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Impact of Intervention by an Antimicrobial Stewardship Team on Conversion from Intravenous to Oral Fluoroquinolones

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Background: Early conversion from intravenous to oral antibiotics plays an important role in lowering the risk of catheter-associated infections, reducing the workload of nurses, decreasing direct and indirect costs, and shortening hospital stays. In August 2015, an antimicrobial stewardship program (ASP) was implemented to facilitate conversion from intravenous to oral administration of fluoroquinolones in our institute. This study evaluated the clinical and economic impact of the intervention.

Materials and Methods: Data were retrospectively collected by reviewing electronic medical records. All hospitalized patients aged 18 and older who met the study inclusion criteria for the conversion were included between August and November 2015. We computed the physicians' adherence rate to the ASP recommendations. We also measured the total use of fluoroquinolones, length of hospital stay, and medication costs.

Results: During 4 months, 129 cases were enrolled in the study. The adherence rate was 79.8%. The average total prescription volume of intravenous fluoroquinolones, the length of hospital stay, and the total cost of the fluoroquinolones statistically significantly decreased in the intervention-adherent group.

Conclusion: Intervention to facilitate conversion from intravenous to oral administration has reduced excess use of intravenous fluoroquinolones and length of hospital stay. With these findings, further implementations of the ASP extending to other antibiotics may be warranted.

Key Words: Antimicrobial stewardship; Fluoroquinolones; Oral antibiotics; Intervention

Introduction

Many studies have reported the unnecessary use of antimicrobials in hospitalized patients is common [1, 2], leading to problems such as increased antimicrobial resistance, *Clostridium difficile* infections, healthcare costs, and adverse drug effects owing to overuse. Therefore, it is important to develop the antimicrobial stewardship program (ASP) according to the cir-

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cumstances of each medical institution, to provide guidance for selecting the optimal antimicrobial as well as optimal dose and length of administration, minimize unnecessary antimicrobial use and provide adequate care to patients [3]. To encourage appropriate use of antimicrobials in hospitals, Seoul National University Bundang Hospital (SNUBH) has implemented the ASP since 2013, including daily antimicrobial prescription review and the intervention for unnecessary double anaerobic antimicrobial prescription, by organizing a team of infectious disease physicians and pharmacists [4].

Conversion from intravenous to oral administration is one of the major recommendations made in the antimicrobial stewardship guidelines by the Infectious Diseases Society of America (IDSA) [3]. In particular, oral fluoroquinolones have a high bioavailability of 80–99%, representing similar pharmacokinetic properties as their intravenous counterpart [5], and economic benefits may be expected upon conversion to oral fluoroquinolones. Ho et al. showed in their study that the conversion from intravenous to oral administration of ciprofloxacin by pharmacists led to a 23% reduction in unnecessary prescription of intravenous medications and subsequently, healthcare costs [6]. Furthermore, Yen's study on the conversion from intravenous to oral administration of levofloxacin resulted in a reduction of 11.1 days of in the length of hospitalization and 40% reduction in the total cost of hospitalization after the intervention [7].

Although the advantages of converting from intravenous to oral antimicrobial administration have been reported in various studies, studies that investigate the clinical and economic effects of such intervention in Korea are lacking. Therefore, the antimicrobial stewardship team at SNUBH started an intervention to facilitate the conversion from intravenous to oral administration of fluoroquinolones in August 2015. In this study, physicians' adherence to the intervention by the antimicrobial stewardship team was investigated and the effect of the intervention was evaluated.

Materials and Methods

1. Study period and subjects

We evaluated patients over 18 years of age who were hospitalized in SNUBH from August 1 to November 30, 2015. Among them, the patients receiving injectable fluoroquinolones including ciprofloxacin, levofloxacin, and moxifloxacin for more than 3 days and were able to take oral antimicrobials were selected for the intervention. If the same patient was re-administered or a different fluoroquinolone was used within the same hospital stay, they were considered separate cases. The following patients were excluded from the intervention: 1) patients in the intensive care units or protected isolation rooms at the time of screening, who were mostly unable to take oral medications or had a severe degree of infections (However, patients who were transferred to general wards were included), 2) patients who were prescribed with prophylactic postoperative antibiotic therapy, 3) patients who had difficulty taking oral medications either due to fasting, dysphagia, or tube feeding, 4) patients who were at risk of insufficient medication absorption due to gastrointestinal surgeries, 5) patients with bone and joint infections in which a 2 to 4 week parenteral therapy is traditionally preferred in the early course of the treatment, 6) patients with a fever within 24 hours before the intervention or who did not show any improvements of the infection, 7) patients who were recommended to replace or discontinue fluoroquinolones due to uncertain indications, 8) patients whose drugs were already converted to oral antibiotics or were discharged from the hospital before the intervention.

