

Increased bleeding risk in a patient with oral anticoagulant therapy and concomitant herbal intake – a case report

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Key words:

hemoptysis, ginger, rivaroxaban,
herbal intake

CASE REPORT

We report the case of a 36-year old male, under stable rivaroxaban therapy for 18 months, who was admitted to our emergency room with sudden onset of hemoptysis.

Anticoagulant therapy was given after recurrent spontaneous deep vein thrombosis (DVT) and a heterozygous Factor-V-Leiden mutation was present. There was no co-medication reported, however, the patient reported a constant intake of three liters of home-brewn ginger tea per day in the last month. The patient was hospitalized to further investigate the reason of hemoptysis.

INTRODUCTION

The use of Novel oral anticoagulants (NOACs) for the treatment of patients with venous thrombotic events (VTE) is now standard of care and demonstrated clinical efficacy and safety in numerous clinical studies (1,2).

Usually, these substances have a low risk for interaction with other medications compared to vitamin K antagonists (VKA), the standard medication given for the treatment of VTE events in the decades before. However, little is known concerning interaction of NOACs with herbal medicinal products (HMP).

The use of HMP is frequent among the population (3). Ginger (*Zingiber officinalis*) is a very common spice used worldwide because of its aromatic taste (4). Zingerone (ZGR), a phenolic alkanone found in *zingiber officinalis*, has been reported to have various pharmacological activities so that many people even use it as a medicine (4,5).

However, little is known about concomitant use regarding potential interactions associated with new oral anticoagulants like rivaroxaban or other factor Xa inhibitors (4,5,6). This may become relevant since the prescription of NOACs significantly increased in the last years (6,7,8).

We report a case of a 36-year old male under rivaroxaban therapy who developed hemoptysis after drinking about 2 to 3 liters of ginger tea per day over a period of one month.

CLINICAL - DIAGNOSTIC CASE

A 36-year old male under continuous rivaroxaban therapy for 18 months was admitted to our emergency room with a sudden onset of hemoptysis appearing for the first time. The patient reported that two hours before he produced about 20 mL of sputum containing significant blood spots. He was free from respiratory tract infections the last month and did not

report any personal or family history consistent with a bleeding diathesis. No other anticoagulant drugs, platelet aggregation inhibitors including NSAIDs, or any other pharmaceutical drugs were taken.

After reviewing a long and detailed medical history, it has been ascertained that the patient has been consuming about 2 to 3 liters of home-brewn ginger tea on a daily basis for over a period of one month.

Anticoagulant therapy was prescribed to prevent recurrence of a VTE event, after he had two spontaneous DVT events in the lower extremities, together with a heterozygous factor V Leiden mutation status. The patient has been under stable NOAC treatment for 18 months without signs of bleeding. The patient was hospitalized to further investigate a reason for hemoptysis.

Laboratory testing showed no abnormalities—renal function was within reference range. The HAS-BLED Score was 0 points, Chest - X-ray was normal, a CT scan of the thorax was also unsuspecting, and ECG was found normal. The Ear Nose Throat (ENT)-specialist excluded a possible bleeding source in the Naso-oro-pharyngeal region.

Since increased consumption of ginger may also affect platelet function, platelet function testing (PFT) was performed 3 days after hospitalization. A PFT is mainly used to detect hereditary platelet function disorders, also to test for efficacy of antiplatelet therapy such as acetylsalicylic acid (ASA) or clopidogrel.

For testing platelet function, the Multiple-Electrode-Analyzer (MEA) using a multiplate system was used. The reference ranges supporting a sufficient antiplatelet effect of ASA are defined between 10 - 50 units using the ASPI test, and 19 - 46 units for clopidogrel in the ADP test, respectively.

In our patient, values in the ASPI test were found to be 69 units and in the ADP test 47 units. The value for the ADP test can be interpreted as a relevant antiplatelet effect caused by ginger, which is almost comparable to the effect of clopidogrel on the platelet function.

Because of the 2-fold thrombotic event and the heterozygous Factor-V-Leiden mutation, the patient was advised to continue rivaroxaban therapy as a long term medication. However, due to the initial hemoptysis, the NOAC treatment of rivaroxaban 20 mg was paused for 48h.

Furthermore, the patient was advised to significantly reduce ginger consumption because of its obvious additional antiplatelet effect when used in such high concentrations. The patient was discharged after 4 days in a good general condition, rivaroxaban was re-started, however in a reduced maintenance dose.

DISCUSSION

The use of NOACs for several indications significantly increased in the last years. Compared to VKA, NOACs have some beneficial effects. In various clinical trials lower bleeding risk and less hospitalization were reported. Furthermore no routine laboratory monitoring is necessary (6). However, little is known about concomitant use of herbal medication and potential interactions with NOAC medication (4,5,6).

Our patient was admitted to our emergency room with hemoptysis appearing for the first time under stable rivaroxaban therapy. The patient has been on rivaroxaban treatment 20 mg for 18 months because of recurrent VTE events. Bleeding complications are possible side effects of anticoagulant treatment.

In the recent medical history no plausible causative reason for the hemoptysis was found. The patient had no personal or familial history consistent with a bleeding diathesis. Neither had

he exposure to anticoagulant drugs other than rivaroxaban, nor to platelet aggregation inhibitors including NSAIDs. The HAS-BLED score, reflecting the bleeding risk of the patient (9), was 0 points under stable anticoagulation therapy for 18 months - it seems unlikely that the anticoagulant treatment alone could have caused the hemoptysis.

After obtaining an extensive medical history, it has been ascertained that the patient increased his intake of homebrew ginger tea up to 2-3 liters daily in the last month.

There are various effects of ginger reported on the human organism, also affecting the coagulation system towards bleeding; an increased use of ginger in combination with the NOAC treatment could therefore have perpetuated hemoptysis in our patient (3,4,5,6). A platelet function testing was performed on the third day after cessation of ginger intake. The result of the PFT showed a markedly decreased platelet aggregation pattern after ADP stimulation, revealing a possible effect of ginger on platelet function which is almost comparable to the effect of treatment with clopidogrel.

Since recurrent spontaneous VTE events demonstrate an indication for long-term anticoagulation. Therefore, our patient received a subsequent dose reduction of Rivaroxaban. This was considered to avoid further bleeding events as it was recently reported to be meaningful in the so called EINSTEIN-CHOICE Study (10).

Furthermore, the patient was advised to lower his ginger consumption.

To summarize, despite the delayed testing of platelet function after three days of withdrawal of ginger intake, we conclude that extensive ginger intake together with rivaroxaban therapy enhanced bleeding risk in our patient, this should be considered in obtaining medical history in patients with unclear bleeding events under DAOK therapy.

TAKE HOME MESSAGES/ LEARNING POINTS

- The use of herbal medicinal products is common among the population. However, little is known about its concomitant use and the potential interactions associated with direct oral anticoagulants.
- Platelet function testing in such situation seems meaningful and may help to support the hypothesis drawn from medical history in patients with unclear bleeding events.

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