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CASE REPORT

Failure of old and new anticoagulants to prevent ischemic stroke in high-risk atrial fibrillation: a case report

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ABSTRACT

Rivaroxaban is an oral anticoagulant that acts as a direct, competitive factor Xa inhibitor. Large randomized clinical trials have shown that, at a daily dose of 20 mg, Rivaroxaban is at least as effective as dose-adjusted warfarin for the prevention of stroke or other embolic complications in patients with nonvalvular atrial fibrillation (AF). The safety and efficacy of combining Rivaroxaban with an antiplatelet agent for secondary stroke prevention has not been established.
We report the case of an elderly patient with permanent AF and coronary heart disease, who had already suffered an ischemic stroke while on warfarin treatment, and was consequently switched to treatment with an association of Rivaroxaban and Aspirin. Her CHA2DS2-VASc score was 9. The patient developed a severe recurrent disabling ischemic stroke. This case goes to show that the novel direct anticoagulants may fail to prevent recurrent stroke in patients at particularly high risk, even when associated with antiplatelet drugs.

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Atrial fibrillation (AF) affects 1-2% of the world's population, and is associated with a four- to six-fold higher risk of stroke in the people concerned.[1] The risk increases with age. In people over 80 years old, AF is directly responsible for one in four strokes.[2] People with AF may experience multiple strokes, some of which occur subclinically and can lead to dementia.[3]

Treating AF individuals with vitamin K antagonists or novel direct anticoagulants reduces the stroke rate by 50% to 66%.

Rivaroxaban, a new oral anticoagulant that electively inhibits factor Xa, has recently been proposed as a novel treatment option that is as warfarin in preventing stroke or systemic embolism in patients as effective at high risk (CHADS > 2), and with a similar rate of major bleeding episodes generally, and fewer intracranial bleeding events.[4]

We report here a case of a 77-year-old woman with AF, resulting in recurrent severe stroke, while on full-dose Rivaroxaban treatment in combination with Aspirin.

Case report

A 77-year-old white woman was admitted to our Internal Medicine Department at Padua University Hospital (Italy) in May 2015 with clinical manifestations suggestive of acute, irreversible stroke. The patient's

clinical history included long-standing high blood pressure and diabetes mellitus, both controlled by adequate therapy. She had experienced an acute myocardial infarction in 1991. She was given anticoagulation treatment with warfarin (INR, 2.0 to 3.0) in 2012 due to an episode of deep vein thrombosis of the lower extremities and AF. In spite of this warfarin treatment, she developed a first episode of reversible ischemic stroke a year later.

After she had recovered, warfarin was replaced with Rivaroxaban 20 mg once a day in combination with 100 mg of Aspirin.

On clinical examination the patient had: a Glasgow coma score of 8 (E4, V2, M2);[5] blood pressure 160/90; heart rate 68 beats per minute; arrhythmia; pupillary anisocoria (left>right); motor aphasia; central 7th cranial nerve deficit; and hyposthenia of the right hemisoma (previously present only on the left). The CHA2DS2-VASC score was 9.

Blood tests revealed: leukocytosis (17.820X10.9/L); a normal platelet count; hyperglycemia (glucose 205 mg/dL); normal troponin I level; a reduced thromboplastin time (56%; normal range 75-112%); an international normalized ratio (INR) of 1.25 (normal 0.88-1.13); and normal values for partial thromboplastin time, renal function and lipid profile. Blood gas analysis revealed: compensated alkalosis.

The first emergency unenhanced brain CT scan showed a large, old ischemic area in the territory of middle right cerebral artery (Figure 1, white arrows). A second brain CT scan showed no clear signs of the new lesion, which only became apparent on the third brain CT scan. The third unenhanced brain CT scan, performed after 72 hours, showed a new ischemic lesion on the left, in the thalamus-capsular area (Figure 1, black arrow). An electrocardiogram confirmed AF. An echocardiogram showed right and left atrial dilation, and color-coded Doppler of the carotid artery revealed low-degree bulb plaque bilaterally. The patient was treated with Aspirin (250 mg i.v.) and a prophylactic dosage of enoxaparin (4000 U) sc. On the second day, the patient's condition became worse, with a Glasgow coma score of 3 (E1, V1, M1), and with clonias and morsus that were treated with levetiracetam 500 mg i.v. three times a day. The patient's neurological status was stable. She was comatose, breathing spontaneously and tetraplegic. On the 7th day her enoxaparin dosage was increased to 4000 U twice a day. The patient died on the 10th day.

Apart from the previous stroke and the atherosclerotic risk factors that made a new event likely,[6] we also investigated whether the patient had a hypercoagulable state. The results were negative, since the values measured for antithrombin III, proteins C and S, lupus anticoagulant, Leiden factor, antiphospholipid antibodies, and prothrombin mutation were all within normal limits. Abdominal ultrasound was also performed to rule out any presence of cancer, and the cancer markers tested (alpha-fetoprotein, CEA, CA 19-9, CA 125, occult blood test, and CYFRA) were all normal.

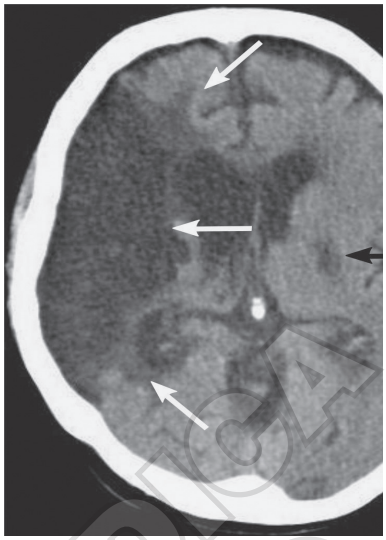

Figure 1.—Unenhanced brain CT scan showing a large old ischemic area in the territory of middle right cerebral artery (white arrows) and a recent left ischemic lesion in the thalamus-capsular area (black arrow).

Discussion

A combination of full-dose Rivaroxaban with 100 mg of Aspirin failed to prevent recurrent stroke in the case reported here. It should be noted that this patient was at particularly high risk of stroke (CHA2DS2-VASC=9), and had already suffered a less severe stroke episode two years earlier while on warfarin. Both episodes are very likely cases of cardioembolic stroke, given the absence of any alternative explanations, although occlusion of the collateral branches of the anterior cerebral artery might also be associated with the patient's hypertension. We were unable to measure the level of Rivaroxaban in the patient's plasma, but the prothrombin time and the anti-Xa assay were long enough to indirectly confirm that the drug had been used. The therapeutic value of associating Aspirin with Rivaroxaban has yet to be confirmed, but this was done because of the patient's previous myocardial infarction and because warfarin had failed to prevent her first episode of stroke.[7] We did not treat the patient with high doses of warfarin because higher INRs are associated with an increased risk of bleeding, as it is the combination of an oral anticoagulant and an antiplatelet agent.[8]

Moreover, a recent study evaluated the efficacy and safety of left atrial appendage occlusion (LAAO) in old subjects, concluding that LAAO was associated with similar procedural success in patients aged <75 and ≥ 75 years, although stratified analysis showed a higher incidence of cardiac tamponade in elderly patients (0.5% *vs*. 2.2%; P=0.04).[9] The patient nonetheless suffered a second irreversible episode of stroke that that led to permanent disability and resulted in death.

Conclusions

Our case report suggests that some individuals with AF are at a particularly high risk of cardio-embolic stroke, and alternative prevention strategies should be investigated for such patients.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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