The patients who had infections by fluoroquinolone-resistant bacteria or were changed to a different class of antibiotics due to treatment failure after the intervention were excluded from analysis. In addition, deceased patients after intervention including patients who died on account of an underlying disease were excluded from analysis because they may lead to bias in the assessment of hospitalization.

2. Intervention methods for the conversion from intravenous to oral administration of fluoroquinolones

The intervention was regularly performed 2 to 3 times a week. A pharmacist of the antimicrobial stewardship team identified study subjects using the program in healthcare information system that tracks antimicrobial use within the hospital and left a note of recommendation for the intervention in the inpatient electronic medical record. The note included the primary site of infection, purpose of antimicrobial administration, type of fluoroquinolones that was being administered, dosage, and treatment period. Also, the information on oral equivalent dose and drug interactions was included. The drafted recommendation was validated by infectious disease physicians who provided additional opinions as needed and co-signed the form. Subsequently, a pharmacist of the antimicrobial stewardship team confirmed adherence to the intervention by analyzing the medical records.

3. Data collection and analysis

Data were collected from electronic medical records and an-

alyzed retrospectively. Age, sex, department, infection site, antimicrobial type and administration duration, length of hospitalization, and period from the intervention to discharge were collected from the electronic medical records, the APACHE II scores [8], the Charlson comorbidity index [9] were calculated using the required data elements available from the electronic medical records, and cost of medication were estimated using the national drug reimbursement rate. Furthermore, whether or not the study subjects were co-administered other intravenous antimicrobials or oral medications at the time of the intervention were evaluated. To evaluate the effect of the intervention, patient records were classified based on physicians' adherence to the intervention and analyzed accordingly.

Cases were defined as 'adherent' if antimicrobial administration was discontinued or converted to an oral antimicrobial agent within 3 days of the intervention, and the rate of adherence to the intervention was calculated accordingly. The duration of antimicrobial administration was defined as the number of days in which fluoroquinolones were administered during hospitalization. Furthermore, periods of intravenous antimicrobial administration and of oral antimicrobial administration were assessed separately. Length of hospitalization was defined as the period between the day of admission and the day of discharge. For the patients who were admitted to the emergency room first, the start day of the hospitalization was considered as the day of admission to the emergency room. Medication cost was defined as the price of fluoroquinolones that were administered based on the maximum drug costs according to national insurance, injection administration fee, and the number of administrations during hospitalization. Oral and intravenous medication costs were examined separately.

4. Statistical analysis

Numerical variables were presented as the median and interquartile range (IQR), and compared using the Mann–Whitney *U* test. Categorical variables were compared using the chi-square test and Fisher's exact test. *P*-value of less than 0.05 was considered as statistically significant. Statistical analysis was performed using SPSS software version 21.0 (IBM Corp., Armonk, NY, USA).

This study was approved by Institutional Review Board of the SNUBH (IRB No: B-1510-318-113).

Results

There were 673 cases of antibiotic courses from 628 hospitalized patients aged 18 years or older who were prescribed intravenous fluoroquinolones for 3 days or longer between August 1 and November 30, 2015. Of those, 518 cases (77.0%) were excluded: 1) 101 (15.0%) were cases for patients in the intensive care units or protected isolation rooms, 2) 42 (6.2%) were cases were prescribed with prophylactic postoperative antibiotic therapy, 3) 188 (27.9%) were cases who had difficulty taking oral medications either due to fasting, dysphagia, or tube feeding, 4) 8 (1.2%) were cases who were at risk of insufficient medication absorption due to gastrointestinal surgeries, 5) 16 (2.4%) was cases with bone and joint infections, 6) 25 (3.7%) were cases with a fever within 24 hours before the intervention or who did not show any improvements of the infection, 7) 65 cases (9.7%) considered changing or discontinuing medications due to uncertain indication of fluoroquinolone administration, 8) 73 (10.8%) were cases whose drugs were already converted to oral antibiotics or were discharged from the hospital before the intervention. Thus, 155 cases (23.0%) were selected as the study subjects to receive the intervention for conversion from intravenous to oral administration. Of the 155 cases, 129 cases were included for the final analysis excluding 8 cases whose antimicrobial prescriptions were converted to another type of intravenous antimicrobial agent due to treatment failure and 18 cases of death during the hospitalization.

