



Case report

A case of drug induced lung injury caused by levofloxacin eye drops

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ARTICLE INFO

Keywords:

Levofloxacin
Eye drop
Ophthalmic solution
Drug-induced lung injury
Eosinophilic pneumonia

ABSTRACT

A 78 year-old man, who received levofloxacin eye drops as a perioperative prophylactic antibacterial agent for cataract surgery, developed pyrexia and dyspnea, followed by respiratory failure. He was diagnosed as drug-induced lung injury due to levofloxacin, and the symptoms improved after the administration of corticosteroids and discontinuation of levofloxacin eye drops. The incidence of levofloxacin-induced lung injury is rare for its frequent prescription. Moreover, eye drops of it has never been reported to cause lung injury. We should be aware of eye drops as a causative dosage forms of drug-induced lung injury.

1. Introduction

Prophylactic antibiotic administration for cataract and vitreous surgery has been reported to significantly contribute to sterilization of the surgical fields [1], and antibiotic ophthalmic solutions such as cepheems and quinolones are used routinely [2]. Drug-induced lung injury due to quinolones is rare, and only six cases associated with tablets or injections have been reported previously [3–8]. Furthermore, most of the adverse effects caused by levofloxacin ophthalmic solutions are local reactions. Here we present the first case of drug-induced lung injury considered to be due to levofloxacin eye drops.

2. Case report

A 78-year-old man was admitted to the Department of Ophthalmology for binocular cataract surgery. He was a current smoker, and had a past history of hypertension and hyperlipidemia. He had been treated with nifedipine, candesartan, atorvastatin, doxazosin and sarpogrelate for three years. However, he had never had an allergic reaction. The history of pre-exposure of levofloxacin was not clear. He had no abnormality in preoperative examination. On the day of admission, levofloxacin eye drops were started as a perioperative prophylactic antibacterial drug, and the operation was performed on the next day without complications. On day 3, he presented with fever and dyspnea but with no change in the surgical sites; he was treated with cefcapene pivoxil. However, the hypoxia and oliguria rapidly worsened, and laboratory examination revealed neutrophilia, elevation of the C-reactive protein, and impairment of liver and kidney function (Table 1). Chest X-ray and computed tomography (CT) showed bilateral non-

segmental consolidation with thickening of the bronchovascular bundles and pleural effusion, mainly in the left upper lobe (Fig. 1). No abnormal findings were noted in electrocardiogram and ultrasound cardiography. As we considered the differential diagnosis (bacterial pneumonia followed by sepsis, acute renal failure, or diastolic heart failure since brain natriuretic peptide [BNP] was 511 pg/mL), continuous hemodiafiltration and treatment with tazobactam/piperacillin (TAZ/PIPC) were started along with ventilatory support in the intensive care unit. After that, the renal function improved, but respiratory failure and fever were prolonged in spite of changing TAZ/PIPC to meropenem (MEPM). Furthermore, an increase in airway pressure with accompanying wheezes developed, but these symptoms were temporarily improved with corticosteroid treatment. Various microbial examinations and tests for autoantibodies were negative (Table 1). On day 10, bronchoalveolar lavage fluid (BALF) was obtained revealing an increase in lymphocytes and eosinophils (Table 1). Based on these results, we considered a diagnosis of drug-induced lung injury, so we stopped nifedipine hydrochloride and sivelestat sodium and changed MEPM to levofloxacin injection. However, the patient's respiratory condition worsened, and liver dysfunction also re-emerged. Therefore, levofloxacin injections were stopped, and we administered steroid therapy. Afterwards, the respiratory failure and liver dysfunction gradually improved. However, since the fever continued, we reconfirmed the patient's list of drugs in detail and found that levofloxacin eye drops had been continued. The drops were immediately discontinued. After that, the fever and respiratory failure resolved, and the patient was extubated on day 22. We made the diagnosis of lung injury induced by levofloxacin eye drops based on the positive results of a drug lymphocyte stimulation test (DLST) of levofloxacin (Table 2) and the episode of

