Fax: 01702221 279
E-mail: doc_akash2002@yahoo.co.uk

Eye (2005) **19,** 484–485. doi:10.1038/sj.eye.6701489
Published online 30 July 2004

Sir,

Use of voriconazole in candida retinitis

Candida retinitis is a sight-threatening ocular infection that frequently occurs as a complication of candidemia. Voriconazole is a recently introduced broad-spectrum antifungal drug. To the best of our knowledge, its use in candida retinitis and candida endophthalmitis has not been reported before.

Case report

A 39-year-old 'terminally ill' woman with known systemic candidiasis secondary to central venous line infection was referred to the ophthalmic 'on call team'. She complained of bilateral simultaneous visual deterioration of 1-week duration. Her past medical history included hyperactive thyroid associated with paroxysmal atrial fibrillation. She had recently undergone major gastrointestinal surgery for extensive small bowel infarction and developed postoperative sepsis. Ocular examination included bedside visual acuity (VA), intraocular pressure measurement using Perkins tonometer, direct ophthalmoscopy, and indirect ophthalmoscopy. Slit-lamp examination was not possible. Her corrected VA was 5/60 in the right eye and 6/60 in the left eye. Anterior segment examination was unremarkable with absence of a relative afferent pupillary defect and normal intraocular pressures. Fundus examination of both eyes revealed multiple, creamy white retinal lesions at the posterior pole (Figures 1 and 2). The overlying vitreous appeared clear, although detailed slit-lamp evaluation was not possible. A diagnosis of bilateral candida retinitis was made. Candida had been cultured from her blood, urine and sputum samples; however, information on drug sensitivities was not available at the time of treatment. Over the next few days, both general and ocular condition deteriorated despite high doses of intravenous fluconazole (800 mg daily for 2 weeks), therefore it was decided to use oral Voriconazole (4 mg/kg bodyweight) instead.

After 2 days, the retinal lesions were seen to decrease in size. The patient was reviewed daily and 2 weeks later the lesions were significantly smaller in size. The same consultant ophthalmologist who had examined the patient prior to treatment with voriconazole noted the post-treatment clinical improvement. Unfortunately, the patient demised due to cardio-respiratory arrest and further follow-up including photographic documentation of clinical improvement following use of voriconazole was not possible.

Comment

Candidiasis is an opportunistic infection of intravenous drug users and debilitated patients. Ocular candidiasis can result from either haematogenous spread or direct inoculation and is characterised by anterior and/or posterior segment inflammation. Candida retinitis is characterised by small, round, white slightly elevated lesions that enlarge and extend into the vitreous cavity-forming floating white colonies. Endophthalmitis

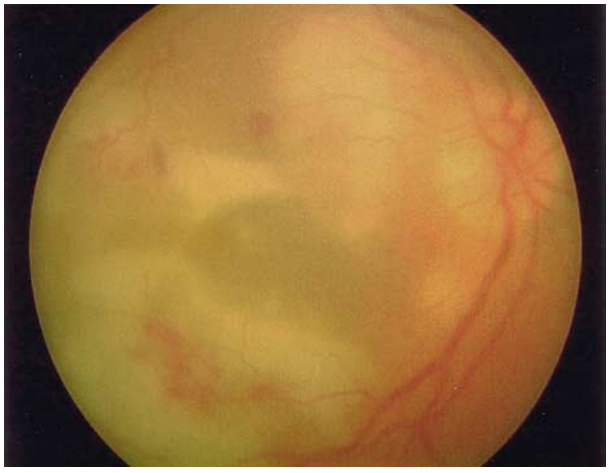

Figure 1 Right eye fundus photograph showing multiple areas of candida retinitis with associated haemorrhages at posterior pole.

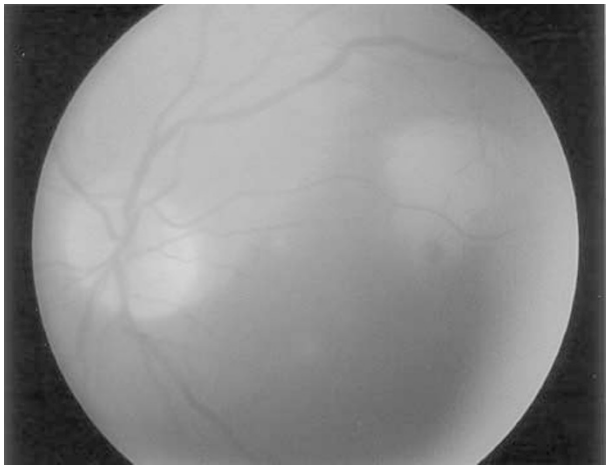

Figure 2 Left eye fundus photograph.

and severe retinal necrosis are seen in the advanced stage.[1] Predisposing factors for endogenous candida endophthalmitis (ECE) include indwelling catheters, bacterial sepsis, prolonged broad-spectrum antibiotic use, and gastrointestinal surgery.[2] In patients with candidaemia, the reported incidence of ECE is 28–37%. In spite of modern antibacterial, antimycotic, and operative therapies, ECE has a very poor prognosis and is associated with high mortality.