1. Adherence to the intervention

A total of 103 cases were adherent to the intervention with an adherence rate of 79.8% (Table 1). The intervention adherence rate for each medication was 79.5% for ciprofloxacin, 75.6% for levofloxacin, and 85.0% for moxifloxacin. Furthermore, of the 103 cases which complied with the intervention within 3 days, 17 cases (16.5%) had their antimicrobials discontinued, 54 cases (52.4%) were converted to oral medication during hospitalization, and 32 cases (31.1%) were converted to oral medication upon discharge but had maintained intravenous medication during hospitalization.

Table 1. Physicians' rate of adherence to an intervention recommending conversion from intravenous to oral administration of fluoroquinolones

	Intervention (n)	Acceptance of the recommendation (n)	Adherence rate (%)
Ciprofloxacin	44	35	79.5
Levofloxacin	45	34	75.6
Moxifloxacin	40	34	85.0
Total	129	103	79.8

2. Comparison of outcomes according to adherence to prescription intervention

Of the 129 cases in the final analysis, 103 cases were categorized as intervention-adherent and 26 as non-adherent. There were no statistically significant differences in age, sex, administered medication, infection site, the APACHE II scores, the Charlson comorbidity index, or combination therapy between the two groups (Table 2).

The duration of intravenous antimicrobial administration was 6 days for the intervention-adherent group and 10.5 days for the intervention-non-adherent group, showing a statistically significant decrease in the intervention-adherent group compared to the intervention-non-adherent group (P <0.001, Table 3). Also, total duration of antimicrobial administration was 7 and 11 days, respectively, showing a statistically significant decrease in the intervention-adherent group (P = 0.034). Length of hospitalization was longer (10 days *vs.* 14.5 days) for the intervention-non-adherent group and the increase was statistically significant (P = 0.004). A statistically significant reduction in the period from the intervention to discharge was found in the adherent group as compared to the non-adherent group (3.0 days *vs.* 8.0 days; P <0.001).

Medication costs of intravenous fluoroquinolones per patient was significantly lower in the adherent group (142,960 Korean won) than the non-adherent group (219,341 Korean won) (P <0.001) (Table 3). Total medication costs of fluoroquinolone therapy including oral medications were 144,004 won and 219,341 won, respectively, which was lower in the intervention-adherent group with statistical significance (P <0.001).

Table 2. Demographic and clinical characteristics of the study cases

	Intervention adherent (n = 103)	Intervention non-adherent (n = 26)	*P*-value
Age, median (IQR)	69.0 (61.0-79.0)	72.0 (64.5-79.0)	0.378
Sex, n (%)			0.222
Male	65 (63.1)	13 (50.0)	
Female	38 (36.9)	13 (50.0)	
Medication, n (%)			
Ciprofloxacin	35 (34.0)	9 (34.6)	0.951
Levofloxacin	34 (33.0)	11 (42.3)	0.374
Moxifloxacin	34 (33.0)	6 (23.1)	0.328
Infection site, n (%)			
Gastrointestinal infections	19 (18.4)	4 (15.4)	1.000
Genitourinary infections	18 (17.5)	4 (15.4)	1.000
Respiratory infections	61 (59.2)	16 (61.5)	0.830
Other[a]	5 (4.9)	2 (7.7)	0.628
APACHE II Score, median (IQR)	11.0 (8.0-14.0)	11.5 (9.0-15.0)	0.395
Charlson comorbidity index, median (IQR)	2.0 (1.0-3.0)	2.0 (1.0-6.0)	0.619
Combination therapy, n (%)	39 (37.9)	13 (50.0)	0.260

[a]Other: surgical site infection, skin and soft tissue infection, or unknown.
IQR, interquartile range.

