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Impact of levofloxacin dose adjustments by dispensing pharmacists on adverse reactions and costs in the treatment of elderly patients

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Ensuring an appropriate dosage of renally eliminated drugs for patients with renal insufficiency is important for preventing adverse drug reactions. We investigated the effectiveness of interventions by pharmacists in a hospital pharmaceutical department. The comparative study was performed at Gifu Municipal Hospital in Japan from March to August 2011, and included an intervention (142 patients) and a control group (98 patients). Upon receiving a prescription of levofloxacin for patients aged $\geq$ 75 years, pharmacists evaluated the patients' kidney function and adjusted the appropriate dosage at the time of dispensation. In the intervention and control groups, levofloxacin-induced adverse reactions developed in 6 of 142 (4.2%) and 13 of 98 (13.3%) patients, respectively ($p < 0.05$). The cost of reducing levofloxacin per patient was ¥191.1 and ¥0 in the intervention and control groups, respectively. The cost per patient for adverse reaction treatments and examinations was ¥15.5 and ¥290.0 in the intervention and control groups, respectively. The intergroup difference in the total cost per patient was ¥465.6. Dose adjustment of levofloxacin at the time of dispensation by the pharmacist for patients aged $\geq$ 75 years resulted in a decrease in the incidence of adverse reactions and cost. These findings can be applied not only to hospitals, but also to community pharmacies, because the intervention, which is a manual system, is simply performed when pharmacists are dispensing drugs.

1. Introduction

Drug-related problems (DRPs) such as adverse drug reactions (ADRs) develop with many medications but should be prevented. Some hospital admissions are associated with DRPs (Leendertse et al. 2010), and as a result, these DRPs are associated with high costs. Approximately 3% to 11% of hospitalizations have been reported to be attributable to drug medications (Beard 1992). In Germany, the percentage hospitalization due to 'possible' serious outpatient ADRs was estimated to be approximately 3.25%, with hospitalization being preventable in 20.1% of the cases (Rottenkolber et al. 2011). In Australia, 2.4% to 3.6% of hospital admissions are related to medications, and between 32% and 69% of these were estimated to be preventable (Roughead et al. 1998). In Japan, 1.7% of hospitalizations were judged attributable to inappropriate drug use, and 81% of them were expected to be preventable with pharmaceutical care by pharmacists (Koinuma et al. 2006).

DRPs are caused by various factors, especially when the appropriate drug, dosage, and duration of treatment are not selected on the basis of the patient's history and available laboratory data. DRPs can be prevented by pharmacists' interventions, which consequently result in cost savings (De Rijdt et al. 2008; Koinuma et al. 2006; Kopp et al. 2007; Lada and Delgado 2007; Mutnick et al. 1997; Rottenkolber et al. 2011; Zermansky et al. 2001). In Japan, cost savings were estimated when pharmacists were actively involved in outpatient treatment (Koinuma et al. 2006). In the UK, clinical medication review by pharmacists reduced costs by £61 per patient yearly (Zermansky et al. 2001). In the US, pharmacists' interventions represented a net therapy cost saving (Mutnick et al. 1997), and potential cost avoidance associated with their interventions in critical care (Kopp et al. 2007) and emergency departments (Lada and Delgado 2007) was shown.

Many drugs and their metabolites are eliminated via the kidneys. Appropriate drug use in patients with chronic kidney disease is important for avoiding ADRs, because the pharmacokinetic parameters are different from those in patients with normal renal function (Hassan et al. 2009a; Kappel and Calissi 2002; Swan and Bennett 1992). Renally eliminated drugs and their metabolites remain in the bodies of patients with renal impairment, and the increased blood concentrations of the drugs and these metabolites often lead to ADRs. DRPs are particularly frequent in patients with renal impairment, and careful dosage adjustment is required to avoid such DRPs in these patients. Several reports have been published on the reduction of both DRPs and the associated medical costs as a result of systems and interventions to ensure appropriate drug use in patients with renal impairment (Chertow et al. 2001; Hassan et al. 2009b; Pai et al. 2009; Peterson et al. 1991; Tawadrous et al. 2011). Computer-guided medication dosing for inpatients with renal insufficiency resulted in improved dosing and cost savings (Chertow et al.

