Candida endophthalmitis associated with intraocular lens implantation: efficacy of fluconazole therapy

Candida-Endophthalmitis nach intraokulärer Linsenimplantation: Wirksamkeit der Fluconazol-Therapie

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Summary. Four patients with *Candida parapsilosis* endophthalmitis following intraocular lens implantation were treated with oral fluconazole. All had failed prior therapy with intravitreal amphotericin B. The only patient who had the lens implant removed was cured after treatment with fluconazole for one year. Three patients who did not have the lens implant removed had resolution of symptoms and return of visual acuity towards normal during the year they were on fluconazole. However, five months after therapy had been stopped, all three had decreasing visual acuity, and in two, culture of vitreous fluid yielded *C. parapsilosis*. Fluconazole may be effective for treatment of endophthalmitis associated with an intraocular lens implant, but only when the implant is removed also.

Zusammenfassung. Vier Patienten mit *Candida parapsilosis*-Endophthalmitis nach intraokulärer Linsenimplantation wurden oral mit Fluconazol behandelt. Bei allen Patienten hatte die vorherige intravitreale Amphotericin B-Therapie versagt. Einem Patienten wurde die implantierte Linse entfernt; er war nach einjähriger Fluconazol-Therapie geheilt. Den drei anderen Patienten wurde die implantierte Linse nicht entfernt. Unter einjähriger Fluconazol-Therapie besserten sich zwar die Symptome, und die Sehschärfe normalisierte sich. Fünf Monate nach Beendigung der Therapie verschlechterte sich jedoch bei allen drei Patienten die Sehfähigkeit wieder, und bei zwei von ihnen konnte aus der Glaskörperflüssigkeit wieder *C. parapsilosis* isoliert werden. Fluconazol kann also bei Endophthalmitis nach Linsenimplantation wirksam sein, jedoch nur wenn das Implantat wieder entfernt wird.

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Introduction

An uncommon and dreaded complication of cataract extraction and intraocular lens implantation is fungal endophthalmitis. Outbreaks and individual case reports of fungal endophthalmitis due to filamentous fungi and yeasts, such as *Candida*, have been described [1–6]. In most reports of fungal endophthalmitis associated with intraocular lens implantation, the outcome has been poor. One reason for this is possibly the poor penetration of most antifungal drugs into the eye [7–9]. Fluconazole is a bis-triazole antifungal agent which has been shown to penetrate into both the vitreous body and aqueous humour of the eye [9, 10]. We report on our experience with fluconazole in the treatment of four patients who had *Candida parapsilosis* endophthalmitis following cataract extraction with implantation of an intraocular lens.

Patients and methods

Four patients with culture-proven *C. parapsilosis* endophthalmitis following implantation of a posterior chamber intraocular lens were evaluated and treated between January 1989 and September 1990. Treatment was 400 mg of oral fluconazole daily, except in one patient who had renal insufficiency and received 200 mg daily. Informed consent was obtained prior to beginning fluconazole therapy. Symptoms and ocular findings were followed monthly for the duration of therapy, which was one year in all patients, and follow-up was carried out for two years after therapy was completed.

Results

The four patients, three of whom were women, were 66 to 74 years of age (Table 1). All had undergone extracapsular cataract extraction and had a posterior chamber intraocular lens implanted. Following the implantation, visual acuity improved in all patients, but one to four months later all experienced a gradual decrease in visual acuity and patients 1, 3 and 4 had intraocular pain.

Over the course of their infection, all four patients had mild to moderate flare and cells in the anterior chamber, keratitic precipitates, and vitritis present. Patient 1 developed an hypopyon, and patient 3 developed a rhegmatogenous reti-

nal detachment. Light perception was intact in all patients. Three patients could see only gross movement in the affected eye. None had any systemic symptoms, such as fever, weight loss or fatigue.

The diagnosis of *Candida* endophthalmitis was made by culture of the vitreous aspirate in two patients and by culture of the vitrectomy and posterior capsulotomy tissue in two patients. The diagnosis was not made until six months after lens implantation in three patients and ten months after implantation in the remaining patient. Prior to the diagnosis of *Candida* infection, all patients had been treated with topical, paraocular or intravitreal cortiosteroids, and patients 1 and 3 had received oral prednisone.

After the diagnosis of *Candida* endophthalmitis was made, initial antifungal treatment in all four patients was intravitreal amphotericin B; in addition, patient 1 had intravenous amphotericin B for one week and flucytosine for two weeks. All patients had transient improvement in vision, but then experienced decreasing visual acuity over the next four to six months. Intravitreal amphotericin B was given again in all patients with only transient improvement of vision.

