Resolution of Macular Edema after Systemic Treatment with Furosemide

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We report two cases of macular edema treated with the oral administration of furosemide. The first case presented here was a 78-year-old male patient with visual disturbance of the left eye. He had been taking an oral agent for diabetes and had chronic renal failure for 7 years. From 10 days prior to the visit, he had visual disturbance of the left eye accompanied by systemic edema. There were no specific findings in the anterior segment, but sub-retinal fluid was observed in the left fundus. Macular edema was observed on fluorescein angiography and optical coherence tomography; therefore, the oral administration of furosemide was initiated. After seven days, the sub-retinal fluid disappeared. The second case was a 43-year-old female patient with visual disturbance of the left eye who had been taking hypoglycemic agents for diabetes for 13 years. There were no specific findings in the anterior segment, but flame-shaped retinal hemorrhages were scattered over both posterior poles, neovascularization was observed in the left eye, and, of particular note, sub-retinal fluid was detected in the macula of the left eye. Macular edema was also observed on fluorescein angiography and optical coherence tomography, and oral administration of furosemide was initiated. After 3 weeks, the macular edema had significantly decreased.

Key Words: Furosemide, Macular edema

Furosemide is widely used as a therapeutic for edema secondary to congestive heart failure, liver cirrhosis, or renal disease. The drug suppresses the reabsorption of sodium and chloride in the distal tubule of the ascending loop of the loop of Henle and thus causes increased excretion of water, potassium, sodium, chloride, and calcium [1]. Ciardella [2] reported the resolution of macular edema after systemic treatment with furosemide in one case of combined diabetic mellitus and nephrotic syndrome. However, macular edema treatment with furosemide has yet to be reported in Asia. Therefore, we report 2 cases of macular edema treated with the oral administration of furosemide.

Case Report

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Case Reports

Case 1

A 78-year-old male patient visited our clinic for visual disturbance of the left eye which had developed one day previously. The patient had no ophthalmologic history, and he had been taking hypoglycemic agents for the control of diabetes mellitus for 3 years and was being medicated for chronic renal failure by the Department of Internal Medicine at our hospital. One day prior to presentation to our department, he developed systemic edema, and oral administration of 160 mg furosemide (Lasix; Handok Pharmaceuticals Co., Seoul, Korea) was administered by the Department of Renal Internal Medicine for the treatment of systemic edema. His blood pressure was 161 / 90. The basic data describing his systemic condition including body weight and height was not taken during his visit to the Internal Medicine Department. He did not have any history of furosemide treatment due to systemic edema. Blood tests at that time revealed an increase of blood urea

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nitrogen (BUN, 47 mg/dL) and creatinine (1.8 mg/dL), and urinary albumin was detected (500 mg/dL). On presentation to our department, the best corrected visual acuity of the right eye was 0.5, and that of the left eye was 0.125. The intraocular pressure of both eyes was within normal range. Upon fundus examination of the left eye, retinal edema was observed in the posterior pole, including the macula. On fluorescein angiography, macular edema caused by vessel leakage was detected in the left eye (Fig. 1A). Macular edema was confirmed by optical coherence tomography (Fig. 1C). Two days after the oral administration of furosemide, the visual acuity of both eyes had improved to 0.6 and 0.3, respectively. After 7 days, the visual acuity of both eyes had improved to 0.9 and 0.6, respectively. Fundus examination and optical coherence tomography revealed complete disappearance of the sub-retinal fluid in the left eye (Fig. 1D). Before the oral administration of furosemide, the right eye showed a mild abnormality on fluorescein angiography (Fig. 1B). Because visual acuity of the right eye improved after administration of furosemide, we speculated that sub-retinal fluid was also present in the right eye.