2001; Tawadrous et al. 2011). A computer-based decision support system can be efficient, but also has problems, including its introduction cost and inconvenience caused by its introduction in community pharmacies because the system is not manual. The incidences of ADRs and associated drug costs were reduced by the following interventions: rounds with the nephrology unit team and dosing adjustment recommendations (Hassan et al. 2009b), a screening program for inappropriate dosages of renally eliminated drugs based on serum creatinine concentration (Peterson et al. 1991), and pharmaceutical care for patients undergoing haemodialysis (Pai et al. 2009). However, most of the reports referred to reductions in drug costs, but not in the cost of treatments and examinations associated with ADRs induced by inappropriate drug use.

To evaluate the degree of renal impairment, a common method is the calculation of creatinine clearance by using the Cockcroft-Gault equation (CLcr, mL/min, Cockcroft and Gault 1976). According to the equation, the CLcr value of older patients gradually decreases and their kidney functions deteriorate. Therefore, caution should be exercised in prescribing renally eliminated drugs to older patients. Patients aged $\geq$ 75 years appear to be at a higher risk for hospitalization for DRPs (Runciman et al. 2003).

Levofloxacin (LVFX) is a fluoroquinolone antibacterial agent (Croom and Goa 2003; Hurst et al. 2002), and LVFX dosage adjustment is required in patients with renal insufficiency because renal and total body clearance are highly correlated with CLcr (Fish and Chow 1997; Rodvold and Neuhauser 2001). LVFX is considered the safest fluoroquinolone; however, its adverse effects should be monitored when it is administered to patients with renal impairment (Liu 2010; Mehlhorn and Brown 2007; Stahlmann and Lode 2010). In Japan, the LVFX oral dose recommended by the manufacturer is 500 mg once daily for patients with a CLcr of $\geq$ 50, 500 mg once on the first day and 250 mg once daily from the second day for patients with CLcr of $<$ 50 and $\geq$ 20, and 500 mg once on the first day and 250 mg once daily every 2 days from the third day for patients with CLcr of $<$ 20.

We investigated the effectiveness of pharmacists' interventions in minimizing ADRs resulting from LVFX administration in elderly patients at a hospital pharmaceutical department. The interventions comprised (1) verification of serum creatinine concentrations by using a computer-based medical records system at the time of LVFX dispensation to patients aged $\geq$ 75 years; (2) evaluation of kidney function on the basis of the calculated CLcr values; and (3) suggestions of appropriate dosages to doctors if needed.

2. Investigations and results

The Fig. shows the flowchart used for selecting the study population. Three hundred patients were included, with 60 exclusions because the LVFX dosages were obviously reduced in their prescription on the basis of kidney function; therefore, the pharmacists did not need to check the CLcr values via the computerized medical records system. Of the remaining 240 patients, 142 were assigned to the intervention group, and 98 to the control group.

The characteristics of the patients in the 2 groups are presented in Table 1. Intergroup differences were not significant. Patients with CLcr levels of $<$ 50 corresponded to 42.2% and 49.0% of the patients in the intervention and control groups, respectively. The number of patients with LVFX-related ADRs or changes in dosage or for whom suggestions were made to doctors is shown in Table 2. The number of patients with adverse reactions assumed to be caused by LVFX was 6 (4.2%) and 13 (13.3%)

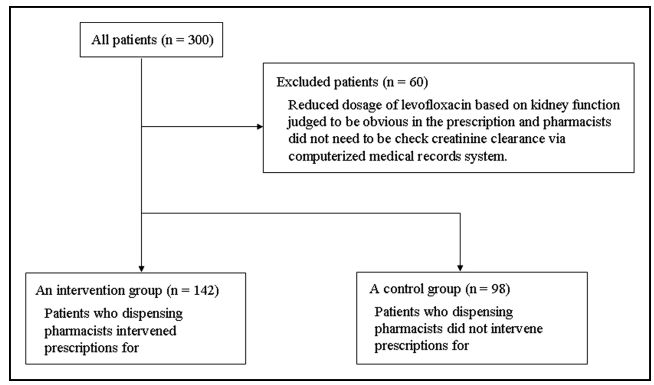

Fig.: Flowchart of the study population.

in the intervention and control groups, respectively. The occurrence rate of the adverse reactions was significantly different between the two groups ($p = 0.028$). Suggestions to doctors and changes in dosage were made for 42.2% and 16.9% of patients in the intervention group, respectively, with the doctors' acceptance rate being 40.0%.

