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原 著

Validity of Recommended Dosage Reduction Criteria for Rivaroxaban in Patients with Renal Impairment

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Summary

To prevent bleeding, dosage reduction of the novel anticoagulant rivaroxaban is recommended in the Dosage and Administration section of the drug package insert for patients with renal impairment. However, the dosage reduction criteria are not always followed in actual clinical settings. We therefore investigated the validity of the recommended dosage reduction criteria for rivaroxaban in patients with renal impairment. Subjects were 18 inpatients with renal impairment who were treated with rivaroxaban between July 2012 and May 2014 at the Japanese Red Cross Medical Center. In this retrospective observational study, patients were divided into the proper dose group (13 patients) and improper dosage group (5 patients) based on their medical records, and trough prothrombin time (PT) was analyzed. In the improper dosage group compared with the proper dosage group, PT was 2.4 s longer (p=0.05) after administration of rivaroxaban and the difference in PTs measured before and after administration was 1.8 s longer (p=0.35). These results suggest that the administration of rivaroxaban tends to increase risk of bleeding in patients with renal impairment if the dosage reduction criteria are not followed.

Key words
anticoagulant, rivaroxaban, renal impairment, prothrombin time

Summary（和文）

新規抗凝固薬Rivaroxabanは、腎機能障害患者の出血リスク管理の観点から、医薬品添付文書の用法用量においては腎機能障害患者に推奨減量基準を設定している。しかし、実際の臨床では、その減量基準が守られていない症例も少なくない。そこで腎機能障害患者におけるRivaroxabanの推奨減量基準（以下、減量基準）の妥当性について検討を行

った。調査は、日本赤十字社医療センターにおいて2012年７月～2014年５月の間にRivaroxabanが投与された腎機能障害を持つ入院患者18名を対象に、診療録による後方視的観察研究を実施した。減量基準に従った群（適正用量群）13名と、減量基準に従わなかった群（非適正用量群）５名に分け、プロトロンビン時間トラフ値（PT）を比較した。結果、非適正用量群の投与後のPTは、適正用量群のそれに比べ、2.4秒延長した（p=0.05）。また、非適正用量群の投与前後のPTの差（⊿PT）は、適正用量群のそれに比べ、1.8秒延長した（p=0.35）。以上の結果から、腎機能障害患者におけるRivaroxaban減量基準を守らないとPTが延長する傾向にあり、その結果出血リスクが増大する可能性が示唆された。

Key words（和文）
抗凝固薬、Rivaroxaban、腎機能障害、プロトロンビン時間

Introduction

Atrial fibrillation is the most common type of arrhythmia encountered in daily clinical practice, and its incidence increases with age. Because atrial fibrillation is known to increase the risk of cerebral infarction, early detection of atrial fibrillation and early initiation of anticoagulant therapy in high-risk patients are important[1].

In Japan, four novel oral anticoagulants (NOAC)—dabigatran, rivaroxaban, apixaban, and edoxaban—are currently approved for the use in anticoagulant therapy, in addition to the conventional warfarin. The preventive effects of these NOACs on atrial fibrillation–associated thromboembolic events– are expected to be similar or even superior to those of warfarin. Because NOACs have fewer interactions with other drugs or food and a greater range of effective blood concentrations, they are widely expected to replace warfarin as highly convenient drug alternatives[2-4].

In April 2012, rivaroxaban, a NOAC and a selective inhibitor of Factor Xa, was approved in Japan for the prevention of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF). The characteristics of rivaroxaban include a once-daily (OD) single-tablet regimen and, unlike warfarin, no need for frequent monitoring of bleeding events due to its stable pharmacokinetic and pharmacodynamic properties. However, because of the potential association between rivaroxaban and a high risk of bleeding in patients with impaired renal function, as reported by previous clinical trials[5,6], the package insert for rivaroxaban recommends reduced dosages according to the severity of renal impairment. Furthermore, because of the high incidence of bleeding in patients with impaired renal function, it is important to perform a clotting test to monitor bleeding events in clinical settings. The simple prothrombin time (PT) test has been shown to be most appropriate for this purpose[7].

The package insert of rivaroxaban recommends dosage reduction criteria for patients with renal impairment. However, these criteria have not yet been validated. Therefore, to investigate the validity of the dosage reduction criteria, we used PT as a clotting test to evaluate bleeding risk in patients with renal impairment in real-world clinical practice.

Methods

1. Study population

Subjects were inpatients with renal impairment (creatine clearance [Ccr] <50ml/min) who had been diagnosed as having NVAF and administered rivaroxaban for the first time between July 2012–May 2014 at the Japanese Red Cross Medical Center, Tokyo, Japan.

2. Research instruments

Clinical records were examined in a retrospective observational manner to extract patient backgrounds (age, sex, weight, Ccr, and rivaroxaban dosage) and PT values. Ccr was calculated using the Cockcroft-Gault equation. The Coagpia PT-N reagent (international sensitivity index, approximately 1.0; Sekisui Medical Co., Ltd., Tokyo, Japan) was used to measure PT.

