SPONTANEOUS INTRAMURAL HEMATOMA AND HEMOPERITONEUM AS SEVERE COMPLICATION OF VITAMIN K ANTAGONISTS THERAPY

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ABSTRACT

Warfarin has been shown to be efficacious in a wide variety of thrombotic disorders, but it has a narrow therapeutic window with respect to the international normalized ratio (INR), and inter-individual variations in response to warfarin doses, which may led to overanticoagulation associated with bleeding, sometimes severe bleeding. Management of this complication needs to be individualized to each patient. We discuss a patient with a recent valvular replacement and hemoperitoneum as adverse event of vitamin K antagonist's therapy.

KEY WORDS: Hemoperitoneum, drug toxicity, warfarin.

CASE REPORT

A patient with severe colicky abdominal pain and a one day history of melanotic emesis and stools is transferred to the emergency room. At admission, the body mass index was 22.9 kg/m2, the blood pressure 110/70, the pulse 90 beats per minute, the temperature 37.2 Cº, and the respiratory rate 20 respirations per minute. There was abdominal bloating, severe pain on palpation of hypogastrium with positive Blumberg sign and no other relevant findings. The complete blood count demonstrated 16.700 leukocytes/mm3, 80% neutrophils, 8.7 mg/dl of hemoglobin, 214.000 platelets/mm3. The partial thromboplastin time (PTT) was 78 seconds and the international normalized ratio (INR) was 6.29. The total abdominal ultrasound (TAU) showed intestinal loops distended with gas and free fluid in the right parietocolic gutter.

The patient had been diagnosed 5 years ago with coronary artery disease (CAD), hypertension, hypercholesterolemia, mild mitral valve insufficiency (MVI) and was treated with enalapryl, furosemide, spironolactone, lovastatin and carvedilol. His condition worsened, causing severe systolic heart failure (25% ejection fraction) requiring valve replacement and a coronary bypass that were performed 6 weeks prior to this event. Thereafter, he started anticoagulation with warfarin and was followed up with monthly INR controls after discharge. The patient had stopped his warfarin treatment when the pain begun three days before this admission.

He was taken to the operation room for an exploratory laparotomy. In surgery, a 50 ml hemoperitoneum, multiple hematomas in the mesocolon and the small intestine (one of them of a considerable size) were found and drained. A slightly cyanotic intestine segment was also found and left untouched. There was no active hemorrhage site or other relevant findings during this procedure.

During postoperative care, the patient developed ecchymosis around the surgical wound and intravenous puncture sites. In addition, he was pale, had diaphoresis and hyporexia. He was given a 10 mg single dose of vitamin K and was begun on enoxaparin 40 mg twice-a-day. His INR remained between 1 and 1.5 for the next 5 days. On the sixth postsurgical day, the patient started to complain from mild colic pain, abdominal bloating and diarrhea. An abdominal X-ray in standing position was taken demonstrating proximal fluid levels with distended loops and absence of distal gas (figure 1). Owing to these findings, the patient underwent a second exploratory laparotomy in which a 2000 ml hemoperitoneum and two small intestinal hematomas were drained and many lax adherences of the small intestine were released; again, no active hemorrhage site was found.

After the operation, the patient was transfused 2 units of globular concentrate and remained three more days hospitalized, during which he endured with a TPT between 30-33 s and an INR of 1.1 while being treated with the same enoxaparin regime. He didn't have any new symptoms after the intervention and was discharged with the same intra-hospital treatment.