Data from the patients who experienced adverse reactions assumed to be LVFX-related are shown in Table 3. A total of 19 patients had adverse reactions assumed to be LVFX-related: 6 in the intervention and 13 in the control group. In the intervention group, the 6 patients were inpatients. In the control group, 2 patients were outpatients and 11 were inpatients. The number of patients with CLcr levels of $<$ 50 was 15 (78.9% of the 19 patients). Three patients with CLcr levels of $<$ 50 had adverse reactions in the intervention group; the LVFX dosage in these 3 patients was not reduced by doctors, although pharmacists suggested a dosage adjustment. One patient was administered loxoprofen, an NSAID. No patients were administered warfarin; 1 patient had a history of epilepsy. The adverse reactions included pruritus, hepatic dysfunction, diarrhoea, nausea, convulsion, and paralysis. A moisturizing agent and steroid ointment were used for the treatment of pruritus, fluid therapy was performed for nausea, and carbamazepine was administered for convulsions. Head banging as a result of falling due to paralysis required computerized tomography. The total cost of reduced LVFX was ¥27,332.1 and ¥0 in the intervention and control groups, respectively, and the corresponding total cost of treatments and examinations related to the ADRs was ¥2,223 and ¥28,423. As shown in Table 2, the cost per patient of reduced LVFX was ¥191.1 and ¥0 in the intervention and control groups, respectively, and the corresponding cost per patient of treatments and examinations as a result of ADRs was ¥15.5 and ¥290.0. The difference in the total cost per patient was ¥465.6 between the groups.

3. Discussion

We investigated the effectiveness of interventions by pharmacists prior to dispensing a drug that requires dosage adjustment in patients with renal insufficiency. The study demonstrated that such intervention reduced the occurrence of ADRs as well as cost.

Patients with CLcr levels of $<$ 50 accounted for 40% to 50% of patients in both the intervention and control groups, which was relatively high. This may be due to inclusion of patients aged $\geq$ 75 years and may also be attributed to the high ratio of patients with serious disease because the prescriptions for inpatients were more than those of outpatients.

Suggestions to doctors and changes in dosage were made for 42.2 and 16.9% of the patients in the intervention group, respec-

Table 1: Characteristics of patients in the intervention and control groups

	Intervention group (n = 142)	Control group (n = 98)	p
Male	90 (63.3%)	69 (70.4%)	0.678 [a)]
Age	81.4 ± 4.7 (80.5)	80.9 ± 5.0 (80)	0.343 [b)]
Inpatient	122 (85.9%)	73 (74.5%)	0.490 [a)]
Creatinine clearance of < 50	60 (42.2%)	48 (49.0%)	0.558 [a)]
Concomitant NSAIDs [c)]	29 (20.4%)	10 (10.2%)	0.078 [a)]
Concomitant warfarin	6 (4.2%)	2 (2.0%)	0.480 [a)]
History of epilepsy	4 (2.8%)	2 (2.0%)	1.000 [a)]

Nominal and continuous valuables are expressed as numbers (%) and mean ± SD (median), respectively. a) Fisher's exact probability test was used. b) Mann-Whitney U test was used. c) NSAID: non-steroidal anti-inflammatory drug.