Case 2

A 43-year-old female patient diagnosed with non-proliferative diabetic retinopathy and under regular ophthalmological examination developed visual disturbance in the left eye. Ophthalmological tests were thus performed. This patient had a disease history of intermittent systemic edema and thus a history of taking furosemide (Lasix). At admission, all blood tests were normal except for the elevation of BUN (44 mg/dL) and creatinine (1.8 mg/dL). In the past, her renal function test was within the normal range. The best-corrected visual acuity of the right eye was 0.5, that of the left eye was 0.4, and the intraocular pressure of both eyes was within the normal range. In the fundus of the right eye, scattered flame-shaped retinal hemorrhages were observed in the posterior pole. In the fundus of the left eye, in addition to scattered flame-shaped retinal hemorrhage, new vessels were also observed (Fig. 2A). On optical coherence tomography, edema was present in the
posterior pole including the macula (Fig. 2B), but routine blood and urine tests were normal. Panretinal photocoagulation and the oral administration of 120 mg furosemide were initiated for the treatment of macular edema, especially serous retinal detachment. After 3 weeks of oral administration of furosemide, macular edema, especially serous retinal detachment, had improved, but visual acuity had not improved (Fig. 2C). Bevacizumab (1.25 mg; Avastin, Genentech, San Francisco, CA, USA) was injected intravitreally at this stage in order to treat the remaining cystoid macular edema and subretinal fluid. One month after the injection, complete resolution of the subretinal fluid and cystoid macular edema was seen, but the visual acuity had still not improved (Fig. 2D).

Discussion
Diabetic macular edema is caused by the accumulation of fluid in the macula secondary to destruction of the inner blood retinal barrier due to changes in retinal capillaries and vascular endothelial cells. Diabetic macular edema may be caused by traction of the vitreous on the retina and retinal vessels. The progression and severity of diabetic macular edema has been shown to be associated with renal diseases. Knudsen et al. [3] reported that, in diabetic macular edema, the macular thickness correlates with the urinary albumin excretion rate and the transcapillary escape rate of albumin, which reflects a change in renal capillary permeability. If diabetes mellitus complications progress to the level of renal capillary injury, with albumin thus excreted in urine, corresponding retinal capillary injuries can also be expected, with destruction of the inner retinal blood barrier and subsequent macular edema. Additionally, we hypothesized that decreased serum albumin level due to the excretion of albumin itself and decreased blood oncotic pressure due to the decreased serum albumin level could cause systemic fluid retention and thus fluid retention in the macula, especially a serous retinal detachment pattern. Thus, furosemide, commonly used as a therapeutic for systemic edema, may also be effective for macular edema, depending on the specific cause. Ciardella [2] explained that macular edema in diabetic retinopathy
patients with nephrotic syndrome is caused by the overload of body fluid and claimed that macular edema could be treated with furosemide by reducing the overload of body fluid.

In our second case, in contrast to the first case, only the subretinal fluid resolved after the use of diuretics. The remaining retinal edema was nearly resolved after the intravitreal injection of bevacizumab. Although the first patient also had diabetes, he did not exhibit diabetic retinopathy. The macular edema in the first patient was thus not due to diabetic retinopathy but to the decrease of osmotic pressure secondary to proteinuria. We suggest that the macular edema in the second patient was due to both diabetic retinopathy and a decrease in osmotic pressure, which implies that macular edema caused by the retention of body fluid may manifest as a structural change such as serous retinal detachment. Furthermore, diabetic macular edema has been previously morphologically classified by the use of optical coherence tomography [4,5]. It is thought that, morphological changes may be classified according to the cause of macular edema, such as fluid retention and the impairment of the inner blood retinal barrier. However, additional studies are required to assess this conclusion.

It should therefore be noted that diabetic macular edema can be caused and aggravated by diabetic systemic complications as well as diabetic retinal disease. Common treatment methods for macular edema include the suppression of capillary permeability (e.g., through laser photoacoagulation and intravitreal injection) and the increase of active water excretion by the retinal pigment epithelium through acetazolamide therapy [6]. Future therapies may also include those already used for treatment of systemic edema; for example, plasma proteins such as albumin and diuretics. Particularly, furosemide may be of help in diabetic patients with systemic edema or albuminuria and structural change of the macula, especially serous retinal detachment. As shown in both cases herein, a waiting period for systemic improvement might be needed before more invasive eye treatment such as intravitreal injection in patients receiving furosemide treatment for acute aggravation of systemic edema.

**Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

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