Table 3. Differences in duration of fluoroquinolone administration, length of hospitalization, period from the intervention to discharge, and cost of fluoroquinolone therapy between intervention-adherent and non-adherent group

	Intervention adherent (n = 103)	Intervention non-adherent (n = 26)	*P*-value
Duration of administration (days)			
IV, median (IQR)	6.0 (4.0-7.0)	10.5 (7.8-14.0)	< 0.001[a]
PO, median (IQR)	1.0 (0-4.0)	0 (0-0)	< 0.001[a]
Total, median (IQR)	7.0 (6.0-10.0)	11.0 (8.0-14.0)	0.001[a]
Length of hospitalization (days)			
Median (IQR)	10.0 (7.0-15.0)	14.5 (11.8-23.3)	< 0.001[a]
Period from the intervention to discharge (days)			
Median (IQR)	3.0 (2.0-5.0)	8.0 (5.0-12.8)	< 0.001[a]
Medication costs (Korean won)			
IV, median (IQR)	142,960.0 (114,368.0-171,774.0)	219,341.0 (182,329.5-366,622.5)	< 0.001[a]
PO, median (IQR)	2,114.0 (0-6,342.0)	0 (0-0)	< 0.001[a]
Total, median (IQR)	144,004.0 (114,516.0-183,826.5)	219,341.0 (182,329.5-366,622.5)	< 0.001[a]

[a]Statistically significant at P <0.05.
IV, intravenous; IQR, interquartile range; PO, per oral.

Discussion

Fluoroquinolones are broad-spectrum antimicrobials frequently prescribed in clinical [10]. The pharmacokinetic profile is similar between oral and intravenous formulations, allowing for easy conversions between the formulations. However, antimicrobials are frequently delivered intravenously in hospitalized patients even if they are capable of taking oral medications [11]. Furthermore, the intervention for conversion of routes of administration to reduce the length of hospital stay and cost is not frequently performed in Korea. Through this study, a hospital-wide policy on the intervention for conversion of intravenous-to-oral fluoroquinolones was suggested, and the effect of the intervention by the antimicrobial stewardship team was examined.

The antimicrobial stewardship guidelines by the IDSA recommend implementing institution-wide patient selection criteria for conversion of intravenous-to-oral antimicrobial administration [3]. In our hospital, the selection and exclusion criteria for patients were clearly established through discussions within the antimicrobial stewardship team of infectious disease physician and pharmacists. Through the policy, patients for whom conversion to oral antimicrobials and adherence by the healthcare providers were possible were identified by re-examining the clinical status of the patient before performing the intervention. Efforts were made to minimize potential negative effects of the conversion to oral medications on the clinical status of the patients. Eight cases who were converted to another family of intravenous antimicrobials owing to treatment failure were excluded from the analysis. Of those, 4 cases were maintained on intravenous antimicrobial administration, 1 case had the antimicrobial administration stopped, and 3 cases were converted to oral antimicrobials after the intervention. Furthermore, 18 cases who died during hospitalization were excluded, of whom 8 cases were maintained on an intravenous antimicrobial, 3 had their antimicrobial administration stopped, 2 were converted to another family of antimicrobials, and 2 were converted to an oral antimicrobial after the intervention, demonstrating that recommendation on conversion to oral antimicrobials did not have an effect on treatment failure or death.

The intervention adherence and the rate of conversion to oral administration are variably reported based on the method of the intervention and the institution. Sevinç et al. implemented a policy on early conversion to oral antimicrobials and reported an increase in the oral conversion rate from 54% to 83% [12]. Schouten et al. reported that the rate of adherence to oral conversion intervention in patients with community-acquired pneumonia is approximately 58%, ranging widely from 22% to 94% depending on the institution that conducted the intervention [13]. In this study, the rate of adherence to the intervention for conversion from intravenous to oral administration of fluoroquinolones was 79.8%, which was relatively high.

Although this study did not investigate the cause of non-adherence to the intervention, it is possible that the patients underwent changes to their health status during the intervention or that the patients were simultaneously receiving intravenous injection of other antimicrobials and therefore the healthcare provider did not feel the need to convert only the fluoroquinolone to oral administration. Of the 26 cases who did not adhere to the intervention, 13 (50%) were co-administered intravenous injections of other antimicrobials, of which piperacillin-tazobactam was the most common, received by 7 cases. Furthermore, in this study, 98 (95.1%) of 103 cases who adhered to the intervention were taking other oral medications and 20 (76.9%) of 26 cases who did not adhere to the intervention were taking other oral medications. Such study results show that there were patients who were continued on the intravenous injection of the medication at the discretion of the healthcare provider, even when they were able to take oral medications. Survey results from prescribing physicians presented in the study by Engel et al. showed that barriers to early conversion to oral antimicrobials frequently included opinions of the supervisor, the time point for the conversion to oral administration falling on a weekend, and simply forgetting to change the prescription [14]. Sevinç et al. also showed a lack of consistent or convincing reasons for non-adherence to the intervention [12].

