nasally instead of the usual posterolateral direction can perforate this membrane. Lueder reported that the success rate of the probing is related to the size of the intranasal cyst[7]; a small cyst can be punctured by the probe, but it is difficult to penetrate a large cyst that rests on the nasal floor.[7]

Our findings are in agreement with these reports. This anatomical feature in infants may be one of the factors that caused the failure of our initial probing, because the probe was directed in the usual posterolateral direction. Moreover, the intranasal cysts did not rest on the nasal floor, and a shallow opening of the nasal cavity was identified between the lowest part of the nasolacrimal duct and the nasal floor. Therefore, the probe could be inserted into this space under direct view with fluoroscopic guidance, and the nasolacrimal patency can be confirmed by injecting contrast medium.

The disadvantages of our procedure are the increased financial costs and radiation exposure, and the procedure requires a radiographic system. However, nasal endoscope also requires additional instruments and radiation exposure is also necessary in CT examination. Moreover, infants are much more radiosensitive than adults to the induction of cancer risk.[11] The radiation exposure dose of our procedure is about 40 μSv, which is lower than that of a chest x-ray (about 80 μSv) and a CT scan (about 6100 μSv).[11]

We recommended our technique as one option for the diagnosis and treatment of dacryocystocele, especially in cases in which the proximal obstruction is functional and a reflux of lacrimal sac contents on digital pressure is present.

However, our dacryocystographic technique should not be performed when there is respiratory distress, acute dacryocystitis, or cellulitis.

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First Person

When testing vision with Allen pictures, I have had more than a few contemporary children with perfectly good vision balk at the picture of a dial telephone—they have no idea what it is and so cannot come up with a word for it. No problem with newer slides showing a push-button phone! And, of course, here in New York City, the bird is, often as not, a "pigeon."

—*Scott E. Brodie*, MD, PhD

Cytomegalovirus as an Etiologic Factor in Corneal Endotheliitis

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Purpose: To investigate clinical manifestations and response to antiviral therapy of 8 patients with cytomegalovirus (CMV)-induced corneal endotheliitis who were diagnosed and treated at 2 university hospitals in Japan.

Design: Retrospective, consecutive, multicenter case series.

Participants: Eight eyes of 8 patients diagnosed with active CMV corneal endotheliitis at Kyoto Prefectural University of Medicine and Ehime University School of Medicine. The diagnosis was made based on the detection by polymerase chain reaction assay of CMV, but not herpes simplex virus (HSV) and varicella zoster virus (VZV) DNA, in the aqueous humor from the affected eye.

Methods: Retrospective review of the clinical manifestations and responses to antiviral treatment.

Main Outcome Measures: Patient profiles, including duration of corneal endotheliitis, systemic disease, intraocular pressure, and clinical manifestation of anterior and posterior segments. The clinical response to systemic and topical antiviral treatment was evaluated by slit-lamp examination. Corneal endothelial density was examined by specular microscopy.

Results: The average observation period after CMV detection was 10.4 months (range, 2–24 months). None of the patients had systemic immunodeficiency. Corneal manifestations included linear keratic precipitates associated with multiple coin-shaped lesions and local corneal stromal edema. Of the 8 patients, 4 had undergone penetrating corneal transplantation. Systemic ganciclovir therapy was used in 7 patients, and in 1 patient, valacyclovir was administered, with the corneal endotheliitis responding quickly to the early administration of galovir. At the final examination, 6 eyes had a clear cornea, but 2 eyes had bullous keratopathy.

Conclusions: Besides HSV and VZV, CMV must be considered as an etiologic agent in patients with corneal endotheliitis. Cytomegalovirus corneal endotheliitis may be a newly identified clinical entity of reactivated CMV in the anterior chamber of individuals free of accompanying systemic symptoms. *Ophthalmology 2008;115:292–297 © 2008 by the American Academy of Ophthalmology.*

The corneal endothelium comprises the innermost layer of the cornea and plays an important role in maintaining corneal clarity. Corneal endotheliitis, a specific inflammation of the corneal endothelium, is characterized by corneal edema associated with linear keratic precipitates and destruction of the endothelium and often leads to severe visual disturbance. Khodadoust and Attarzadeh.[1] who first reported bilateral recurrent corneal edema associated with linear keratic precipitates similar to endothelial rejection lines, proposed the designation *presumed autoimmune corneal endotheliopathy*. However, later observations that some patients with corneal endotheliitis responded poorly to corticosteroid therapy suggested an infectious disease origin.[2] Some reports suggested herpes simplex virus (HSV) as an etiologic agent for corneal endotheliitis,[3,4] and HSV and varicella zoster virus (VZV) have been detected in the corneal endothelium,[5] aqueous humor,[6–8] and trabeculae[8,9] of patients with corneal endotheliitis. An association between herpes virus and corneal endotheliitis was supported by the favorable response of corneal endothelial lesions to topical and systemic acyclovir treatment,[10] and corneal endotheliitis is now considered one of the clinical entities of corneal infection with herpes virus species.[11,12] However, the aqueous humor of patients with corneal endotheliitis

Originally received: January 27, 2007.
Final revision: April 4, 2007.
Accepted: April 6, 2007.
Available online: July 31, 2007. Manuscript no. 2007-125.

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Supported in part by research grants from the Ministry of Education, Culture, Sports, Science, and Technology, Tokyo, Japan.

The authors have no commercial or financial interests associated with the article.

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ISSN 0161-6420/08/$–see front matter
doi:10.1016/j.ophtha.2007.04.053