Abbreviations: CT, computed tomography; BNP, brain natriuretic peptide; TAZ/PIPC, tazobactam/piperacillin; MEPM, meropenem; BALF, bronchoalveolar lavage fluid; DLST, drug lymphocyte stimulation test; PMDA, Pharmaceuticals and Medical Devices Agency; EP, eosinophilic pneumonia

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<https://doi.org/10.1016/j.rmcr.2018.03.010>

Received 6 March 2018; Received in revised form 15 March 2018; Accepted 15 March 2018

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Table 1
Laboratory findings on postoperative day 2.

CBC			Blood chemistry			(1 → 3)-β-D-glucan		
WBC	12780	/μL	TP	5.3	g/dL	<i>Aspergillus</i> antigen	< 5.0	pg/mL
Neu	90	%	Alb	2.4	g/dL	<i>Cryptococcus</i> antigen		negative
Lym	7	%	T-bil	1.6	mg/dL	<i>C. pneumoniae</i> IgG		positive
Eos	0	%	AST	92	U/L	<i>C. pneumoniae</i> IgA		negative
RBC	3.67 × 10 ⁶	/μL	ALT	130	U/L	<i>C. pneumoniae</i> IgM		negative
Hb	11.6	g/dL	LDH	234	U/L	<i>M. pneumoniae</i> antibody		negative
Ht	34.0	%	BUN	60.1	mg/dL	Rapid-Antigen Tests		
Plt	17.5 × 10 ⁴	/μL	CRE	2.77	mg/dL	Influenza		negative
Coagulation test			Na	138	mEq/L	<i>Legionella pneumophila</i>		negative
PT-INR	1.27		K	4.8	mEq/L	<i>Streptococcus pneumoniae</i>		negative
APTT	29.8	s	Serology			Culture		
Fib	795	mg/dL	CRP	26.45	mg/dL	Blood, Sputum, Urine, BALF		negative
FDP	3.0	ng/mL	KL-6	188	U/mL	BALF (day10)		
Arterial blood gases			SP-D	534	ng/mL	Total cell counts	3.2 × 10 ⁵	%
mask with reservoir 10L/min			IgE	892.8	IU/mL	Mac	14.4	%
pH	7.318		Anti-nuclear antibody	< 40	titer	Neu	34.6	%
pO ₂	62.0	Torr	RF	< 10	IU/mL	Lym	36.2	%
pCO ₂	40.7	Torr	MPO-ANCA	< 1.0		Eos	14.8	%
HCO ₃	20.3	mEq/L	PR3-ANCA	< 1.0		CD4/8	2.55	

Abbreviation: BALF, bronchoalveolar lavage.

