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Amikacin therapy for urinary tract infections caused by extended-spectrum β-lactamase-producing *Escherichia coli*

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Background/Aims: The number of urinary tract infections (UTIs) caused by extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-EC) is increasing. In an outpatient setting, there are limited therapeutic options to treat ESBL-producing pathogens. We evaluated the outcomes of amikacin outpatient parenteral antibiotic therapy (OPAT) for UTIs caused by ESBL-EC in patients not pre-treated with carbapenem.

Methods: We retrospectively evaluated the outcomes of amikacin OPAT for UTIs caused by ESBL-EC.

Results: From November 2011 to October 2012, eight females, who could not be hospitalized for carbapenem treatment, were treated with amikacin OPAT for nine episodes of non-bacteremic ESBL-EC UTIs. Seven of the eight patients had one or more comorbidities. Of the nine UTI cases, three had symptomatic lower UTIs and six had non-bacteremic upper UTIs. In all of the cases, symptomatic and laboratory improvements were observed following amikacin OPAT. One patient showed a delayed relapse with bilateral microabscesses 3 weeks after treatment cessation; however, a clinical and microbiological cure was eventually reached. All of the patients were able to tolerate amikacin OPAT without any significant nephrotoxicity or ototoxicity.

Conclusions: Amikacin OPAT represents a feasible therapeutic option for non-bacteremic UTIs caused by ESBL-EC in settings with limited resources.

Keywords: Amikacin; Beta-lactamases; Outpatients; Urinary tract infections

INTRODUCTION

Escherichia coli is the most common pathogen in urinary tract infections (UTIs). Recently, an increase in the number of cases with extended-spectrum β-lactamase-producing *E. coli* (ESBL-EC) has been observed in outpatient settings [1,2]. Carbapenems are considered the drugs of choice for serious infections with ESBL-producing organisms. Although treatment once daily with ertapenem is now available, therapeutic options remain limited in many clinical settings. In ESBL-EC UTIs, patients sometimes show a partial response to non-carbapenem empirical antibiotics. It has been suggested that amikacin can be administered in cases of suspected infection with drug-resistant Enterobacteriaceae [3-5]. However, there is little clinical data available on amikacin monotherapy for ESBL-EC UTIs [6]. We evaluated the outcomes of amikacin outpatient parenteral antibiotic therapy (OPAT) for UTIs caused by ESBL-EC in patients who had not been pre-treated with carbapenem.

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METHODS

Patients and hospital setting

This study was conducted at Yeouido St. Mary's Hospital, which is a 500-bed, university-affiliated tertiary hospital in Seoul, Korea. The medical records of all of the patients who received amikacin OPAT between November 2011 and October 2012 were retrospectively reviewed. During the study period, ertapenem was not available at this hospital. Patients with UTIs caused by ESBL-EC with relatively mild symptoms, who could not be hospitalized, were treated by OPAT and administered with amikacin once daily. This study was approved by the Institutional Review Board of Yeouido St. Mary's Hospital (IRB No. SC14RISI0004).

Study design and definitions

The following were reviewed: comorbidities, initial symptoms and characteristics of UTIs (upper or lower, complicated or uncomplicated), laboratory data (urinalysis and renal function before and after OPAT), microbiological results, improvements in symptoms 3 to 5 days after starting OPAT, and additional studies of anatomical or functional abnormalities if indicated. Antimicrobial susceptibility results were determined by *in vitro* susceptibility testing using Microscan (Siemens Inc., Renton, WA, USA). All of the aforementioned variables could be identified for the episodes included in this analysis. Amikacin dose and dosing interval were determined by body weight and renal function. Dose adjustment was performed according to the estimated glomerular filtration rate (eGFR) as calculated by the Modification of Diet in Renal Disease (MDRD) study equation [3]. Follow-up urine cultures were performed if patients had persistent pyuria or symptoms after amikacin OPAT had been administered for > 3 days. Outcomes were defined as cure, persistence, relapse, or reinfection [7]. Acute kidney injury was defined as a ≥ 50% increase in serum creatinine levels developing in < 7 days, or a urine output < 0.5 mL/kg/hr for > 6 hours according to the Risk, Injury, Failure, Loss, End-stage classification (RIFLE) [8]. Ototoxicity was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by the National Cancer Institute [9].

