

Ischemic stroke in an elderly patient on apixaban

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Abstract

Mr. LPH, an 86 year old patient taking warfarin for atrial fibrillation (AF) is admitted for a vertebral fracture. His calculated CHADS₂ score was of 6. A suboptimal control of diabetes was detected. Metformin and glyburide were increased. Four days after discharge, Mr. LPH was readmitted due to diarrhea and hyperglycemia. Metformin was discontinued. Glyburide dose was adjusted. INR dosage results fluctuated during hospital stay over and under therapeutic values. Warfarin was discontinued and apixaban 2.5 mg twice daily was started. Mr. LPH was later admitted for a pulmonary severe sepsis. His infection was complicated by two AF episodes. After the last episode, Mr. LPH presented dysarthria, facial asymmetry and left hemiparesis. On the cerebral scan, we observed a right Sylvian artery stroke.

Conclusion: In this case, the 2.5 mg apixaban dose was used and may explain the stroke. It occurred after two consecutive AF episodes making it the most likely cause. The choice of the low drug dosage may have been in response to caution and patient frailty. The patient was stable on warfarin for the past 14 years and the fluctuating INR episode can be explained by drug interaction. Glyburide may enhance the anticoagulation effect of warfarin.

Keywords

1. Empirical dose adjustments may sometimes be hazardous.
2. The direct oral anticoagulants dose should be that of clinical trials.
3. The balance between risks and benefits of anticoagulation in elderly patients remain a challenge.

Case Description

Mr. LPH, an 86 year old, 70.4 kg male patient was admitted to a geriatric care unit on January 17th, 2015 after he tripped on his kitchen carpet and fell to the floor. He was known for ischemic heart failure, non valvular atrial fibrillation (AF) and 2 myocardial infarctions. He also suffered a subdural hemorrhagic stroke in 2001, hypertension, type 2 diabetes and prostate cancer. His calculated CHADS₂ score was of 6. His creatinine blood level was 68 µmol per liter and stable throughout the hospital stay.

Acting physician diagnosed a C3 vertebral fracture. Three days later, a suboptimal control of diabetes was detected. Mr. LPH took metformin 850 mg twice daily and glyburide 2.5 mg daily. Glycated hemoglobin was 8.5%. Blood sugar level ranged from 7.8 to 20.5 mmol/L and 83% of results were over 11.1 mmol/L. Metformin was increased to 500 mg 3 times per day and glyburide was increased to 5 mg twice daily. Saxagliptin was added. The patient was discharged on February 2nd.

Four days later, Mr. LPH was readmitted due to diarrhea. Metformin was discontinued because it was thought responsible for diarrhea. The morning glyburide dose was increased to 10 mg on February 6th and supertime dose was reduced to 2.5mg on February 12th. After a hypoglycemia episode on February 17th, oral agents for diabetes were discontinued and replaced with insulin therapy. INR dosage results fluctuated during hospital stay over and under therapeutic values and warfarin doses was adjusted accordingly. Warfarin was discontinued and apixaban 2.5 mg twice daily was started.

On September 27th, 2015, Mr. LPH was admitted for a pulmonary severe sepsis. His infection was complicated by delirium and AF. Eight days later, He suffered a second AF episode. The next day, Mr. LPH presented dysarthria, facial asymmetry and left hemiparesis. On the cerebral scan, we observed a right Sylvian artery stroke.

Analysis and Discussion

Atrial fibrillation is the most commonly encountered arrhythmia in elderly patients. It affects 9% of adults aged 80 years or older [1]. Vitamin K antagonists have been the first line agent for stroke prevention in patients suffering from AF for many decades. In the past years, direct oral anticoagulants such as apixaban are now available [2]. In the ARISTOTLE study, apixaban was compared to warfarin showing a superior reduction of stroke or systemic embolism with a hazard ratio of 0.79(CI:0.66-0.95). Major bleeding was significantly lower in the apixaban group with a hazard ratio

of 0.69 (CI:0.60-0.80) [3]. While most patients were on the 5 mg dose, the half dose was used when two of the following criteria were present: age 80 years and older, weight of less than 60 kg or a serum creatinine level of 133 μmol per liter or more. Of note, this dose was only used in 4.6% of all study subjects.

In this case, the 2.5 mg apixaban dose was used despite the presence of only the age criteria. This subtherapeutic dose may explain the stroke. It occurred after two AF episodes making it the most likely cause. Mr. LPH didn't show any evidence of a thromboembolism or cardioembolic event prior to the stroke. Complete blood count and electrolytes were within normal values and he wasn't a stimulant drug user.

This case highlights the difficulty for physicians to ensure an effective and safe anticoagulation in elderly frail patients. In a recent report, an 86 year old woman with a creatinine clearance of 21 ml/min presented persistent epistaxis. The anti-factor Xa assay showed a supratherapeutic anticoagulation [4]. In this case, a lower dose was chosen resulting in an ischemic stroke event. The choice of the low drug dosage may have been in response to caution and patient frailty.

Vitamin K antagonists remain a valid choice in stroke prevention. In this case, Mr. LPH was on a stable dose of warfarin prior to the first admission and didn't suffer any thromboembolic episode in the 14 years it was used. Therefore a spontaneous fluctuating INR episode is surprising. In this case, the fluctuation can be explained by drug interaction. Glyburide may enhance the anticoagulation effect of warfarin [5]. Glyburide dosage change and consequent warfarin dosage adjustment led to supra and sub therapeutic INR level.

Conclusion

Empirical dose adjustments may sometimes be hazardous. The direct oral anticoagulants dose should be that of clinical trials. Warfarin remains a valid option especially in frail patients or in severe renal failure until further evidence is available. The balance between risks and benefits of anticoagulation in elderly patients remain a challenge.

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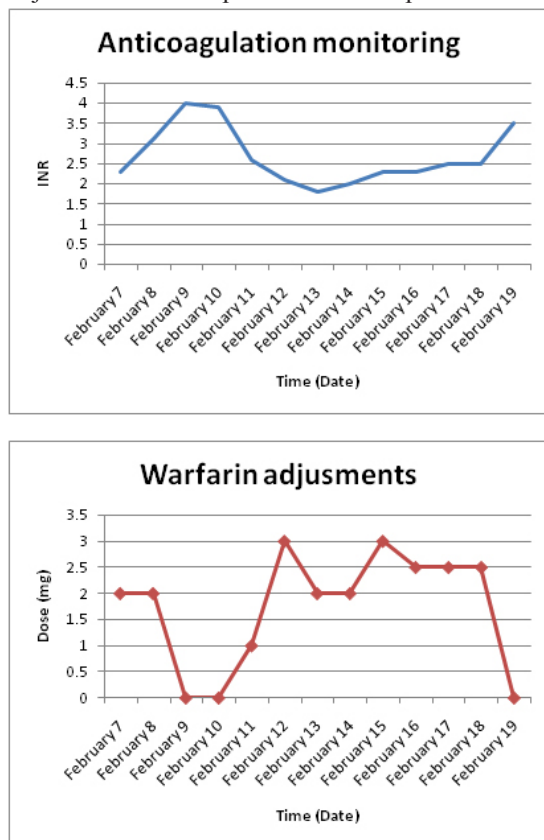


Figure 1: Patient anticoagulation monitoring and warfarin dose adjustments

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