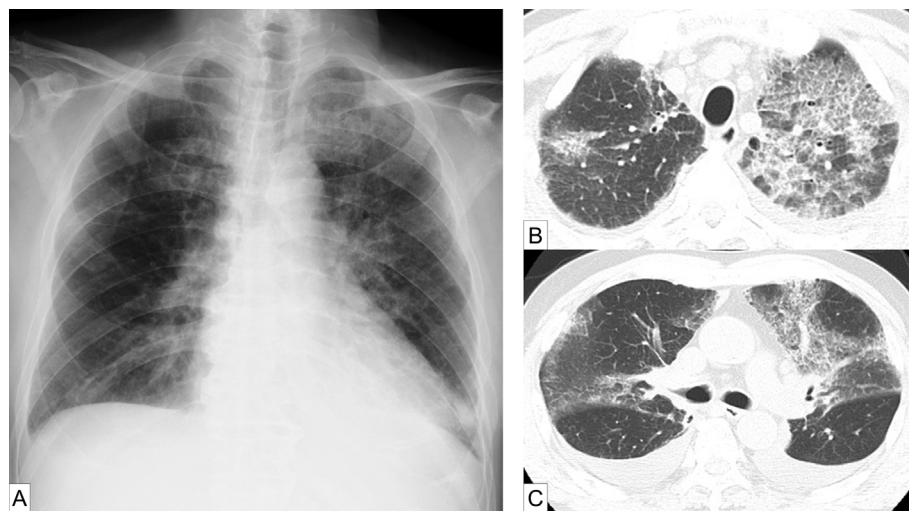


Fig. 1. Chest X-ray and chest plain computed tomography (CT) on postoperative day 2. (A) Chest radiograph showed ground glass attenuations (GGAs) and consolidation in the right upper lung fields and left upper and middle lung fields. (B) and (C) CT showed bilateral non-segmental consolidation and GGAs with thickening of bronchovascular bundles and pleural effusion mainly in the left upper lobes.

Table 2
Drug-induced Lymphocyte Stimulation Test.

Drugs	Measured value (cpm)	Stimulation Index (%)
levofloxacin intravenous drip infusion	1237	327
levofloxacin ophthalmic solution	917	242
fosfomycin (intravenous)	328	86
cefcape pivoxil	341	90
tazobactam piperacillin	331	87
meropenem	331	87
diclofenac ophthalmic solution	243	64
control	378	

Bold font: positive for DLST.

deterioration after levofloxacin injection. The patient was discharged on day 57, and he was weaned from steroids gradually without recurrence (Fig. 2).

3. Discussion

We experienced a suspected case of levofloxacin eye drops induced lung injury. Drug-induced lung injury caused by levofloxacin is rare

compared with the frequency of its use, but it is a serious adverse event. Table 3 shows a summary of reported cases of drug-induced lung injury due to quinolones. To the best of our knowledge, there are only four cases of drug-induced lung injury due to levofloxacin, which were induced by tablets or injections [3–6]. As for other quinolones, there was only one case associated with ciprofloxacin and tosufloxacin, respectively [7,8]. Levofloxacin ophthalmic solution is one of the most widely used antimicrobial eye drops in the world, and adverse effects are mostly local reactions. Systemic adverse effects are very few and include only anaphylaxis and contact dermatitis [9,10]. As far as we could investigate in the published literature and in information about cases of suspected adverse drug reactions reported to the Pharmaceuticals and Medical Devices Agency (PMDA), drug-induced lung injury due to ophthalmic antibacterial agents has never been reported; thus, this is the first reported case of drug-induced lung injury due to levofloxacin eye drops [11].

The pathophysiologic mechanism of drug-induced lung injury is mostly unknown except for a small number of drugs; basically, it is considered that drugs have direct toxicity, act like a hapten, or mimic an antigen that activates immune cells [12]. Levofloxacin ophthalmic solution is absorbed into the systemic circulation from the nasal mucosa via the conjunctival blood vessels and the nasolacrimal ducts after ocular administration, but its plasma concentration is extremely low as compared with oral administration. One possibility is that this case was

