Successful Use of a New Oral Anti–coagulant in a Stroke Patient with Poor Prothrombin Time Control Even After Warfarin Treatment

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ABSTRACT

A 76-year-old woman presented to our hospital with right-side motor weakness. She was diagnosed with paroxysmal atrial fibrillation in June 2010 and underwent treatment with warfarin and a class Ic anti-arrhythmic drug (flecainide). However, during the follow-up period, her international normalized ratio could not be controlled despite laborious adjustment of warfarin dose. Therefore, warfarin treatment was discontinued and dual antiplatelet agent therapy was initiated. Three months after stopping warfarin treatment, she presented to an emergency clinic with right-side motor weakness and was diagnosed with acute middle cerebral artery occlusion. However, as she did not wish to take warfarin, the author prescribed treatment with a new oral anti-coagulant (NOAC) in order to prevent the development of further stroke.

Key Words: ▪ atrial fibrillation ▪ stroke ▪ new oral anti-coagulant

Introduction

For the last several decades, vitamin K antagonists (VKAs) have been the primary medication in anti–coagulant therapy for the prevention and treatment of thrombotic events. Due to the individual variation in prothrombin time (PT) responses, individualized adjustment of the VKA dose is essential to manage the international normalized ratio (INR); however, this places a significant practical burden on both the physician and patient. Appropriate INR management is very difficult in some cases, which makes the application of therapy involving fixed doses of oral anti–coagulants an attractive option for practical reasons. New oral anti–coagulants (NOACs) have recently been developed to prevent embolic stroke and to reduce the incidence of major bleeding in comparison with that associated with VKA use. In the present report, the author presents a case with poor INR control with warfarin treatment that was successfully treated with a NOAC to prevent embolic stroke recurrence.
A 76-year-old woman was referred to our institution in June 2010 for the evaluation of newly diagnosed atrial fibrillation that occurred 3 days after an episode of transient right-side motor weakness. She had been diagnosed with essential hypertension 15 years previously and was taking losartan (50 mg q.d.) and hydrochlorothiazide (12.5 mg q.d.). Her body temperature was 36.7°C, her pulse rate was 78 beats per minute, and her blood pressure was 126/78 mmHg. Her radial pulse was irregular, and a grade III systolic murmur could be heard in her mitral valve area.

**Case**

**Figure 1.** The initial electrocardiogram shows atrial fibrillation. ST segment depression is noted in the anterolateral leads.

**Figure 2.** The coronary angiogram shows significant atherosclerotic stenosis with ectatic formation (white arrows) in the middle segment of the left anterior descending artery on the right anterior cranial view (A) and the right anterior caudal view (B).
She showed no neurologic deficit and was mentally alert.

As previously stated, the patient had experienced transient right-side motor weakness (for approximately 2 hours) 3 days previously and had been admitted to undergo evaluation of new-diagnosed paroxysmal atrial fibrillation. Her hemogram values, biochemical marker levels, and thyroid hormone levels were within normal limits. The initial electrocardiogram (ECG) confirmed the presence of atrial fibrillation (Figure 1). Transthoracic echocardiography showed normal left ventricular systolic function (ejection fraction, 58%) and grade II mitral regurgitation. The left atrium was mildly enlarged (diameter, 42.4 mm). Because the anterolateral ECG leads showed ST segment depression (Figure 1), she underwent a coronary angiogram, which indicated a fixed atherosclerotic lesion in the middle segment of the left anterior descending artery and showed 70% stenosis (Figure 2). Percutaneous coronary intervention was not performed as she did not experience any chest pain or discomfort. Therefore, the author decided to use a class Ic anti-arrhythmic drug (flecainide) and warfarin to prevent embolic stroke, based on her CHADS\textsubscript{2} score of 4 (1 point for hypertension, 1 point for age ≥75 years, and 2 points for history of transient ischemic attack).

However, despite the frequent blood sampling and visits to the outpatient clinic (which the pa-
The patient complained about), her INR could not be controlled during the follow-up period. After 3 months, her ECG showed normal sinus rhythm (Figure 3), after which she refused to take warfarin regardless of our recommendations. Hence, she was treated with a combination of two anti-coagulants (aspirin and clopidogrel). After 3 months, she presented to our emergency clinic with right-side motor weakness and slurred speech. Diffusion magnetic resonance images (MRI) showed acute left middle and posterior cerebral artery infarction (Figure 4). Following recovery, the author recommended that the patient should continue treatment with warfarin to prevent embolic stroke. She accepted our recommendation at that time and continued with warfarin treatment after discharge. However, despite several warfarin dose titrations, her PT/INR control was found to be poor at every visit to the clinic (Figure 5). Moreover, when the INR increased to above 3.5, she complained about gum bleeding. As the INR was consistently outside the target range of 2.5–3.5, the author decided to switch the treatment from warfarin to a NOAC.

At present, the patient has not experienced embolic stroke or any major or minor bleeding events. In addition, she reported that she is satisfied with the convenience of the new regimen.

**Discussion**

NOACs have been introduced worldwide to improve anti-coagulation therapy. In patients who show poor PT/INR control with warfarin, NOACs may provide a particularly promising alternative. Unlike warfarin, which has a narrow therapeutic window and requires individualized dosing based on the INR, NOACs have a wide therapeutic window, thereby facilitating fixed dosing without the need for laboratory monitoring or dose titration. Several clinical studies on NOACs are currently investigating protocols for dose adjustment, managing bleeding events, and other such factors. However, only a few studies have described patient adherence to NOACs. Hence, the author believes that more sustainable methods for improving patient adherence to NOACs are needed.

Patients may be more motivated to take anti-hypertensive medication if they perceive a tangible benefit such as reduction of headache or reduced chest flutters. However, in the absence of such benefits, the adherence may drop—in particular, this phenomenon may be observed in patients undergoing warfarin treatment (most users are chronic atrial fibrillation patients), even though they regularly undergo inconvenient dose monitoring.

Although NOACs are currently being prescribed worldwide, it is uncertain whether accurate data on complications are being reported. Major bleeding complications have been noted with NOAC use; however, it is not possible to make definitive conclusions due to the lack of data on comparisons with VKA use under real-world conditions.

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conditions. Patients in clinical trials of NOACs are generally highly motivated to comply with the requirement for regular visits and follow-up calls and provided education regarding their disease state and the importance of medication adherence (monitored via pill counts). However, given the lack of a requirement for regular coagulation monitoring, this may not be observed for some patients who are prescribed NOACs in the real-world setting. This is especially critical in chronic atrial fibrillation patients, most of whom have not experienced a thrombotic event. The requirement for INR monitoring in patients receiving warfarin treatment effectively enables the monitoring of adherence. Furthermore, the twice-daily dosing schedules of some NOACs may be more difficult for some patients to adhere to as compared to a daily regimen. At present, in South Korea, the markedly higher costs of NOACs should also be carefully considered. Even for patients with insurance that covers NOACs, physicians should ascertain how much the patients pay for the treatment with NOACs compared with warfarin. High drug costs may result in reduced medication adherence.

In the present case, the patient wished to discontinue blood sampling and complained of minor bleeding (gum bleeding). She requested to receive NOAC treatment, regardless of the cost, and has adhered to her medication thus far. Thus, the author recommends that NOACs should be considered for selected patients who wish to avoid the limitations associated with conventional VKA treatment.

References