A case of bilateral leg edema associated with levofoxacin
A case report

Jeonggu Na, MD\textsuperscript{a}, Tae Won Lee, MD\textsuperscript{a,c}, Eunjin Bae, MD, PhD\textsuperscript{a,c}, Eun Ju Lee, MD\textsuperscript{b}, Ha Nee Jang, MD\textsuperscript{b,c}, Hyun Seop Cho, MD\textsuperscript{b,c}, Se-Ho Chang, MD, PhD\textsuperscript{b,c,d}, Dong Jun Park, MD, PhD\textsuperscript{b,c,d,*}

Abstract

Rationale: A number of medicines are associated with edema. However, only 2 cases of edema of both lower legs, associated with levofoxacin, have been reported.

Patient: We report the case of levofoxacin-associated bilateral leg edema in an 81-year-old male. The patient was referred to the Division of Nephrology due to edema limited to both lower legs, which had developed 1 day before. He had undergone supraglottic laryngectomy due to supraglottic cancer in our institution 6 months ago. He had been admitted to the Department of Otolaryngology due to persistent aspiration and general weakness 5 days ago.

Diagnosis: The patient had no underlying diseases that could result in edema. No abnormalities were detected in several diagnostic tests. He strongly denied using other medications including herbal or traditional remedies, recreational drugs, or drugs of abuse. The patient had been intravenously administered levofoxacin at 750 mg per day 5 days earlier; on this basis levofoxacin-induced edema was suspected.

Interventions and outcomes: Levofoxacin was immediately withdrawn and conservative management (salt restriction and withdrawal of intravenous fluid) was initiated. His edema was completely restored within 3 weeks after withdrawal of levofoxacin.

Outcomes: The patient stopped taking levofoxacin and he did not have any recurrent edema until his death due to uncontrolled pneumonia.

Lessons: Levofoxacin should be added to the list of drugs associated with the development of bilateral leg edema. This might obviate the need for time-consuming studies for diagnostic purposes and application of ineffective or harmful treatments.

Abbreviations: ADR = adverse drug reaction, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = Blood urea nitrogen, CCB = calcium channel blockers, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, ECG = electrocardiography, HPF = high-power field, NSAIDS = non-steroidal anti-inflammatory drugs, NT-proBNP = N-terminal prohormone of brain natriuretic peptide, RBC = red blood cell, RLL = right lower lung, TSH = thyroid stimulation hormone, WHO-UMC = World Health Organization-Uppsala Monitoring centre.

Keywords: adverse drug reactions, edema, levofoxacin

Editor: N/A.

Informed consent was obtained from the patient for publication of this case report and accompanying images, but this case report did not require an ethics committee approval according to the current laws in our hospital.

The authors have no funding and conflicts of interest to disclose.

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/8WN8Bb

\* Department of Internal Medicine, Gyeongsang National University Changwon Hospital, Changwon, \textsuperscript{b} Department of Internal Medicine, Gyeongsang National University Hospital, \textsuperscript{c} Department of Internal Medicine, College of Medicine, Gyeongsang National University, Jinju, Republic of Korea.

Correspondence: Dong Jun Park, Department of Internal Medicine, Changwon Hospital and College of Medicine, Gyeongsang National University, Changwon, Republic of Korea (e-mail: dpdp@naver.com).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2019) 98:30(e16581)

Received: 24 January 2019 / Received in final form: 21 May 2019 / Accepted: 2 July 2019
http://dx.doi.org/10.1097/MD.0000000000016581

1. Introduction

Levofoxacin is a third-generation fluoroquinolone antibiotic with broad-spectrum activity and is typically prescribed to treat bacterial infections including acute bacterial sinusitis, pneumonia, urinary tract infection, and chronic prostatitis.\textsuperscript{1,2} It may also be used to manage tuberculosis, meningitis, or pelvic inflammatory disease along with several other agents.\textsuperscript{3} Levofoxacin is particularly effective against Gram-positive bacteria such as \textit{Streptococcus pneumoniae} and \textit{Enterococcus} spp., and atypical organisms, such as \textit{Mycoplasma} and \textit{Chlamydia} species.\textsuperscript{4,5} The common and benign side effects associated with levofoxacin include diarrhea, nausea, headache, and insomnia; these result in discontinuation of the drug in 4.3% of patients.\textsuperscript{4,5} Serious side effects may include tendon damage, inflammation, rupture, seizure, and psychosis.\textsuperscript{4,6} Only 2 cases of levofoxacin-associated leg edema have been reported in the literature: one Letter to the Editor\textsuperscript{7} and 1 case report.\textsuperscript{8} We report here the case of a male patient with pneumonia who developed levofoxacin-associated bilateral leg edema and review the relevant literature.
2. Case report