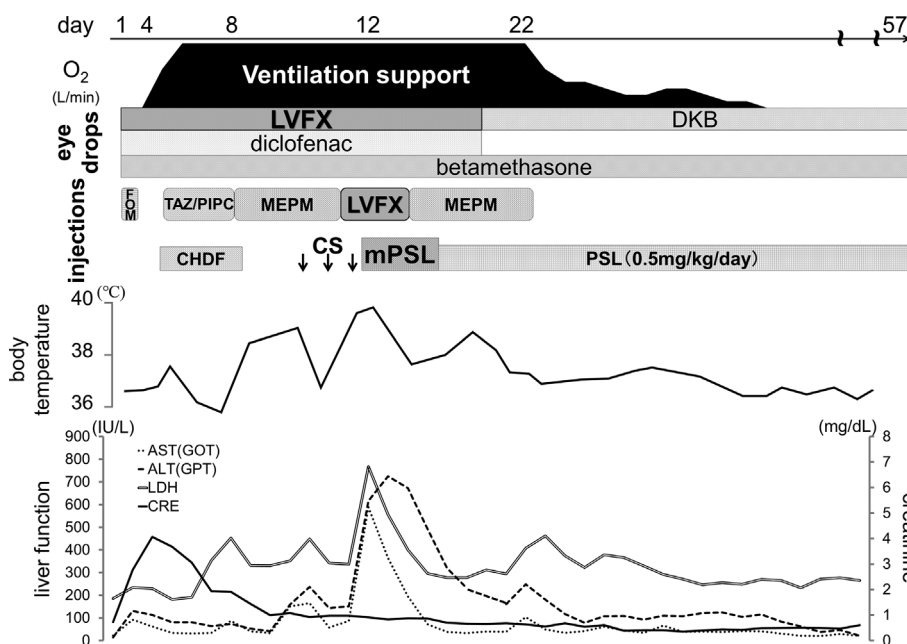


Fig. 2. Clinical course. Steroid therapy and levofloxacin withdrawal resulted in improvement of respiratory failure and liver function. FOM, fosfomycin; LVFX, levofloxacin; DKB, Dibekacin; TAZ/PIPC, tazobactam/piperacillin; MEPM, meropenem; CHDF, continuous hemodiafiltration; CS, corticosteroids; mPSL, methylprednisolone; PSL, prednisolone.

Table 3
Clinical features of fluoroquinolone-induced pneumonia.

Authors	Suspected Drugs	Form	Age	Sex	Peripheral Eosinophil	IgE (IU/L)	BAL (%) Eos/Lym	Pathological Diagnosis (Collection Method)	LST	Challenge Test	Therapy
Fujimori et al. [3]	levofloxacin	tablet	76	F	24% (2784/μl)	112	55/24	eosinophilic pneumonia (TBLB)	positive (LMIF)	NR	drug withdrawal
Tohyama et al. [4]	Levofloxacin shin-i-seihai-to	tablet	55	F	6.2% (390/μl)	197	12/34	organizing pneumonia (TBLB)	positive (DLST)	NR	drug withdrawal
Sibusa et al. [5]	levofloxacin roxoprophen	tablet	39	M	0%	NR	43/0	NR	positive (DLST)	NR	steroid
Nicola et al. [6]	levofloxacin	injection	44	M	NR	NR	28/15	eosinophilic pneumonia (TBLB)	NR	positive	steroid
Steiger et al. [7]	ciprofloxacin	tablet	68	F	NR	NR	87/0	hypersensitivity pneumonitis (SLB)	negative (DLST)	NR	steroid
Kimura et al. [8]	tosufloxacin	tablet	74	M	7% (931/μl)	16196	21/38	eosinophilic pneumonia (TBLB)	negative (DLST)	positive	steroid
This case	levofloxacin	eye drop; injection	78	M	0%	892.8	14.8/36.2	not done	positive (DLST)	positive	steroid

Abbreviation: NR, not recorded; Eos/Lym, eosinophil/lymphocyte; TBLB, transbronchial lung biopsy; SLB, surgical lung biopsy; LST, lymphocyte stimulation test; LMIF, lymphocyte migration inhibitory test; DLST, drug lymphocyte stimulation test.

sensitized by an extremely small amount of levofloxacin in the systemic circulation. Although the patient did not show any local symptoms after ocular instillation, another possibility is sensitization by the antigen presented to the Langerhans cells in the conjunctiva, followed by pulmonary injury expressed as a delayed type of allergy [13,14]. DLST indicates the presence of sensitized lymphocytes, and the patient had a positive DLST for levofloxacin [15]. Based on all of these findings, we concluded that delayed allergy due to cellular immunity caused this adverse effect.