RESULTS

Patient characteristics

During the study period, nine episodes of ESBL-EC UTIs in eight women were treated by amikacin OPAT, and seven of the patients were postmenopausal. Patient characteristics are listed in Table 1. The median age was 66 years (range, 28 to 83). All seven postmenopausal women had comorbidities, including diabetes and a history of UTIs in the previous year. Seven cases

Table 1. Patient characteristics of those receiving amikacin outpatient parenteral antibiotic therapy

Case	Patient	Sex/Age, yr	Comorbidities	Previous UTI	Radiologic study	Functional abnormality
1	A	F/74	Chronic bronchitis	Yes	ND	Normal
2	B	F/69	DM, dyslipidemia	Yes	ND	ND
3	C	F/63	DM, HTN, dyslipidemia	Yes	Hydronephrosis, both	No reflux in VCUG
4	C	F/64	DM, HTN, dyslipidemia	Yes	Bilateral renal microabscesses	ND
5	D	F/60	DM, MS & AS s/p MVR, AVR	Yes	ND	Neurogenic bladder
6	E	F/69	DM, subclinical hypothyroidism	Yes	ND	ND
7	F	F/83	HTN, CKD, AF, SSS, SNHL	Yes	Parenchymal thinning	OAB
8	G	F/54	PSKT	Yes	ND	VUR on graft kidney
9	H	F/28	None	No	ND	ND

UTI, urinary tract infection; ND, not done; DM, diabetes mellitus; HTN, hypertension; VCUG, voiding cystourethrogram; MS, mitral stenosis; AS, aortic stenosis; s/p, status post; MVR, mitral valve replacement; AVR, aortic valve replacement; CKD, chronic kidney disease; AF, atrial fibrillation; SSS, sick sinus syndrome; SNHL, sensory neural hearing loss; OAB, overactive bladder; PSKT, post-kidney transplantation; VUR, vesicoureteral reflux.

(77.8%) were community-associated ESBL-EC UTIs, and two (22.2%) were healthcare-associated ESBL-EC UTIs. Two-thirds of patients (6/9, 66.7%) had been exposed to antibiotics in the 30 days prior to infection with the ESBL-EC UTIs.

Clinical courses and treatment outcomes of amikacin OPAT

Three patients had lower UTIs and six had non-bacteremic upper UTIs. Three had complicated UTIs (episodes 3, 4, and 8). The median duration of amikacin OPAT was 10 days (range, 7 to 42). Due to the prolonged duration of symptoms, patients with lower UTIs (patients A, D, and E) had a 7-day OPAT course instead of a short 3-day course. All of the patients showed symptomatic and laboratory improvements by the end of the amikacin treatment; outcomes are shown in Table 2. Eight of the nine episodes (88.9%) were defined as being cured.

Patient C had a history of recurrent UTIs with hydronephrosis without a definite obstructive lesion. She experienced a delayed relapse 21 days after completing OPAT for episode 3. In this relapse, designated Episode 4, bilateral multiple microabscesses were identified in a kidney computed tomography scan. The patient refused hospitalization for personal reasons, and instead, underwent amikacin OPAT to treat the renal abscesses. In this case (Episode 4), a clinical and microbiological cure was reached after 6 weeks of therapy. Patient G, a kidney transplant recipient who was taking 7.5 mg prednisolone and 50 mg cyclosporine, experienced persistent pyuria with recurrent urinary symptoms for several months despite repeated treatment with quinolones, cephalosporins, and trimethoprim-sulfamethoxazole. The patient had vesicoureteral reflux in the grafted kidney. Patient G started amikacin OPAT with a dose modification, based on an inter-departmental consultation between a nephrologist and infectious diseases specialist, because she refused hospitalization for carbapenem treatment.