In patient 1 the lens implant was removed, but in the other three patients the implant was not removed either because the patient was a poor operative risk (patients 2 and 4) or because of secondary problems of retinal detachment and low intraocular pressure (patient 3).

During fluconazole therapy the three patients

Table 1. Treatment and outcome in 4 patients with *Candida* endophthalmitis following intraocular lens implantation

Patient no.	Age/Sex	Treatment prior to fluconazole therapy				Outcome
		Surgery	Steroid therapy	Intravitreal antifungals	Implant removed	
1	66/M	Posterior capsulotomy, vitrectomy × 2	Topical, paraocular, oral	Amphotericin × 2	Yes	Lens removed, (+) *C. parapsilosis*. 2 years post-Flu, V.A. 20/25 and no inflammation
2	70/F	Posterior capsulotomy, vitrectomy × 2	Topical, intravitreal	Amphotericin × 2	No	V.A. improved from count fingers to 20/40. 5 months post-Flu, vitreous (+) *C. parapsilosis*
3	74/F	Posterior capsulotomy, vitrectomy × 3, scleral buckle	Topical, paraocular × 2, oral	Amphotericin × 3 Miconazole × 1	No	V.A. 20/70 post-Flu 5 months post-Flu, increasing inflammation, Flu begun again 7 months later
4	70/F	Posterior capsulotomy, vitrectomy × 2	Intravitreal, topical	Amphotericin × 2	No	V.A. improved from count fingers to 20/40. 4 months post-Flu, vitreous (+) *C. parapsilosis*

V.A. = visual acuity; Flu = fluconazole.

with ocular pain had relief and all patients had improvement in visual acuity and a decrease in inflammation noted on examination. The patient who had the lens implant removed had return of his visual acuity to 20/25, has done well for over two years since fluconazole was stopped, and presumably is cured. The three patients in whom the lens implant was not removed did well while on fluconazole, but all relapsed with decreasing visual acuity four to five months after therapy was stopped. Two patients had vitreous aspiration performed four and five months after therapy was stopped, and both showed growth of *C. parapsilosis* on culture.

Discussion

Post-surgical *Candida* endophthalmitis is a subacute to chronic infection appearing weeks to months after surgery [2, 3, 11]. It mimics infection with other pathogens of low virulence, such as *Propionobacterium acnes*, which is found more frequently as a cause of post-operative endophthalmitis in patients with intraocular lens implants [3]. Post-surgical fungal endophthalmitis typically results in indolent, smouldering intraocular inflammation with mild pain and external signs similar to the findings with *P. acnes* infection. Pain, decreased visual acuity, and intraocular inflammation are also seen in post-operative, non-infectious uveitis, which is a more common complication than infection during the post-operative period.

The similarity in findings between post-operative sterile uveitis and infection with pathogens of low virulence probably explains why all of our patients and most reported cases of post-operative *Candida* endophthalmitis were initially treated with corticosteroids. Although valuable in decreasing inflammation, it is likely that the use of corticosteroids increased the progression of *Candida* infection in these patients.

It is essential that in all cases of post-operative endophthalmitis cultures be performed to ascertain if micro-organisms are present. The highest yields are from vitreal aspirates or vitrectomy [2]. Organisms are often present in low numbers and need to be assiduously sought by appropriate culture techniques, including use of aerobic and anaerobic growth conditions and use of several different media to allow growth of both bacteria and fungi.

C. parapsilosis has been implicated in previous reports as a cause of post-operative endophthalmitis following cataract extraction alone [11, 12] and with intraocular lens implantation [1, 2, 6].

Most notable was an outbreak of *C. parapsilosis* endophthalmitis traced to contaminated balanced salt solution used intra-operatively [1, 2]. Thirteen cases were documented to be culture positive for *C. parapsilosis*, and the implicated lot of irrigating solution also yielded *C. parapsilosis* [1]. All of these patients had an indolent post-operative endophthalmitis with symptoms and signs similar to those noted in our patients.

Although a less common cause of fungaemia than *C. albicans*, *C. parapsilosis* is frequently implicated as a cause of infection in patients receiving total parenteral nutrition and in those with prosthetic devices, and is often a nosocomially acquired infection [13–16]. *C. parapsilosis* appears to be less pathogenic than *C. albicans* or *C. tropicalis* on the basis of experimental animal studies [13], and patients with *C. parapsilosis* fungaemia appear to have a lower mortality than those with fungaemia due to *C. albicans* and *C. tropicalis* [13, 14, 16].