We diagnosed lung injury induced by levofloxacin eye drops because of the following points: an episode of deterioration after levofloxacin injection, negative results of the examination for infections and autoimmune diseases, and improvement after administration of steroids and discontinuation of levofloxacin administration by both injection and eye drops. In addition, positive DLST results with only levofloxacin eye drops and injection (Stimulation Index 242, 327), even during steroid administration, helped to confirm the diagnosis (Table 2). In the past reports of quinolone-induced lung injury (Table 3), three of five cases had a positive DLST, resulting in the same positive rate of 60.0%

that Kondo et al. reported [16]. We consider that DLST is a meaningful test when a drug challenge test is difficult, as in the current case.

In this case, the radiographic findings showed non-segmental consolidation, ground glass attenuations with thickening of the broncho-vascular bundles, pleural effusion and mild lymphadenopathy. BALF analysis revealed higher lymphocyte number compared to eosinophil number. These results indicated the possibility of eosinophilic pneumonia (EP) pattern or organizing pneumonia pattern. Although we could not make a pathological diagnosis due to the patient's severe respiratory failure, we finally assessed pulmonary condition of this case as EP pattern based on the BALF analysis showing increased eosinophil number and increased total serum IgE level. EP case showing higher lymphocyte number compared to eosinophil number in BALF was reported [8]. In addition, previously reported cases diagnosed as fluoroquinolone-induced pneumonia tended to show EP pattern than other patterns (Table 3). And we also considered the possibility that eosinophil in BALF may have been affected by the corticosteroid, as BALF was performed after its administration. Moreover, levofloxacin has low cardiotoxicity, and there are only four reports of pulmonary edema or

cardiac failure in the information about reported cases of suspected adverse drug reaction by PMDA [11,17]. However, based on the elevation of the BNP and radiographic changes, it is also possible that diastolic heart failure may have occurred concomitantly.

There were some limitations in this case. We could not completely confirm the diagnosis as having lung injury induced by levofloxacin eye drops because we could not exclude the possibility that lung injury was induced by other drugs such as meropenem or diclofenac [18,19], or infection was complicated with lung injury. In addition, we could not do rechallenge test of levofloxacin eye drops because drug induced lung injury was life-threatening.

The basis of the treatment of drug-induced lung injury is to discontinue the causative drug immediately. In this case, fever and respiratory failure were prolonged even after initiation of steroid administration and finally improved after discontinuation of levofloxacin eye drops. Levofloxacin, which has high efficacy and tolerability, is widely used in various dosage forms. As cataracts are still the most common cause of blindness, cataract surgery is expected to continue to increase in the future [20]. Drug-induced lung injury may occur with any drug and by any route of administration; eye drops are especially easy to overlook as causative drugs, and special attention is required.

Conflict of interest

The authors have no potential conflicts of interest to disclose.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

