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Short Communication

Does Levofloxacin Induce Hemolytic Uremic Syndrome in Patients Infected with Verotoxin-Producing *Escherichia coli* O157 Infections?

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SUMMARY: Fifteen Japanese colitis patients, aged above 16 years old, infected with verotoxin-producing *Escherichia coli* O157 (VTEC O157) were divided into 2 treatment groups. Of the 15 patients, 6 (mean ± SD, 41.3 ± 19.0 years old) were treated with levofloxacin (LVFX), while the remaining 9 patients (32.0 ± 10.0 years old) were not treated with any antimicrobial agents. All patients complained of abdominal pain and bloody stool and were not administered antidiarrheals. Hemolytic uremic syndrome (HUS) did not develop in any of the 6 patients treated with LVFX, but developed in 1 of the 9 patients not treated with antimicrobial agents. No statistical difference was found in the occurrence rate of HUS between LVFX-treated patients and patients not treated with antimicrobial agents. Our results suggest that oral administration of LVFX is not associated with risk of HUS in hemorrhagic colitis patients aged above 16 years infected with VTEC O157.

Escherichia coli O157 was first cultured in the United States from the stool of clusters of colitis patients, presenting with abdominal pain and bloody stool (1). Since then, *E. coli* O157 is well known as one of the causative agents of hemorrhagic colitis. Hemolytic uremic syndrome (HUS) is a condition characterized by hemolytic anemia, thrombocytopenia, and acute renal failure. At present, verotoxin has been identified as the cause of postdiarrheal HUS. Some serotypes of *E. coli* produce verotoxin and are a cause of hemorrhagic colitis and HUS, however, verotoxin-producing *E. coli* (VTEC) O157 is considered the predominant cause of hemorrhagic colitis and HUS. Sulfa-containing and β-lactam antimicrobial agents are reported to be associated with the risk of HUS in patients infected with VTEC (2); in contrast, fosfomycin is reportedly found to decrease the risk of HUS (3). The use of antimicrobial agents for patients with VTEC O157 infection is controversial. Fluoroquinolones, levofloxacin (LVFX) being one of them, are widely used against bacterial colitis in Japan. In our hospital, some physicians administer fluoroquinolones to patients infected with VTEC, with suspected or confirmed colitis. Other physicians administer different antimicrobial agents; while still others do not administer any antimicrobial agents according to their own policy. It is unknown whether LVFX increases the risk of HUS in adult and adolescent patients with VTEC O157 infections. In this study, we examined whether administration of LVFX increased the risk of HUS in adult and adolescent patients infected with VTEC O157, with painful bloody diarrhea.

Six Japanese colitis patients, aged above 16 years (mean ± SD, 41.3 ± 19.0 years), infected with VTEC O157 were treated with oral administration of LVFX; while 9 Japanese colitis patients, aged above 16 years (32.0 ± 10.0 years), infected with VTEC O157 were not administered any antimicrobial agents from 1997 to 2010 at the Department of Infectious Diseases, Tokyo Metropolitan Bokutoh General Hospital. Attending physicians decided to treat the patients with LVFX or without antimicrobial agents based on their own policy. Infection with VTEC O157 was confirmed by stool culture in all patients. All patients complained of abdominal pain and bloody stool. The profiles of the patients are shown in Table 1. Sex distribution, incidence of elevated leukocytes, and type of verotoxin did not differ significantly between the 2 groups as determined by Fischer's exact test. Student's *t* test showed that there was no significant difference in age between the groups. All LVFX-treated patients received 500 mg of LVFX

Table 1. Patient profiles

	Treatment with LVFX (n = 6)	Not treatment with antimicrobial agents (n = 9)
Age (yr)		
mean ± SD	41.3 ± 19.0	32.0 ± 10.0
Range	17–67	22–53
Sex (% male)	33.3	22.2
Bloody stool (%)	100	100
Abdominal pain (%)	100	100
Elevated leukocytes (≧10,000/mm^3)		
No. of patients	4	4
Elevated BT (≥37.5°C)		
No. of patients	0	0
Type of verotoxin		
No. of patients		
VT1 and VT2	4	7
VT2	2	2

LVFX, levofloxacin; BT, body temperature; VT, verotoxin.

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daily for 5 days, and the duration of the illness when starting the LVFX therapy was 2–6 days (mean ± SD, 3.3 ± 1.5 days).