Treatment of fungal endophthalmitis is difficult. Amphotericin B has been used successfully to treat haematogenously acquired *Candida* endophthalmitis [17, 18]. In a rabbit model of haematogenous *Candida* endophthalmitis, intravenous amphotericin B was superior to intravenous fluconazole in eradicating the fungus from both the choroid-retina and the vitreous body [19]. Intraocular administration of amphotericin B has also been used successfully in some cases of *Candida* endophthalmitis [2, 6, 11, 20].

Post-surgical exogenously acquired *Candida* endophthalmitis appears to be more difficult to treat than haematogenously acquired infection [21]. The infection is usually very low grade with minimal inflammation, thus leading to low concentrations of antifungal drugs in the tissues [7, 9]. Also, the presence of a foreign body, in the case of infection following intraocular lens implantation, makes eradication of fungal infection difficult [3, 4]. One additional point that may be important is that although *Candida* infection may be sight-threatening, many patients and physicians are unwilling to use long-term systemic amphotericin B to treat this localized infection [2, 7, 20]. This is especially true in elderly individuals, who receive most intraocular lens implants, and who are more likely to have pre-existing renal insufficiency and tolerate amphotericin B less well [22].

The best reported results for treating *Candida* endophthalmitis associated with an infected lens implant are those which utilized vitrectomy combined with intravitreal injection of amphotericin B and systemic amphotericin B and flucytosine [2, 6]. In 13 patients, Stern *et al.* reported that visual acuities of 20/60 or better were obtained

in five patients treated this way; however, two patients had negative cultures to begin with and one required subsequent removal of the lens [2]. Thus, only two of 11 patients who had cultures positive for *C. parapsilosis* had a good result with this method of treatment. Three patients required removal of the lens, only one of whom had a good outcome. Stransky's patient had a good response to pars plana vitrectomy, intravitreal amphotericin B, and systemic flucytosine, but she did not have a lens implant in place [11].

All of our patients failed treatment with vitrectomy and intravitreal amphotericin B. Although the initial response to intravitreal amphotericin B was favourable, decreasing visual acuity and relapse with positive cultures ultimately followed. The course was indolent, so that relapse was not obvious for several months. In every case, either the patient was unwilling or unable to take systemic amphotericin B, or the physician caring for the patient was unwilling to embark on this course of therapy. The one patient who did have amphotericin B refused to take more than seven days of therapy.

Fluconazole is very attractive as therapy for *Candida* endophthalmitis. It has been used to treat a variety of different types of *Candida* infections, can be used safely for prolonged periods of time, and has been shown to achieve good concentrations in many body fluids, including the eye [9, 10, 18]. In rabbits, Walsh *et al.* showed that fluconazole concentrations in the vitreous and the choroid were approximately 50% of those found in plasma at peak plasma concentrations and almost twice as high as plasma concentrations 24 h after an intravenous dose of fluconazole [10]. These results confirmed those of Savani *et al.* [9], who showed in rabbits that fluconazole penetrated the aqueous humour and vitreous body even in the absence of inflammation, an important point in patients such as ours with low-grade inflammation.

However, data obtained in rabbits with experimental *Candida* endophthalmitis raise questions about the efficacy of fluconazole in treating *Candida* endophthalmitis [9, 19]. Fluconazole proved to be less effective than either amphotericin B or other azoles, even though higher drug levels were measured for fluconazole than for the other drugs [9, 19]. It should be noted that the rabbit model of haematogenously acquired *Candida* endophthalmitis does not replicate *Candida* infection of an intraocular lens implant, nor does short-term therapy of seven to 24 days used in these studies necessarily predict what will occur in patients treated for much longer.

Prior experience with fluconazole for *Candida*

endophthalmitis in humans has been reported in eight patients [23–26]. In seven patients with haematogenous endophthalmitis, clinical success was noted with fluconazole given in doses of 100 mg to 400 mg daily for 3–5 weeks [24–26]. Only one of these patients had cultures performed [26]; follow-up in four patients for 4–7 months confirmed probable cure in all four [25, 26]. Another patient was treated with 100 mg fluconazole daily for 15 weeks for *C. parapsilosis* endophthalmitis following corneal transplant. This patient's infection recurred 12 weeks after therapy was stopped [23].

Although all of our patients improved clinically, only one, the patient who had the lens implant removed, was cured. If at all possible, both removal of the foreign body and antifungal therapy should be carried out to enhance the possibility for a cure. If it is difficult to remove the implant, as occurred with several of our elderly patients, then chronic suppression with a relatively non-toxic oral drug, such as fluconazole, is a reasonable option. In this case, therapy probably should be continued for life to suppress recurrence of the infection.

Acknowledgement

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