An 81-year-old male patient was referred to the Division of Nephrology due to edema limited to both lower extremities starting the day before. He had undergone supraglottic laryngectomy due to supraglottic cancer in our institution 6 months ago and was subsequently followed up at an otolaryngology clinic. His medical history included chronic obstructive pulmonary disease (COPD). He used a SPIRIVA (tiotropium bromide) inhaler for COPD management twice per day. The patient had quit smoking 6 months ago and had experienced dysphagia and odynophagia after the operation. He was admitted to the Department of Otolaryngology due to pneumonia 5 days before. Levofloxacin 750 mg per day and cefepime 3 g per day were intravenously administered for his pneumonia as recommended by the Division of Pulmonology. He did not complain of edema in both legs at the time of admission. He strongly denied use of other medications including herbal or traditional remedies, recreational drugs, or drugs of abuse, except for 6.25 mg of zolpidem. He did not have sleep apnea.

The patient had a chronically ill appearance and was cachectic and, after admission, spent most of the time supine. His vital signs were as follows: blood pressure, 130/60 mmHg; heart rate, 81 beats/min; respiratory rate, 22/min; and body temperature, 37.8°C. His body weight was 38 kg at the time of hospitalization. On chest auscultation, a coarse breathing sound and rale sound were audible in the right lower lung (RLL) field, and his heartbeat was regular without murmur. His conjunctivae were mildly anemic and the sclerae were not icteric. There were no palpable lymph nodes and no neck vein engorgement in the head or neck area. Organomegaly was not seen in the abdomen. No edema was found on his back. However, there were 3 positive pretibial pitting edema on both lower extremities. (Fig. 1). No skin color changes were detected on either lower extremity.

The results of initial laboratory tests were as follows: blood pressure, 130/60 mmHg; heart rate, 81 beats/min; respiratory rate, 22/min; and body temperature, 37.8°C. His body weight was 38 kg at the time of hospitalization. On chest auscultation, a coarse breathing sound and rale sound were audible in the right lower lung (RLL) field, and his heartbeat was regular without murmur. His conjunctivae were mildly anemic and the sclerae were not icteric. There were no palpable lymph nodes and no neck vein engorgement in the head or neck area. Organomegaly was not seen in the abdomen. No edema was found on his back. However, there were 3 positive pretibial pitting edema on both lower extremities. (Fig. 1). No skin color changes were detected on either lower extremity.

The results of initial laboratory tests: hematocrit 36% (39–52%), hemoglobin level of 11.5 g/dL (13–17 g/dL), white blood cell count of 18,141/mm³ (4000–10,000/mm³); neutrophils, 90.3%; lymphoid cells, 7.1%; monocytes, 2.4%; and platelet count of 364,000/mm³ (130,000–400,000/mm³). The results of liver function tests were as follows: alkaline phosphatase 60 IU/L (35–130 IU/L), aspartate aminotransferase 32 IU/L (0–37 IU/L), alanine aminotransferase 32 IU/L (0–41 IU/L), protein 6.5 g/dL (6.6–8.7 g/dL), albumin 3.7 g/dL (3.5–5.2 g/dL) and glucose 114 mg/dL. His blood urea nitrogen and creatinine levels were 19.1 mg/dL (6.0–20.0 mg/dL) and 0.64 mg/dL (0.6–1.2 mg/dL), respectively. The patient’s electrolyte results were: a sodium level of 136.4 mmol/L (135–145 mmol/L), potassium level of 4.7 mmol/L (3.3–5.1 mmol/L), and chloride level of 95.5 mmol/L (98–110 mmol/L). The total T3 level was 74.88 ng/dL (80–200 ng/dL), the thyroid-stimulating hormone level was 2.43 mIU/L (0.27–4.2 mIU/L), and the free T4 level was 1.20 ng/dL (0.93–1.70 ng/dL). The N-terminal prohormone of brain natriuretic peptide (NT-proBNP) level was 213 pg/mL (0–125 pg/mL) and his C-reactive protein level was 105.1 mg/L (0–5 mg/L). Urinalysis revealed no protein or blood by dipstick test and a red blood cell (RBC) count of 1 to 4 per high-power field.