The presence or absence of HUS in patients treated with LVFX and in patients treated without antimicrobial agents was studied retrospectively. HUS was defined as acute onset of the triad of hemolytic anemia (hemoglobin level ≤ 10 g/dl); evidence of erythrocyte fragmentation on a peripheral blood smear, thrombocytopenia (platelet count $\leq 10 \times 10^4/mm^3$), and acute renal failure (rapid progression of oliguria with serum creatinine levels of >1.1 mg/dl). Differences in proportions were analyzed using Fisher's exact test.

HUS was not identified in any of the patients treated with LVFX, but was found in 1 of the 9 patients who were not treated with any antimicrobial agents; HUS was found in a 22-year-old woman on the 10th day of the illness. The HUS occurrence rate was not significantly different between patients treated with LVFX and those not treated with antimicrobial agents ($P = 0.6$). All isolated VTEC O157 specimens were sensitive to LVFX.

VTEC produces verotoxin in the intestinal cavity and this toxin is absorbed into the blood stream, when it is thought to induce microvascular endothelial injury, which is pathognomonic for HUS (4). The administration of various antimicrobial agents leads to the release of verotoxin from VTEC in in vitro experiments (5–7) and ofloxacin rapidly induces an increase in the expression of the *stx* gene in in vitro experiments (8). According to the studies mentioned above, we surmise that a large volume of verotoxin is released into the intestinal lumen from VTEC destroyed by antimicrobial agents in colitis patients treated with antimicrobial agents, and this verotoxin is absorbed into the blood, subsequently inducing HUS. However, this hypothesis has not been confirmed in colitis patients infected with VTEC who were treated with fluoroquinolones; furthermore, it is reported that no verotoxin was detected in the stool of pediatric patients infected with VTEC O157 after fluoroquinolone was administered (9). In our study, a significant difference in the appearance rate of HUS was not found between patients (aged above 16 years) treated with LVFX or not treated with antimicrobial agents. Despite the small number of patients in our study, our results indicated that LVFX is not associated with HUS in patients aged above 16 years who are infected with VTEC O157. It is reported that oral fluoroquinolone therapy administered within 3 days of the illness onset is effective in preventing the development of HUS in pediatric colitis patients infected with VTEC O157 (9), and LVFX was administered within 2–6 days (3.3 ± 1.5 days) of the illness onset in our patients. Collectively, the results of our study and an earlier report may suggest that fluoroquinolone therapy is effective in preventing the development of HUS in cases where fluoroquinolones are administered in the early phases of VTEC infection.

Conflict of interest None to declare.

REFERENCES

1. Riley, L.W., Remis, R.S., Helqerson, S.D., et al. (1983): Hemorrhagic colitis associated with a rare *Escherichia coli* serotype. N. Engl. J. Med., 308, 681–685.
2. Wong, C.S., Jelacic, S., Habeeb, R.L., et al. (2000): The risk of the hemolytic-uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 infections. N. Engl. J. Med., 342, 1930–1936.
3. Ikeda, K., Ida, O., Kimoto, K., et al. (1999): Effect of early fosfomycin treatment on prevention of hemolytic uremic syndrome accompanying *Escherichia coli* O157:H7 infection. Clin. Nephrol., 52, 357–362.
4. Gerber, A., Karch, H., Allerberger, F., et al. (2000): Clinical course and the role of Shiga toxin-producing *Escherichia coli* infection in the hemolytic-uremic syndrome in pediatric patients, 1997–2000, in Germany and Austria: a prospective study. J. Infect. Dis., 186, 493–500.
5. Karch, H., Strckbine, N.A. and O'Brien, A.D. (1986): Growth of *Escherichia coli* in the presence of trimethoprim-sulfamethoxazole facilitates detection of Shiga-like toxin producing strains by colony blot assay. FEMS Microbiol. Lett., 35, 141–145.
6. Walterspiel, J.N., Ashkenazi, S., Morrow, A.L., et al. (1992): Effect of subinhibitory concentrations of antibiotics on extracellular Shiga-like toxin I. Infection, 20, 25–29.
7. Grif, K., Dierich, M.P., Karch, H., et al. (1998): Strain-specific differences in the amount of Shiga toxin released from enterohemorrhagic *Escherichia coli* O157 following exposure to subinhibitory concentrations of antimicrobial agents. Eur. J. Clin. Microbiol. Infect. Dis., 17, 761–766.
8. Kimmitt, P.T., Harwood, C.R. and Barer, M.R. (1999): Induction of type 2 Shiga toxin synthesis in *Escherichia coli* O157 by 4-quinolones. Lancet, 353, 1588–1589.
9. Shiomi, M., Togawa, M., Fujita, K., et al. (1999): Effect of early oral fluoroquinolones in hemorrhagic colitis due to *Escherichia coli* O157:H7. Pediatr. Intern., 41, 229–232.