Table 2: Number of patients with adverse reactions assumed to be caused by levofloxacin, suggestions to doctors, changes of dosages, and costs

	Intervention group (n = 142)	Control group (n = 98)	p
Occurrence of adverse reactions	6 (4.2%)	13 (13.3%)	0.028 *
Suggestions to doctors	60 (42.2%)	–	–
Changes in dosage	24 (16.9%)	–	–
Cost per patient of reduced LVFX [a)]	¥191.1	¥0	
Cost per patient for treatments and examinations related to the ADRs [b)]	¥15.5	¥290.0	–

* indicates that a significant difference between the 2 groups was found using Fisher's exact probability test. Valuables are expressed as numbers (%). a) LVFX: levofloxacin, b) ADR: adverse drug reaction.

tively. The doctors' acceptance rate was 40.0%, which was due to the fact that doctors tended to decide on not reducing the LVFX dosage for patients with CLcr levels of 45 to 50 and for the prescriptions with dosing periods of 2 to 3 days. Further education of doctors may be necessary regarding dosage adjustments for renally eliminated drugs. Patients with CLcr levels of < 50 numbered 15 out of 19 (78.9%).

Of the 19 patients with adverse reactions to LVFX, one received NSAIDs, but the patient had no convulsion or epileptic episodes. The use of LVFX with NSAIDs has been shown to possibly influence the occurrence rate of convulsion and epilepsy, particularly in the elderly (Liu 2010; Stahlmann and Lode 2010). Of the 19 patients with ADRs, none was administered warfarin. Bleeding tendency as a result of warfarin being administered with fluoroquinolones has been reported (Ravnan and Locke 2001). No bleeding tendency, such as that associated with headache and bloody faeces, was observed in any patient. One patient with a history of epilepsy experienced an LVFX-induced convulsion during the study. However, the CLcr level of the patient was not < 50, suggesting that convulsion was not due to an increase in the LVFX concentration in blood. A history of epilepsy and a LVFX dose unadjusted for renal insufficiency may be also risk factors for the occurrence of convulsive seizures in patients receiving LVFX (Stahlmann and Lode 2010).

The adverse reactions observed in this study included the previously reported dose-dependent adverse reactions of fluoroquinolones related to the central nervous system (Liu 2010; Stahlmann and Lode 2010). For example, the patients with CLcr levels of 24 (No. 8), 33 (No. 12), and 35 (No. 13) experienced head banging as a result of falling due to quadriplegia, stiff right leg and slightly stiff left leg, and visual hallucinations. The CLcr levels in these patients were < 50, and the adverse reactions observed were due to increased LVFX concentration in their blood. The ADRs might have been prevented with an LVFX dosage adjustment as a result of an intervention by the dispensing pharmacist. The patient with a CLcr level of 76 (No. 19) had a convulsion. In this case, the CLcr was > 50, but the incidence of convulsions should be monitored carefully, particularly in patients with CLcr levels < 50. The patient with a CLcr level of 24 (No. 8) was an outpatient who had an appointment to consult a doctor soon; head computerized tomography was performed for this patient. The patient with a CLcr level of 33 (No. 12) was an in-patient, but stayed at home with the doctor's permission. When the accident occurred, the patient's family telephoned the hospital and the patient rested at home according to the doctor's directions. In these cases, the accidents were not critical; however, more clinical resources, such as treatment, examination, and doctor's involvement, were required in these cases. In the case of a critical accident, the monetary cost would be greater.

The number of patients with ADRs assumed to be caused by LVFX was 6 (4.2%) and 13 (13.3%) in the intervention and control groups, respectively. The occurrence rate of adverse reactions was significantly lower in the intervention group than in the control group ($p = 0.028$). The total cost per patient was lower by ¥465.6 in the intervention group than in the control group. These results suggest that both the occurrence of adverse reactions and the costs were reduced. Tawadrous et al. (2011) indicated that clinical decision support systems to improve kidney-related drug prescription were effective for the appropriate use of drugs and correction of inappropriate dosage. The use of clinical decision support systems led to cost reductions, and a large portion of the reduction was due to the lower amount of drugs administered owing to dosage adjustment (Chertow et al. 2001; Falconnier et al. 2001; Tawadrous et al. 2011). Furthermore, the use of the clinical decision support systems reduced the occurrence of ADRs (Evans et al. 1999). Regarding interventions by pharmacists, in Malaysia, rounds with the nephrology unit team and dosing adjustment recommendations by a clinical pharmacist when needed influenced ADRs and saved about US$2,250 in drug costs over 4 months (Hassan et al. 2009b). In the US, a screening program involving clinical pharmacists and patients with serum creatinine concentrations of > 1.5 mg/dL was conducted to avoid inappropriate dosages of renally eliminated; the initiative reduced the net cost by US$5,040 per year (Peterson et al. 1991). However, the cost associated with ADRs was not evaluated in the aforementioned reports.

