

Two Ischemic Stroke Cases Accruing Despite High INR Levels

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Abstract

Warfarin is a vitamin K antagonist commonly used in the treatment and prevention of thromboembolic cases worldwide. Its therapeutic range is narrow and is followed by the international normalized ratio (INR). Ischemic conditions are observed at low INR levels whereas bleeding is seen at higher INR levels. A 45-year-old woman and a 79-year-old man using warfarin were admitted to the emergency department with a neurological deficit. Ischemic stroke was revealed via radiological imaging in both patients. However, INR levels were significantly higher in laboratory tests (11.44 and 12.37 kU/L). Ischemic stroke occurred although bleeding is normally expected at such high INR levels. Contrary to many studies published in the literature, this case report revealed interesting information in terms of its conclusions.

Keywords: Ischemic stroke, high INR levels, warfarin overdose, emergency medicine

Özet

Warfarin, dünya çapında tromboembolik vakaların tedavisinde ve önlenmesinde yaygın olarak kullanılan bir K vitamini antagonistidir. Terapötik aralığı dardır ve bunu uluslararası normalleştirilmiş oran (INR) ile takip edilir. Düşük INR seviyelerinde iskemik durumlar gözlenirken, daha yüksek INR seviyelerinde kanama görülür. Warfarin kullanan 45 yaşında kadın ve 79 yaşında erkek hasta nörolojik defisit ile acil servise başvurdu. Her iki hastada da radyolojik görüntüleme ile iskemik inme saptandı. Ancak INR düzeyleri laboratuvar testlerinde (11.44 ve 12.37 kU/L) anlamlı olarak daha yüksekti. Bu kadar yüksek INR seviyelerinde normal olarak kanama beklenmesine rağmen iskemik inme meydana geldi. Literatürde yayınlanan birçok çalışmanın aksine bu olgu sunumu sonuçları açısından ilginç bilgiler ortaya koymuştur.

Anahtar Kelimeler: İskemik inme, yüksek INR seviyeleri, warfarin doz aşımı, acil tıp

Introduction

Warfarin is a vitamin K antagonist commonly used in the treatment and prophylaxis of thromboembolic diseases. It is extensively used in diseases such as prosthetic heart valve diseases, dilated cardiomyopathy, atrial fibrillation (AF), deep vein thrombosis (DVT), and pulmonary embolism (PE)¹. In particular, anticoagulation, which is well controlled with warfarin, can prevent more than half of the strokes associated with AF and heart valve replacements². The therapeutic index of warfarin is narrow, followed by the international normalized ratio (INR). INR provides a standard scale for monitoring patients receiving oral anticoagulant therapy. The rate of prothrombin time (PT) of the patient is calculated as its rate to the control PT obtained using a thromboplastin reagent, an international reference developed by the World Health Organization (WHO)³. In this case report, we will present two stroke cases occurring despite high INR levels, which is not encountered in the literature.

Case 1

A 45-year-old woman was admitted to the emergency department with complaints of, dizziness, nausea, and numbness in the left arm. We learned that she had been taking 5 mg of warfarin daily for her previous occlusive cerebrovascular disease. The patient was conscious. Her general state was good, Glasgow Coma Scale (GCS) was 15, and vital signs were stable. Her neurological examination showed dysarthria and 4/5 muscle strength hemiparesis in her left upper and lower extremities. The patient had no stiffness and no additional pathological reflexes. In the blood sampling, Hemoglobin was found as 9.7 g / dl, WBC was 15.070 and PLT was 272.000. His electrocardiogram (ECG) showed sinus rhythm. No electrolyte imbalance was detected in the biochemical analysis. INR was found as 11.44 kU / L (studied twice). In the cranial imaging of the patient, computerized brain tomography (CBT) showed chronic ischemic changes, while magnetic resonance imaging (MRI) showed a 10 mm diameter diffusion restriction on the left

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Figure 1: Magnetic resonance imaging of Case 1

side of the brain stem (Figure 1). The patient was admitted to the intensive care unit for follow-up by consulting with the neurology clinic. In the subsequent examination of the patient, antiphospholipid antibodies (APS), anticardiolipin antibodies (ACA) and antinuclear antibodies (ANA) were found to be negative.

Case 2

A 79-year-old male patient was admitted to the emergency department with dysarthria and blurred consciousness. The patient had a history of hypertension, AF, and chronic kidney disease. He had confusion, his orientation and cooperation were impaired and his GCS was 10. His vital signs were stable, blood glucose level was found as 128 mg / dl, BUN was 34.02 mg / dl, creatinine was 1.94 mg / dl, and INR was 12.37 kU / L (studied twice). We learned that the patient had been using 5 and 2.5 mg of warfarin every other day. Computerized brain tomography revealed periventricular white matter density and diffuse diminution, and heterogeneous hypodense lesion area in the occipital lobe on the left side (Figure 2). Subsequent MRI revealed diffusion in both cerebellar hemispheres at the occipital lobe of the left central subcortical area. In the hyperintense ADC map of the images, signal limitation areas which were compatible with hypointense acute ischemia in the millimeter size in the thalamus on the left and in the periventricular white matter on the right were observed (Figure 3). The patient