Antimicrobial susceptibility

All of the clinical isolates included in this study were susceptible to amikacin. Susceptibility rates for gentamicin and tobramycin were 11.1% (1/9 susceptible, 8/9 resistant) and 0% (0/9 susceptible, 3/9 intermediate,

Table 2. Clinical courses and patient outcomes after amikacin outpatient parenteral antibiotic therapy

Case	Patient	Diagnosis[a]	Treatment duration, day	Pyuria, /HPF		Urine culture at the end of OPAT	Outcome	Interval to the next symptomatic UTI, day	Cr, mg/dL		Ototoxicity
				Pre	Post				Pre	Post	
1	A	Lower	7	30–49	1–3	ND	Cure	286	1.03	0.89	No
2	B	Upper	7	10–19	0–1	ND	Cure	83	0.83	0.74	No
3	C	Upper	7	> 100	10–19	No growth	Relapsed	21[b]	1.64	1.15	No
4	C	Upper	42	> 100	4–9	No growth	Cure	184[b]	1.48	1.25	No
5	D	Lower	10	50–99	1–3	ND	Cure	352	1.06	0.84	No
6	E	Lower	7	> 100	0–1	ND	Cure	None[c]	0.88	0.94	No
7	F	Upper	14	> 100	1–3	ND	Cure	56	1.64	1.89	Known SNHL
8	G	Upper	14	> 100	0–1	ND	Cure	35[b]	3.64	4.76	No
9	H	Upper	10	> 100	1–3	No growth	Cure	None[c]	0.71	0.68	No

HPF, high-power field; OPAT, outpatient parenteral antibiotic therapy; UTI, urinary tract infection; ND, not done; SNHL, sensory neural hearing loss.
[a]Diagnosis categorized by upper or lower UTI, regardless of the complication.
[b]Next UTI episode caused by extended-spectrum β-lactamase-producing *Escherichia coli*.
[c]Next symptomatic UTI episode was not developed.

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6/9 resistant), respectively. Only one isolate (11.1%) was susceptible to quinolone. Four isolates (44.4%) were susceptible to cefepime, with a minimal inhibitory concentration (MIC) range of ≤ 1 to 4 mg/L. The susceptibility rates for cefoxitin, trimethoprim/sulfamethoxazole, and piperacillin/tazobactam were 44.4%, 11.1%, and 44.4%, respectively.

Adverse events for amikacin OPAT

In patient G, the serum blood urea nitrogen/creatinine increased from 43.2/3.64 to 55/4.76 mg/dL (eGFR, 13.85 to 10.16 mL/min/1.73 m^2) after amikacin treatment; however, there was no significant decrease in renal function according to the RIFLE classification. This may have been due to the combined effects of treatment and other factors such as immunosuppressant administration, graft kidney reflux, and rejection. There were no subjective changes in hearing and no tinnitus or vertigo in any of the patients according to the CTCAE. Patient F had sensory neural hearing loss prior to treatment, but there was no further deterioration after amikacin treatment. There was no significant nephrotoxicity or ototoxicity in any of the patients.

DISCUSSION

ESBL-EC is increasing in hospital- and community-acquired UTIs. Carbapenem is the drug of choice for severe bacteremia infections caused by ESBL-producing pathogens. However, with the exception of ertapenem, carbapenem administration requires hospitalization, has a high cost, and also has the problem of resistance. A number of studies have attempted to identify alternatives to carbapenems [10-13]. In this study, we demonstrated the use of amikacin OPAT for UTIs caused by ESBL-EC, as few reports exist on the use of aminoglycosides in ESBL-producing pathogens.

Alternatives to carbapenems include β-lactam/β-lactamase inhibitors, fourth-generation cephalosporins, tigecycline and several oral antibiotic agents such as fluoroquinolones, fosfomycin, or nitrofurantoin [10-13]. One meta-analysis showed a lower mortality for carbapenem treatment compared to non-β-lactam/β-lactamase inhibitors. However, the studies included in this meta-analysis were heterogeneous for pathogens, treatment options, and infection sources [10]. Another study of alternative ESBL-EC treatments showed that non-carbapenem antibiotics were as effective as carbapenems for the treatment of acute pyelonephritis [13].