3. Statistical analysis

Patients were assigned to the proper or improper dosage groups depending on whether rivaroxaban was given in accordance with the dosage reduction criteria for patients with renal impairment (**Table 1**). The PT test was performed before the administration of rivaroxaban and immediately before the administration on the following day (the PT trough value), and the difference in PT values (hereinafter ΔPT) measured before and after rivaroxaban administration were calculated.

Instead of unstable peak PT values, which vary among individuals[8,9], stable trough PT values were used in this study. In addition, patients were stratified according to the severity of renal impairment (moderate impairment, Ccr 30–49 ml/min; severe impairment, Ccr 15–29 ml/min) to compare the ΔPT values between the proper and improper dosage groups.

IBM SPSS Statistics 20.0 software was used for statistical analysis. Mann-Whitney's U-test was performed to compare data with significance set at $p<0.05$.

Table 1. Dosage reduction criteria for rivaroxaban in patients with renal impairment

CCr (mL/min)	Dose
>50	15 mg once daily (normal dosage)
30-49	10 mg once daily
15-29	10 mg once daily (careful administration)
<15	Contraindicated

4．Ethical approval

This study was approved by the Ethics Committee of the Japanese Red Cross Medical Center (Approval No. H26-538) and by the Ethics Committee of Showa Pharmaceutical University (Approval No. H26-13). Because of the retrospective observational nature of the study, no individuals were harmed.

Results

1．Patient background

Table 2 presents the characteristics of all 18 patients enrolled in this study. Table 3 presents the characteristics of patients by dosage group.

Table 2. Patient characteristics

Characteristic	All (n=18)
Age, yr	
Median	87
Interquartile range	59-103
Sex, n (%)	
Male	14 (78)
Female	4 (22)
Body weight, kg	
Median	48
Interquartile range	37-81.5
Rivaroxaban dosage, n (%)	
Proper dosage	13 (72)
Improper dosage	5 (28)
Baseline creatinine clearance, ml/min *	
Median	46.1
Interquartile range	37-81.5
30-49 ml/min, n (%)	12 (77)
15-29 ml/min, n (%)	6 (33)

* Creatinine clearance was calculated with the use of the Cokcroft-Gault formula.

Table 3. Patient characteristics by dosage group

Characteristic	Proper dosage (n=13)	Improper dosage (n=5)	*p* value
Age, yr			
Median	84	77	0.11
Interquartile range	71-103	59-87	
Sex, n (%)			
Male	9 (69)	5 (100)	—
Female	4 (31)	0 (0)	
Body weight, kg			
Median	49.4	55.1	0.22
Interquartile range	37-81.5	48-64.4	
Baseline creatinine clearance, ml/min †			
Median	38.4	42.6	0.59
Interquartile range	21.1-49.1	27-49.1	
30-49 ml/min, n (%)	9 (69)	3 (60)	
15-29ml/min, n (%)	4 (31)	2 (40)	
Baseline prothrombin time, sec			
Median	12.3	13.7	0.1
Interquartile range	9.8-16.2	12.1-18.6	

† Creatinine clearance was calculated with the use of the Cokcroft-Gault formula.

2. PT values after rivaroxaban administration and ΔPT values between before and after administration

Table 4 shows median post dose PT values of 13.8 and 16.2 s in the proper and improper dosage groups, respectively, with a difference of 2.4 s between the groups (p=0.05). Median ΔPT values were 0.9 and 2.7 s in the proper and improper dosage groups, respectively, with a difference of 1.8 s between the groups (p=0.35) **(Fig. 1)**.

Table 4. PT values after rivaroxaban administration and bleeding

	Proper dosage (n=13)	Improper dosage (n=5)	*p* value
Postdose prothrombin time (trough), sec			
Median	13.8	16.2	0.05
Interquartile range	10.2-27.4	13.4-31.4	
Adverse event, n			
Bleeding	0	0	—