While use of amphotericin B and fluconazole in invasive fungal infections is well documented, the optimal management of candidal retinitis has not been determined.[3] Amphotericin penetrates poorly into ocular fluids, is toxic, and must be given intravenously. Fluconazole is a bis-triazole derivative proven highly effective against candida. However, it is more effective in preventive use than in therapeutic use against ECE. In the treatment of patients with marked vitreous infiltrates from ECE, pars plana vitrectomy, appropriate systemic, and intravitreal antifungal medication are generally recommended.

Voriconazole, a member of second-generation antifungal triazoles, is a broad-spectrum antifungal agent with demonstrated *in vitro* activity against azole resistant species of *Candida* and *Aspergillus*.[4] Voriconazole has good oral and parenteral bioavailability.[5,6] Voriconazole exhibits nonlinear pharmacokinetics. An apparent low volume of distribution (21/kg) suggests widespread distribution of the drug throughout the body tissues and fluids. Voriconazole levels in the cerebrospinal fluid appear to be the same as in serum. Information on penetration to sites such as eye is limited. The chief adverse effects reported are transient visual disturbances, hepatotoxicity, and skin reactions. Visual disturbances include enhanced light perception, blurred vision, photophobia, and colour vision changes.[5,7] These have been reported in 23–35% of patients. They generally occur within 30 min of dosing and most frequently during the first week of therapy.[7] The majority of these events are mild and resolve even if treatment is continued.

Lewis *et al*[8] studied antifungal activity in an *in vitro* model of Candidia catheter-related bloodstream infection. They ranked overall antifungal activity as amphotericin B > voriconazole > fluconazole.

Garbino *et al*[4] reported successful treatment of *Paecilomyces lilacinus* endophthalmitis with oral voriconazole. Treatment with voriconazole was considered when the patient failed to improve on systemic fluconazole and oral itraconazole.

In our patient, the treatment was switched to oral voriconazole following deterioration on intravenous fluconazole.

Conclusion

Candida endophthalmitis can be the only manifestation of disseminated candidiasis. Early recognition is essential to prevent irreversible loss of vision. This case report suggests that voriconazole may have a role as primary treatment of endogenous candida endophthalmitis or in patients resistant to fluconazole.

References

1 Kanski JJ. *Clinical Ophthalmology*, 4th ed. Butterworth Heinemann: Great Britain, 1999.
2 Brod RD, Flynn HW, Clarkson JG, Pflugfelder SC, Culbertson WW, Miller D. Endogenous candida endophthalmitis: management without intravenous Amphotericin B. *Ophthalmology* 1990; **97**(5): 666–674.
3 Akler ME, Vellend H, McNeely DM, Walmsley SL, Gold WL. Use of fluconazole in the treatment of candidal endophthalmitis. *Clin Infect Dis.* 1995; **20**(3): 657–664.
4 Garbino J, Ondrusova A, Baligvo E *et al*. Successful treatment of *Paecilomyces lilacinus* endophthalmitis with voriconazole. *Scand J Infect Dis* 2002; **34**: 701–703.
5 Chandrasekar PH, Manavathu E. Voriconazole: a second generation triazole. *Drugs Today* 2001; **37**(2): 135–148.
6 Purkins L, Wood N, Ghahramani P, Greenhalgh K, Allen MJ, Kleinermans D. Pharmacokinetics and safety of voriconazole following intravenous to oral-dose escalation regimens. *Antimicrob Agents Chemother* 2002; **46**(8): 2546–2553.
7 Ghannoum MA, Kuhn DM. Voriconazole-better chances for patients with invasive mycoses. *Eur J Med Res*. 2002; **7**(5): 242–256.
8 Lewis RE, Kontoyiannis DP, Darouiche RO, Raad II, Prince RA. Antifungal activity of amphotericin B, fluconazole, and voriconazole in an *in vitro* model of candidia catheter related bloodstream infection. *Antimicrob Agents Chemother.* 2002; **46**(11): 3499–3505.