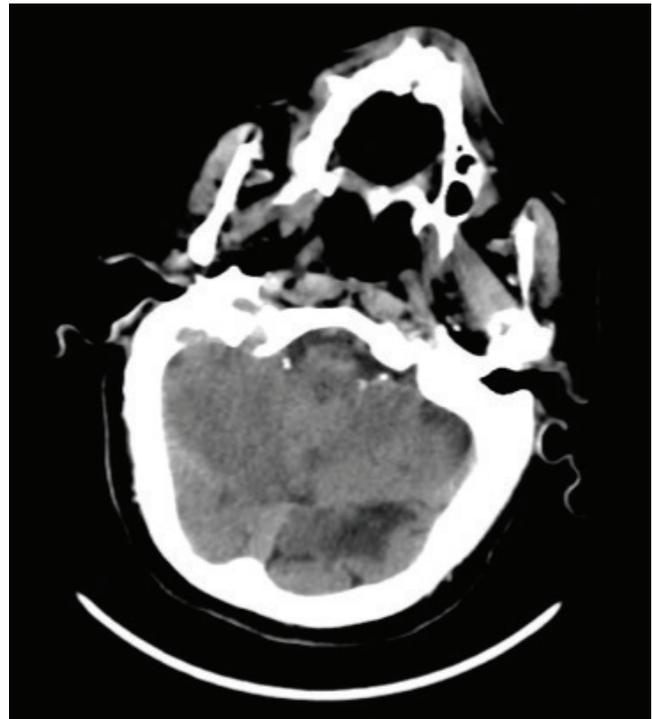


Figure 2: Computerized brain tomography of Case 2

was admitted to the intensive care unit in consultation with the neurology clinic.

Discussion

Warfarin inhibits the synthesis of vitamin K-dependent coagulation factors, including factor II, VII, IX and X and anticoagulant proteins C and S⁴. The therapeutic range of warfarin is narrow. In particular, it is difficult to use as it is influenced by many factors such as dose adjustment, genetic factors, drug interactions, and diet. The targeted INR value is usually 2 to 3 in patients with AF, DVT / PE, and occlusive cerebrovascular disease. The targeted INR value in patients with prosthetic heart valve disease is 2.5-3.5⁵. The most common side effect is bleeding⁶⁻⁷. Especially in cases whose INR values exceed 4.5, the risk of major bleeding increases². Intracranial hemorrhage (ICH) is considered as the most dangerous bleeding complication of anticoagulant therapy. In warfarin-dependent ICHs, the mortality rate is high and a large proportion of these patients die within 30 day⁸. In most of the bleeding, INR values are high. Many side effects have been reported in the literature due to warfarin use. Most of the rare side effects have been reported in case reports. In those reports, acute kidney injury, skin lesions, hepatotoxicity, and penile gangrene despite the normal INR level have been reported⁹⁻¹¹. In another study, nonhaemorrhagic arthritis findings independent from INR values have been reported in 61 patients using vitamin K antagonist¹². The risk of thromboembolism

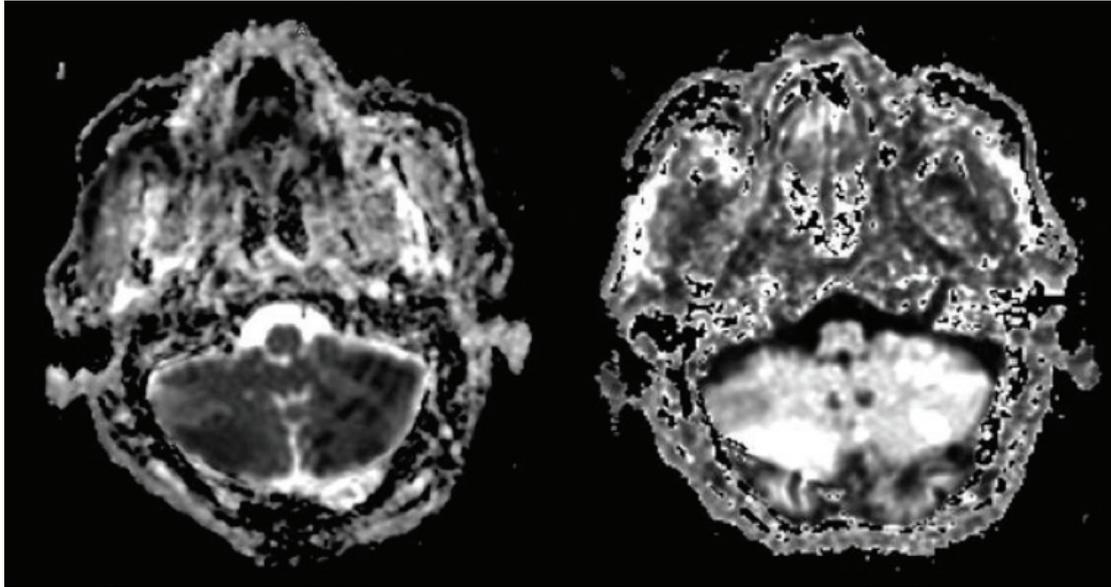


Figure 3: Magnetic resonance imaging of Case 2

increases dramatically in lower INR values, especially below 1.9-2.0¹³. Bleeding is observed in higher INR values. In our cases, INR values were significantly higher than the therapeutic range (11.44 and 12.37). Normally, bleeding was expected to be with those INR levels. However, ischemic stroke developed in those two patients. In the first case, a history of previous ischemic stroke and a relatively young age strengthened the possibility of a genetic predisposing factor in the foreground. Although APS, ACA, and ANA were negative in this case, protein C, protein S and factor V Leiden mutation could not be investigated due to technical deficiency. In the second case, the risk factor for thromboembolic events is AF and partly advanced age. However, the likelihood of developing ischemic stroke at such high INR levels is unexpected in both cases, regardless of the underlying condition.

Conclusion

As a result, unlike many studies published in the literature, this case report revealed interesting information. More detailed studies on this issue may be reported to support our findings.

Declarations: We previously presented our case report as an oral presentation in XVII. Ulusal Acil Tıp Kongresi & 8. Intercontinental Emergency Medicine ve 8. International Critical Care Congress in 2021 in Antalya.

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