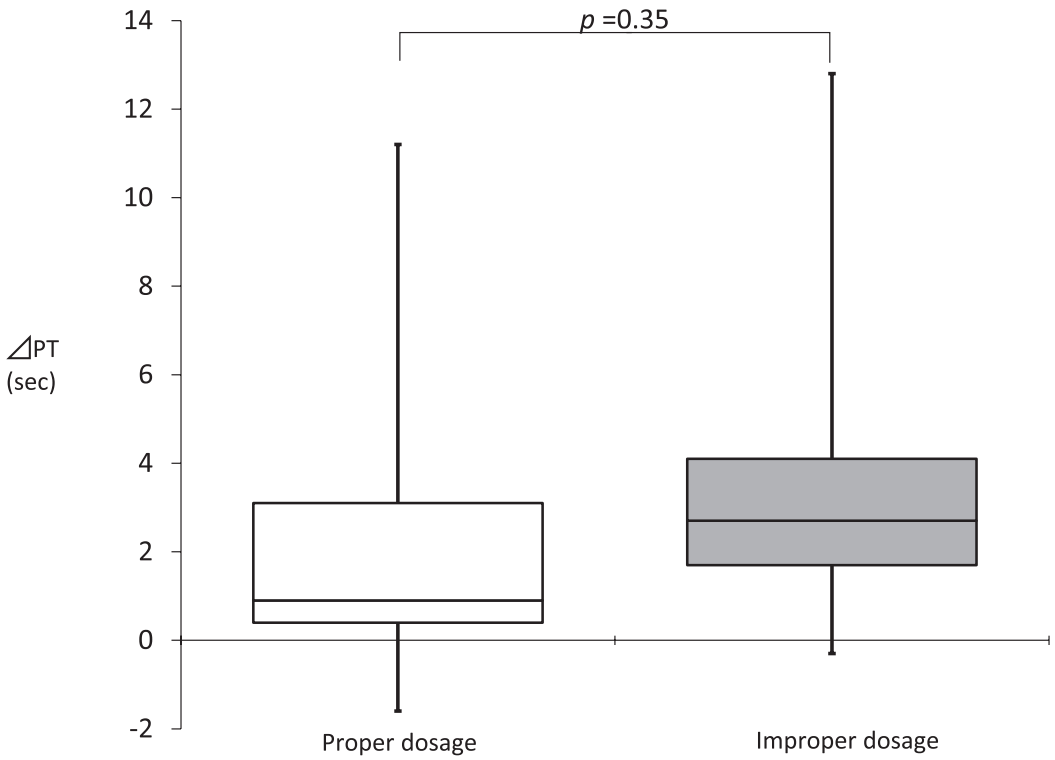

Fig. 1. Difference in PT values (ΔPT values) before and after rivaroxaban administration

3．Side effects

No side effects such as upper gastrointestinal bleeding were observed in either group (Table 4).

4．Differences by disease severity in ΔPT values in patients with renal impairment

4-1. Post dose ΔPT values in patients with moderate renal impairment

A total of 12 patients had moderate renal impairment (Ccr, 30–49 ml/min), of whom 9 and 3 belonged to the proper and improper dosage groups, respectively. The median ΔPT values were 0.9 and 1.7 s in the proper and improper dosage groups, respectively, with a difference of 0.8 s between the groups (p=0.92).

4-2. Post dose PT and ΔPT values in patients with severe renal impairment

A total of 6 patients had severe renal impairment (Ccr, 15–29 ml/min), of whom 4 and 2 were in the proper and improper dosage groups, respectively. Median ΔPT values were 1.75 and 8.45 s in the proper and improper dosage groups, respectively, with a difference of 6.7 s between the groups (p=0.06).

Discussion

The aim of this study was to investigate the validity of the recommended dosage reduction criteria for rivaroxaban in patients with renal impairment in real-world clinical practice. This observational study, in which an increase in PT values was used as an indicator of bleeding risk, provided useful insights into how inappropriate dosing of rivaroxaban affects patients with renal impairment.

Post dose PT values and ΔPT values before and after rivaroxaban administration tended to increase in the group of patients administered an improper dosage of rivaroxaban, compared with those in the group of patients administered the proper dosage of 10 mg rivaroxaban. In the previous study investigating the effect of 10 mg rivaroxaban in patients with renal impairment, the post dose PT value was 11.6 s[9]. Reagents used in PT measurement are known to affect PT values. However, because both the PT reagent used in the previous study (HemosIL® RecombiPlasTin 2G) and the one used in the present study (Coagpia® PT-N) have an international sensitivity index of 1.0, it is appropriate to compare the PT values of 11.6 s and 13.8 s obtained after the administration of 10 mg rivaroxaban in the previous and present studies, respectively. Furthermore, the post dose PT value was 16.2 s in patients with renal impairment in the improper dosage group. This result is consistent with the previous study's finding of prolonged PT in patients with renal impairment after the administration of an inappropriate dosage of rivaroxaban. Together, the findings of these studies elucidate the validity of the criteria for rivaroxaban reduction. Furthermore, stratification analysis based on disease severity revealed a marked increase in PT values when rivaroxaban was administered at an improper dosage in patients with renal impairment, so we can conclude that the dosage reduction criteria are valid and should be followed in clinical practice.

This study has some limitations, including its small sample size, single-center design, and short follow-up observation. Further investigation is therefore needed in order to verify the present findings. However, this study was the first to investigate the validity of the dosage reduction criteria for rivaroxaban in patients with renal impairment, and will serve as basic data for the use of post dose PT values and ΔPT values before and after drug administration to evaluate rivaroxaban-induced bleeding risks in patients with renal impairment.

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