D Varma[1], HR Thaker[2], PJ Moss[2], K Wedgwood[3] and JR Innes[4]

[1]Department of Ophthalmology
Royal Victoria Infirmary, Claremont Wing
Queen Victoria Road, Newcastle upon Tyne
NE1 4LP, UK

[2]Castle Hill Hospital Hull, UK

[3]Hull Royal Infirmary, Anlaby Road, Hull, UK

[4]Eye Department, Hull Royal Infirmary
Anlaby Road, Hull, UK

Correspondence: D Varma
Tel: + 44 191 2824410

Fax: + 44 191 2275246
E-mail: deepalivarma@hotmail.com

Eye (2005) **19,** 485–487. doi:10.1038/sj.eye.6701427
Published online 23 April 2004

Sir,

Buphthalmos in trisomy 13

Trisomy 13 is the rarest and most severe of the three viable autosomal trisomies, the others being 18 and 21. It is also the chromosomal abnormality most commonly associated with severe ocular defects, including microphthalmos, iris coloboma, and retinal dysplasia. The clinical picture of trisomy 13 was described in 1656 by Thomas Bartholin, and in 1960, Klaus Patau[1] reported the finding of an extra D chromosome in such a patient, now known to be an additional chromosome 13. The typical dysmorphic features include microcephaly, hypertelorism, micrognathia, low-set ears, cutis aplasia, cleft lip and palate, and polydactyly. Internal structural defects affecting the heart and brain are common, with high mortality in the neonatal period. Survivors exhibit severe developmental delay.

Case report

The neonate we describe was a female born prematurely by caesarean section at 28 weeks gestational age. The mother, age 39 years, had pre-eclampsia and the foetus was growth retarded, weighing just 630 g at birth. She was noted to have micrognathia and microstomia, low-set ears, bifid uvula, wide scalp defect between anterior and posterior fontanelles, and bilateral talipes. Ocular examination showed hyperteleorism. The globes were buphthalmic and bilateral corneal stromal oedema was present, obscuring fundal detail. Examination with the indirect ophthalmoscope revealed aniridia and some evidence of an iris root only. Intraocular pressures by Perkins applanation tonometry were 30 mmHg OD and 40 mmHg OS. Treatment with topical dorzolamide was commenced; however, before the eyes could be re-evaluated, a diagnosis of Patau's syndrome was confirmed cytogenetically, and in view of severe respiratory difficulty all treatment was withdrawn.

Comment

In his original description of a patient with trisomy 13, Patau states 'no organised ocular tissue could be seen or palpated'. Case series detailing the ocular characteristics of trisomy 13 have since been published.[2–4] The most frequent findings are microphthalmia, coloboma of the iris and ciliary body, and retinal dysplasia. Other abnormalities described include PPHV, cataract, cyclopia, and primary aphakia. We have found four previously reported cases of congenital glaucoma associated with trisomy 13.

The first such description is by Keith[4] in a review of ocular manifestations and histopathology in 10 cases of trisomy 13. He noted bilateral buphthalmos in one case, gestational age not stated. No iris defect is described. Hinzpeter *et al*[5] reported a trisomy 13 neonate born at 35 weeks gestational age with corneal diameters of 15×15 mm bilaterally, and IOPs of 33 mmHg OD and 50 mmHg OS. Histological examination demonstrated anterior inserted iris root but normal iris leaf. Lichter and Schmickel[6] described a trisomic infant born at term, who developed corneal enlargement and clouding at 4 months of age. IOPs were 59 and 40 mmHg. The iris appeared normal. In 1981, Reardon *et al*[7] reported an unusual trisomy 13 mosaic, the predominant cell line being trisomic for the distal portion of the long arm of chromosome 13. Born at 37 weeks gestation, ocular examination showed left microphthalmos and iris coloboma. Glaucoma of the right eye was recognised at 1 year with buphthalmos. The right iris was atrophic with stromal defects inferiorly. IOP was 50 mmHg OD, 15 mmHg OS.

The case of trisomy 13 we have described is notable both for established buphthalmos at just 28 weeks gestational age, and the lack of iris. The early delivery of this infant tells us that buphthalmos can take place as early as the second trimester, contrasting with presentation at 1 year of age in the case of the trisomy 13 mosaic. Mosaicism was excluded in our case on the basis of a 10 cell karyotype, coupled with the severity of the phenotype.

The second unusual finding, the almost complete lack of iris tissue, has not been described in the literature in association with trisomy 13, nor is it a feature of the above cases of glaucoma in trisomy 13. Iris coloboma, however, is a typical feature and while we have not excluded specific secondary chromosomal defects, a severe colobomatous-type defect would seem the most likely aetiology.

A normal chromosome 13 complement seems to be essential for the proper development of the eye, and while trisomy 13 often results in a microphthalmic eye at birth, it can exceptionally give rise to buphthalmos. Hoepner and Yanoff[8] emphasised a characteristic 'dysembryogenesis' of the anterior segment in a histological review of trisomy 13 patients, finding microphthalmic eyes with immature drainage angles. We speculate that if the drainage structures are disproportionately underdeveloped compared with the