Over the last decade, the use of aminoglycosides has decreased, even for gram-negative bacterial infections. On the other hand, broad spectrum antibiotics such as third or fourth generation cephalosporins, β-lactam/β-lactamase inhibitors and carbapenems are widely prescribed in many cases over a prolonged duration. In many countries, amikacin is more effective against ESBL-producing and quinolone-resistant *E. coli* than other aminoglycosides [4,14-16]. In our study, amikacin performed best in *in vitro* susceptibility tests. When, administered once daily, it produces a peak serum concentration above therapeutic drug levels and maintains a high concentration in the urine. In addition, based on animal pharmacodynamic data, urine concentrations above the MIC of most gram-negative bacteria are maintained at least 4 days after the last amikacin dose [3]. In terms of the *in vitro* susceptibility, pharmacokinetics, pharmacodynamics, and post-antibiotic effects of aminoglycosides, amikacin can be used for non-severe ESBL infections such as UTIs if susceptibility results were identified.

The major issue of aminoglycoside use concerns its toxicity. In this study, although we did not routinely perform audiometry before and after amikacin treatment, there was no clinically significant decrease in renal function, and ototoxicity was not observed, even in elderly patients. The rate of aminoglycoside-related nephrotoxicity is 8% to 14% [3], which increases at higher doses, with prolonged therapy of 10 days or more, and with the co-administration of nephrotoxic agents. Here, with the exception of one case (Episode 4), amikacin OPAT was completed within 2 weeks, which likely accounts for the lower rate of adverse events.

We identified that amikacin OPAT could lead to a clinical and microbiological cure in UTIs caused by ESBL-EC without carbapenem treatment, even in complicated cases. In addition, we presented time interval data of the development of the subsequent symptomatic UTIs. However, it was unclear whether any subsequent UTI episodes were related to the amikacin OPAT or other medical conditions, including age and other comor-

bidities.

There were several limitations to this study. First, this was a retrospective study of a small number of patients. It was not possible to compare the outcome of amikacin OPAT with that of ertapenem. A retrospective study reported that ertapenem OPAT could effectively treat UTIs caused by ESBL-producing organisms and could help to reduce medical cost by reducing hospitalization [17]. However, ertapenem treatment costs 9- to 16-fold more for daily antibiotics than amikacin, based on patients with normal renal function. Additional studies are needed to evaluate the efficacy, adverse events, and cost-effectiveness of amikacin OPAT compared to ertapenem. Second, audiometry was not routinely conducted because it was difficult to check in a timely manner, and sometimes patients refused due to the additional cost of this test. In principle, auditory function should be closely monitored during treatment, particularly in high-risk patients.

Despite these limitations, there were several strengths in this study. First, we summarized diverse characteristics, including anatomical and functional abnormalities in patients with UTIs. Second, we included ESBL-EC UTI cases where the patients had mild symptoms and in cases where there was a difficulty in hospitalization. Such cases are common in outpatient clinics; thus, our data on amikacin OPAT for ESBL-EC is useful in a "real-world" context. Third, we excluded patients who were treated with carbapenem before amikacin OPAT, as this may have influenced the outcomes of the amikacin treatment.

In conclusion, our study provides data that can help clinicians decide whether to administer aminoglycosides. In settings with limited resources, amikacin OPAT can be a feasible treatment option for mild to moderate non-bacteremic UTIs caused by ESBL-EC if patients are closely monitored for renal function and ototoxicity. Thus careful patient selection and close monitoring for potential toxicity based on local epidemiology is important for the successful use of this therapy. Additional prospective studies with a larger number of patients are required to fully determine the efficacy of aminoglycoside use in ESBL-producing pathogens.

KEY MESSAGE

1. Alternative treatment with non-carbapenem antibiotics can be considered for extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-EC), if they are active *in vitro*.
2. Amikacin therapy administered once daily to outpatients can be a feasible treatment option for mild to moderate urinary tract infections caused by ESBL-EC, in cases of adverse drug reactions to carbapenem or in settings with limited resources, provided that patients are closely monitored for renal function and ototoxicity.

Conflict of interest

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

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