The limitations of this study include the retrospective nature of the survey, with biases that could potentially affect the results.

Table 3: Information on patients with adverse reactions assumed to be caused by levofloxacin

Group	Patient No.	Dosing period (days)	Sex	Age (years)	Inpatient or outpatient	CLcr[a)] (mL/min)	NSAID[b)]	Warfarin	History of epilepsy	Adverse reactions induced by levofloxacin	Treatments and examinations of adverse reactions	Drug fee (yen)	Examination fee (yen)
	1	4	female	80	inpatient	40	no	no	no	pruritus	treatment by steroid ointment and heparinoid ointment	2,223	–
	2	3	male	76	inpatient	45	no	no	no	slight jaundice	observation	–	–
intervention	3	7	female	87	inpatient	47	yes	no	no	body pruritus	treatment with a moisturizing agent (an over-the-counter drug)	0	–
	4	2	male	82	inpatient	71	no	no	no	hepatic dysfunction and skin erythema	observation for the both symptoms	–	–
	5	7	male	78	inpatient	74	no	no	no	hepatic dysfunction	observation	–	–
	6	3	male	76	inpatient	102	no	no	no	diarrhea	observation	–	–
	7	5	female	85	inpatient	20	no	no	no	nausea	observation	–	–
	8	14	male	86	outpatient	24	no	no	no	head banging by falling due to quadriplegia	head computerized tomography	–	12,450
	9	4	female	81	inpatient	27	no	no	no	conjunctival injection and nausea	observation for conjuctival injection and treatment by fluid therapy for nausea	241	–
	10	3	male	95	inpatient	31	no	no	no	vomiting	change from peripheral to total parenteral nutrition	14,427	–
	11	7	male	77	inpatient	32	no	no	no	back pruritus	treatment with heparinoid lotion	695	–
	12	3	male	78	inpatient	33	no	no	no	stiff right leg and slightly stiff left leg	observation	–	–
control	13	3	male	81	inpatient	35	no	no	no	visual hallucination and body pruritus	observation for visual hallucination and treatment with diphenhydramine cream for body pruritus	162.5	–
	14	3	male	81	inpatient	35	no	no	no	body pruritus	treatment with zinc oxide ointment	119	–
	15	4	male	81	inpatient	35	no	no	no	pruritus	treatment with diphenhydramine cream	32.5	–

Table 3: (*Continued*)

Group	Patient No.	Dosing period (days)	Sex	Age (years)	Inpatient or outpatient	CLcr[a)] (mL/min)	NSAID[b)]	Warfarin	History of epilepsy	Adverse reactions induced by levofloxacin	Treatments and examinations of adverse reactions	Drug fee (yen)	Examination fee (yen)
	16	7	male	79	outpatient	40	no	no	no	skin eruption	observation	–	–
	17	3	male	76	inpatient	40	no	no	no	diarrhea	observation	–	–
	18	4	male	79	inpatient	45	no	no	no	diarrhea	observation	–	–
	19	5	male	79	inpatient	76	no	no	yes	convulsion	treatment with increased carbamazepine, and subsequent nausea, treated by fluid therapy	296	–

a) CLcr: creatinine clearance, b) NSAID: non-steroidal anti-inflammatory drug.

However, none of the pharmacists had any knowledge about the study during the investigation period. Pharmacists randomly received prescriptions and could not select prescriptions. The pharmacists might have suggested an LVFX dose adjustment to doctors while providing pharmaceutical services other than dispensation, for example, when providing pharmaceutical services in wards, such as drug explanation and compliance confirmation, which require a doctor's consent in Japan. Given that suggestions made during that time would decrease intergroup differences, the results of this study remain robust.