A chest X-ray showed pneumonic infiltration in the RLL, emphysema in both lungs, and no cardiomegaly (Fig. 2). There was no evidence of congestive heart failure (CHF) or pulmonary hypertension on electrocardiography (ECG) or cardiac echocardiography. The ultrasonography findings of the abdomen and pelvic organs and of color Doppler imaging of the lower extremities were also normal. There was no significant change in the patient’s body weight 5 days after admission and no difference in the input/output balance despite administration of intravenous fluid (1,000 mL per day). Levofloxacin was immediately withdrawn and cefepime was maintained, a decreased intake of salt was recommended, and intravenous fluid was withdrawn. The patient did not receive diuretics to control his edema. The patient’s edema had improved slightly 5 days after levofloxacin withdrawal, but at the time of discharge he still had edema and his body weight was not significantly different from that at the time of admission. His edema was found to have disappeared 2 weeks after discharge during follow-up in the outpatient clinic. No levofloxacin re-challenge was carried out because the patient did not consent. The edema had not recurred at the 6-month follow-up. Unfortunately, the patient subsequently died because of uncontrolled recurrent pneumonia.

3. Discussion

We have described a case of levofloxacin-associated bilateral leg edema that developed 5 days after initiation of levofloxacin therapy. This case report is meaningful in that levofloxacin is an
important etiology of drug-induced edema. Therefore, our findings may prevent wasting of time looking for other causes and application of ineffective or harmful treatments. The patient’s edema was completely resolved by immediate withdrawal of levofloxacin and conservative management within about 3 weeks. Several conditions that could precipitate edema were ruled out and so the evidence indicated that the edema resolved after withdrawal of the causative agent.

Two other cases of levofloxacin-associated bilateral leg edema have, to our knowledge, been reported in the English-language literature. Jobo et al described the case of a 64-year-old patient who complained of acute bilateral leg edema after 3 days of levofloxacin therapy for management of a complicated urinary tract infection. However, that report was a Letter to the Editor.

Conceivably, they could not represent the patient’s edema picture. Hyman et al reported the second case of levofloxacin-induced bilateral leg edema. They focused on stasis dermatitis, a severe complication of leg edema. The patient had recurrent bilateral leg edema due to levofloxacin that improved after drug withdrawal. The authors stated that the timing of the onset and resolution of the edema with respect to the administration and termination of the drug was the most important clinical clue. This case report may be meaningful in that it is the first typical case report. We also demonstrated a causal relationship based on the timing of the onset and resolution of edema by the same method.

The possibility of a medication as a cause should be excluded in patients with edema. The following classes of medications are commonly associated with edema: antidiuretics (monoamine oxidase inhibitors, trazodone), anti-hypertensives (beta-blockers, calcium-channel blockers (CCB), clonidine, hydralazine, methyl-dopa, minoxidil), antivirals (acyclovir), chemotherapeutics (cyclophosphamide, cyclosporine, mithramycin), cytokines (interferon, granulocyte colony-stimulating factor, interleukin-2), non-steroidal anti-inflammatory drugs (NSAIDs), and hormones (androgens, corticosteroids, estrogen, progesterone). CCBs and NSAIDs are the agents most commonly implicated in edema. Edema reportedly develops in 50% [11] of patients using CCBs and in 5% of those using NSAIDs. The underlying mechanism involves the retention of salt and water with increased capillary hydrostatic pressure. Therefore, levofloxacin should be added to the classes of medications associated with the development of peripheral edema, although the underlying mechanisms are unclear.