- [1] Y. Inoue, M. Usui, H. Shiota, T. Yamazaki, Preoperative Disinfection Study Group. Perioperative disinfection of the conjunctival sac with antibiotics and iodine compounds: a prospective randomized multicenter study, *Jpn. J. Ophthalmol.* 52 (2008) 151–161.
- [2] K. Matsuura, T. Mori, T. Miyamoto, C. Suto, Y. Saeki, et al., Survey of Japanese ophthalmic surgeons regarding perioperative disinfection and antibiotic prophylaxis in cataract surgery, *Clin. Ophthalmol.* 8 (2014) 2013–2018.
- [3] K. Fujimori, Y. Shimatsu, E. Suzuki, M. Arakawa, F. Gejyo, Levofloxacin-induced eosinophilic pneumonia complicated by bronchial asthma, *Nihon Kokyuki Gakkai Zasshi* 38 (2000) 385–390 (in Japanese, Abstract in English).
- [4] M. Tohyama, N. Arakaki, K. Tamaki, T. Shimoji, A case of drug-induced pneumonitis due to levofloxacin and kanpo medicine, *Nihon Kokyuki Gakkai Zasshi* 44 (2006) 951–956 (in Japanese, Abstract in English).
- [5] T. Shibusa, K. Onuma, A case of possible drug-induced lung injury caused by levofloxacin, *Nihon Kyoubu Rinsho* 74 (2015) 691–696 (in Japanese, Abstract in English).
- [6] N. Facciolongo, F. Menzella, C. Castagnetti, A. Cavazza, R. Piro, et al., Eosinophilic infiltrate in a patient with severe legionella pneumonia as a levofloxacin-related complication: a case report, *J. Med. Case Rep.* 4 (2010) 360.
- [7] D. Steiger, L. Bubendorf, M. Oberholzer, M. Tamm, J.D. Leuppi, Ciprofloxacin-induced acute intestinal pneumonitis, *Eur. Respir. J.* 23 (2004) 172–174.
- [8] N. Kimura, E. Miyazaki, O. Matsuno, Y. Abe, T. Tsuda, Drug-induced pneumonitis with eosinophilic infiltration due to tosufloxacin tosylate, *Nihon Kokyuki Gakkai Zasshi* 36 (1998) 618–622 (in Japanese, Abstract in English).
- [9] M. Saito, T. Nakada, Contact urticaria syndrome from eye drops: levofloxacin hydrate ophthalmic solution, *J. Dermatol.* 40 (2013) 130–131.
- [10] Santen Pharmaceutical Co., Ltd. Cravit ophthalmic solution 0.5%, Iyakuhin interview form Internet. Tokyo: Pharmaceuticals and Medical Devices Agency. www.info.pmda.go.jp/go/interview/1/300237_1319742Q1039_1_1F [3 May 2018] (in Japanese).
- [11] Information about reported cases suspected adverse drug reaction. Pharmaceuticals and Medical Devices Agency. http://www.info.pmda.go.jp/fsearchnew/jsp/menu_fukusayou_base.jsp [Accessed 3 May 2018] (in Japanese).
- [12] K. Kubo, A. Azuma, M. Kanazawa, H. Kameda, M. Kusumoto, et al., Consensus statement for the diagnosis and treatment of drug-induced-lung injuries, *Respir. Investig.* 51 (2013) 260–277.
- [13] T.E. Gillette, J.W. Chandler, J.V. Greiner, Langerhans cells of the ocular surface, *Ophthalmology* 89 (1982) 700–711.
- [14] D.P. Metz, A.S. Bacon, S. Holgate, S.L. Lightman, Phenotypic characterization of T cells infiltrating the conjunctiva in chronic allergic eye disease, *J. Allergy Clin. Immunol.* 98 (1996) 686–696.
- [15] W.J. Pichler, J. Tilch, The lymphocyte transformation test in the diagnosis of drug hypersensitivity, *Allergy* 59 (2004) 809–820.
- [16] A. Kondo, Drug-induced pneumonitis, *Kekkaku* 74 (1999) 33–41 (in Japanese).
- [17] C. Carbon, Levofloxacin adverse effects, data from clinical trials and pharmacovigilance, *Therapie* 56 (2001) 35–40.
- [18] Al Celik, A. Deniz, M. Tangalay, M.B. Karaaslan, Bağır Kılıç, Eosinophilic myocarditis associated with eosinophilic pneumonia and eosinophilia following antibiotic and narcotic analgesic treatment, *Türk Kardiyol Dern Ars* 44 (2016) 511–513.
- [19] H. Khalil, E. Molinar, J.K. Stoller, Diclofenac (Voltaren)-induced eosinophilic pneumonitis. Case report and review of the literature, *Arch. Intern. Med.* 26 (1993) 1649–1652.
- [20] R.R. Boume, G.A. Stevens, R.A. White, J.L. Smith, S.R. Flaxman, et al., Causes of vision loss worldwide, 1990–2010: a systemic analysis, *Lancet Glob. Health* 1 (2013) e339–349.