We demonstrated that LVFX dosage adjustments by dispensing pharmacists for patients aged ≥ 75 years decreased the occurrence of ADRs and reduced cost. In Japan, some doctors provide a prescription showing the serum creatinine concentration of patients, and our hospital directors are discussing this practice. Many doctors provide laboratory data to patients, as do all of the doctors in our hospital. At present, pharmacies receiving prescriptions in our hospital can check the serum creatinine concentration of the patient if necessary. The intervention described in this study is manual and simple. Therefore, our results can also be applied in community pharmacies.

4. Experimental

4.1. Design and setting

This was a retrospective comparative study performed in the pharmaceutical department at Gifu Municipal Hospital, Japan, from 1 March to 31 August 2011. An intervention and a control group were compared, and patients aged ≥ 75 years who were prescribed LVFX by the hospital doctors were included. The study was approved by the Ethics Committee of Gifu Municipal Hospital. The hospital is an acute-care general hospital with various clinical departments and 609 general beds. The pharmaceutical department provides instructions to the patients about the drugs administered in the hospital wards and is involved in centralized drug distribution and sterile mixing of anticancer drugs and total parental nutrition. In Japan, pharmaceutical services are solely provided by pharmacists because there are no technicians to assist them. As one of the centralized procedures in the pharmaceutical department, all the pharmacists must dispense drugs prescribed by doctors in the hospital. A prescription is printed automatically in the pharmaceutical department and a pharmacist dispenses the drugs according to the prescription. The prescription and dispensed drugs are verified by another pharmacist. A computerized medical records system has been introduced in the hospital, and all of the pharmacists can check medication history, laboratory data, and staff records of patients.

4.2. Interventions by pharmacists

The interventions by the pharmacists consisted of the following steps. The first step involved checking of serum creatinine concentrations by using the computerized medical records system when a pharmacist dispensed LVFX to patients aged ≥ 75 years. The second step was to evaluate the patients' kidney function on the basis of the calculated CLcr value. The third step was to suggest an appropriate drug dosage to doctors if necessary based on the package leaflet information provided by the manufacturer. At the time of LVFX dispensation, the interventions were attempted by specific pharmacists, and other pharmacists were not involved in the interventions. The specific pharmacists and other pharmacists randomly received LVFX prescriptions. Patients who received or did not receive interventions were assigned to an intervention group and a control group, respectively.

4.3. Data collection and analysis

We estimated the occurrence rate of ADRs caused by LVFX by using a computerized medical records system based on the Global Trigger Tool (Institute for Health Care Improvement, US. Classen et al. 2011; Naessens et al. 2010; Schildmeijer et al. 2012). The Global Trigger Tool enabled us to identify adverse events and measure their occurrence rate. Direct costs were evaluated as one of the outcomes of this study, and included the cost of reducing the LVFX dosage and treatments required because of ADRs. However, the hospitalization cost, including the costs of patient care and other drugs were excluded, because these were inclusive costs related to the diseases diagnosed, length of stay, and difficulty in estimating the length of stay prolonged by ADRs. Furthermore, we investigated sex, age, in/outpatient status, CLcr, concomitant non-steroidal anti-inflammatory drug (NSAIDs) and warfarin administration, and history of epilepsy by using the computerized medical records system. If administered concomitantly with fluoroquinolone, NSAIDs might enhance the risk of convulsions (Liu 2010; Stahlmann and Lode 2010), and the concentration of warfarin in blood might increase (Ravnan and Locke 2001). A history of epilepsy has also been shown to be a contributing factor for the increase in convulsions in patients receiving fluoroquinolones (Stahlmann and Lode 2010). The CLcr value was calculated using the Cockcroft-Gault equation. If body weight was not measured, the average Japanese body weights reported by the Japanese government on the basis of data related to each generation and sex were used for CLcr calculation. Fisher's exact probability test was used to test differences between data, with the exception of age in the intervention and control groups; the Mann-Whitney U test was used to analyse age data. Results with a p value of < 0.05 were considered statistically significant. All costs were calculated according to the medical treatment fees in Japan in 2011, and are presented in Yen.

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