The diagnosis of an adverse drug reaction (ADR) is based on exclusion of other systemic diseases such as CHF, renal conditions, hepatic insufficiency, chronic venous insufficiency, pulmonary hypertension, obesity, and deep vein thrombosis or use of medicinal products such as herbal or traditional remedies, recreational drugs, or drugs of abuse. In this case, CHF and pulmonary hypertension were excluded based on findings of a chest X-ray, ECG, and cardiac echocardiography. The patient’s NT-proBNP level was not significantly elevated. Other diseases were excluded by thorough medical examinations such as laboratory biochemical tests, abdominal and pelvic USG, and Doppler imaging of the extremities. He had neither a history nor symptoms—such as brown hemosiderin skin deposits, dermatitis, and ulceration on both legs—of chronic venous insufficiency. The possibility of a medication as a cause of his edema was excluded by history taking.

The next step is to determine whether a suspected ADR is caused by a particular medicine, by calculating the probability of causation. There are two formal methods for calculating the probability of causation: the Naranjo probability scale and the World Health Organization-Uppsala Monitoring Center (WHO-UMC) causality categories. The patient’s Naranjo probability score was 6 (probable causal relationship) and his WHO-UMC causality category was “probable”. The dose-dependence of the ADR in this case could not be investigated. We did not perform a levofloxacin re-challenge due to the risk involved and because the patient did not consent. However, because the edema resolved after withdrawal of levofloxacin and did not recur during the follow-up period, an ADR to levofloxacin is the most likely cause.

In conclusion, levofloxacin should be added to the list of drugs associated with the development of bilateral leg edema. This might obviate the need for time-consuming studies and prevent the application of ineffective or harmful treatments.

Author contributions

Conceptualization: Jeonggu Na, Tae Won Lee, Eunjin Bae, Ha Nee Jang.

Data curation: Jeonggu Na, Ha Nee Jang, Hyun Seop Cho.

Formal analysis: Jeonggu Na, Tae Won Lee, Eunjin Bae.

Investigation: Jeonggu Na, Ha Nee Jang.

Methodology: Jeonggu Na, Hyun Seop Cho.

Supervision: Se-Ho Chang, DongJun Park.

Validation: Jeonggu Na, Tae Won Lee, Eunjin Bae.

Writing – original draft: Jeonggu Na.

Writing – review & editing: Eun Ju Lee, Se-Ho Chang, Dong Jun Park.

Dong Jun Park orcid: 0000-0001-5233-537X.

References

[1] Davis R, Bryson HM. Levofloxacin. A review of its antibacterial activity, pharmacokinetics and therapeutic efficacy. Drugs 1994;47:677–700.

[2] Rodvold KA, Piscitelli SC. New oral macrolide and fluoroquinolone antibiotics: an overview of pharmacokinetics, interactions, and safety”. Clin Infect Dis 1993;17(Suppl 1):S192–9.

[3] John A. Bosso . New and Emerging Quinolone Antibiotics. J Infect Dis Pharmacother 1998;2:61–76.

[4] Liu FH. Safety profile of the fluoroquinolones. Drug Saf 2010;33:353–69.

[5] Stahlmann R, Lode H. Safety considerations of fluoroquinolones in the elderly. Drug Aging 2010;27:193–209.

[6] Khaq Y, Zhanel GG. Fluoroquinolone-associated tendinopathy: a critical review of the literature”. Clin Infect Dis 2003;36:1404–10.

[7] Hyman DA, Cohen PR. Stasis dermatitis as a complication of recurrent levofloxacin-associated bilateral leg edema. Dermatol Online J 2013;19:20399.

[8] Ely JW, Osheroff JA, Chamblis ML, et al. Approach to leg edema of unclear etiology. J Am Board Fam Med 2006;19:148–60.

[9] Traves KP, Suddiford JS, Pickle S, et al. Edema: diagnosis and management. Am Fam Physician 2013;88:102–10.

[10] Topham EJ, Mortimer PS. Chronic lower limb oedema. Clin Med 2002;2:28–31.

[11] Freshman WH. Effects of nonsteroidal anti-inflamatory drug therapy on blood pressure and peripheral edema. Am J Cardiol 2002;89:18D–23D.

[12] Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239–45.