In this study, a pharmacist in the antimicrobial stewardship team retrospectively examined all fluoroquinolone prescriptions to select study subjects and performed the intervention by leaving a note of recommendation on the electronic medical record. However, many studies have shown that an automatic intervention upon input of a prescription by a healthcare provider can effectively reduce unnecessary use of intravenous antimicrobials. The study by Fischer et al. showed that the intervention for oral conversion of 5 medications, which have the same bioavailability as their intravenous and oral formulations, including levofloxacin, using an automatic prescription system had an average adherence rate of 21.6% and reduced the use of intravenous medication by 34.5% [15]. Furthermore, according to Hulgan et al., the intervention for conversion to oral administration using an automatic prescription system that selected suitable patients taking levofloxacin or ciprofloxacin by looking

at other prescribed oral medications and their ability to ingest solid food led to a similar volume of total fluoroquinolones used, but the rate of use of oral medications increased from 56% to 62%, with statistical significance [16]. Therefore, it is suggested that implementation of automatic intervention for conversion of the route of administration into the hospital's healthcare information system using a clinical decision support system will decrease the workload of the pharmacist and increase the efficiency of the intervention.

According to the study by Davis et al., conversion to oral administration directly performed by a pharmacist in patients with community-acquired pneumonia who were administered moxifloxacin resulted in decreased antimicrobial cost and a statistically significant increase in the success rate of clinical treatment in those that received the intervention [17]. Furthermore, various oral antimicrobials with high bioavailability, other than fluoroquinolones, are used in the clinic, and their conversion to oral administration resulted in a comparable cure rate as their intravenous counterparts [18]. In this study, the intervention for conversion from intravenous to oral administration not only increased the convenience of administration for the patients and reduced medical costs associated with intravenous injections but also decreased the total length of antimicrobial administration and hospitalization. Therefore, it is suggested that the active intervention for conversion of various antimicrobials to oral administration is needed, for both clinical and cost-effective standpoints.

The limitations of this study include that it was a single-center study performed for a comparably short period of time. However, our study highlighted a significant role of the interdisciplinary team in an ASP including physicians and pharmacists that was successfully adapted in Korea and documented statistically significant clinical and economic benefits by the intervention. Also, the cases for the intervention were selected using more stringent criteria in this study in order to minimally impact on the clinical course of the disease and secure the intervention acceptance by the prescribers. Although acceptance rate of the intervention was 79.8% in this study, only 23.0% of all adult patients who were given fluoroquinolone injections for 3 days or more were included as subjects of the intervention, therefore the effect of the intervention could appear higher than it is in reality. However, we believe that 23.0% of all hospitalized patients prescribed with fluoroquinolone injections represented a sizable patient group who could get benefits from the intravenous-to-oral conversion in our institution, indicating a clinical significance with the high acceptance rate. An additional limitation was rooted from our intervention methods being delivered in 2 to 3 times a week rather than delivered in real-time due to limited manpower. Therefore, we believe that an intervention using healthcare information technology such as clinical decision support system could be an alternative in the future. Lastly, our study could not evaluate comprehensive economic outcomes. Since this observational study was conducted retrospectively, the diseases of the study patients were not standardized, the total cost of hospitalized care could not be analytically compared and the economic effect of intervention could only be limited to medication costs. However, considering that the hospitalization period was significantly shortened in the adherent group and the disease severities were not significantly different between the groups, there is a strong likelihood that the total cost of hospitalization would have been decreased with the intervention.

In conclusion, through this study, the favorable effect of implementation of active intervention for conversion from intravenous to oral administration by an institutional interdisciplinary antimicrobial stewardship team was observed. A large-scale prospective multicenter study including the adaptation of a clinical decision support system is needed.

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Conflicts of Interest

No conflicts of interest.

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