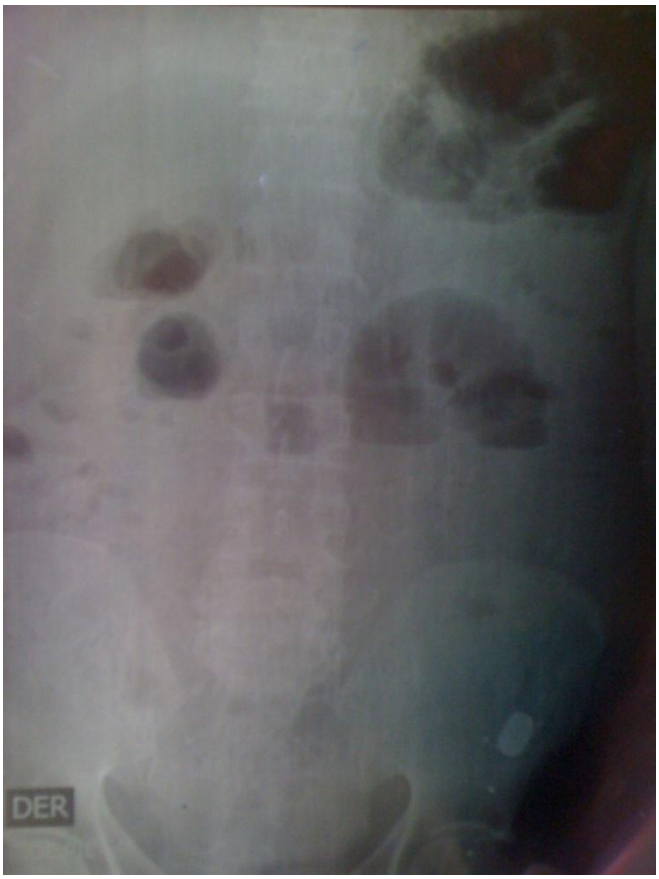

Figure 1. Standing abdominal radiography showing proximal fluid levels with distended loops and absence of distal gas.

DISCUSSION

Warfarin and other vitamin K antagonists (VKA) are extensively used for preventing thrombosis and thromboembolism and their efficacy has been demonstrated to outweigh risks for more than 50 years in a wide variety of clinical thrombotic disorders, including venous thromboembolism, stroke prevention in non-valvular atrial fibrillation, and prevention of systemic emboli in patients who have myocardial infarction or prosthetic heart valves (1) such as the one of this report. VKA are also commonly used in North America for prevention of venous thromboembolism following orthopedic surgery.

Patients with prosthetic valvular replacement are highly prone to forming thrombi on the surface of the implanted valves and develop embolism episodes. According to the American Heart Association guidelines in valvular disease management, patients with mitral replacement need to accomplish and maintain INR between 2.5 and 3.5, and every patient needs an individual titration of the anticoagulant dose (2).

VKA have a narrow therapeutic window, whereby thrombotic events and bleeding are associated with sub-optimal therapy and over anticoagulation, respectively. Haemorrhagic complications in patients taking VKA are the most common iatrogenic events (13% of hospital admissions for overall drug-related adverse events) (2). Warfarin circulates primarily bound to albumin, and only the non–protein-bound material is biologically active (3). Any substance that also bounds to albumin may displace warfarin from its protein binding sites and thereby increase the biologically active form (4). Warfarin metabolism occurs in liver by the P450 (CYP2C9) system, whose mutation or interference by various drugs can markedly impair the drug's metabolism (5). This explains why dose-response relationship to warfarin therapy varies widely between individuals and the wide range of drug interactions (Table 1) (6). Even, acetaminophen at usual doses for a week may result in excessive warfarin anticoagulation (7).

Additionally to chemical compound interactions or genetic factors, many other influence the treatment outcome in individual patients, such as inaccuracies in laboratory testing, noncompliance of patients and abnormal liver function. Because of this problematic use and in order to improve safety, patients need to have their INR frequently monitored in order to modify dosage assertively (3) this may be attained by either controls at health care centers or point-of-care testing (8), which is considered by many as a more desirable option in favor of the patient's comfort.

The patient in this case report didn't clearly know the precautions he needed to have, such as knowing his target INR value, minimizing wounds, consuming a uniform quantity of green vegetables daily, and to avoid taking over-the-counter medicines without a prescription. It is also worrying to know that he had INR controls scheduled once every two months considering that he had only been on treatment during six weeks.

DRUGS INTERACTING WITH WARFARIN	
Potentiate	Clotrimazole, erythromycin, fluconazole, isoniazid, metronidazole, miconazole, amiodarone, clofibrate, propafenone, propranolol, and sulfinpyrazone; phenylbutazone; piroxicam, alcohol (only with concomitant liver disease) cimetidine; and omeprazole.
Inhibit	Griseofulvin, rifampin, nafcillin, barbiturates, carbamazepine, chlordiazepoxide, cholestyramine, sucralfate, large amounts of avocado and foods with high vitamin k content such as green vegetables.

Table 1. Some drugs and foods that may interact with warfarin (3).

French clinical practice guidelines on the management of patients on VKA in at-risk situations, classify bleeding into severe or potentially severe if there is external bleeding that cannot be stopped or there is haemodynamic instability, life-threatening bleeding or bleeding that compromises function (intracranial, intraspinal, intraocular, retroorbital, haemothorax, haemoretroperitoneum, haemopericardium, deep muscle haematoma, neural compression syndrome, acute gastrointestinal bleeding and haemarthrosis). Bleeding that meets none of these criteria is defined as non-severe (2) and this kind accounts for the majority of cases. Approximately 1% of warfarin-treated patients develop serious complications out of which intra-cranial, intra-abdominal hemorrhages and hemorrhagic shock are the most common (5) (6) (7).

There are some risk factors identified for major bleeding, such as advanced age (65 or older), female gender, alcoholism, cancer, hypertension, cerebral vascular disease, history of gastrointestinal bleeding, serious heart disease, and renal insufficiency (9) (10) (11) (12) (13).

Besides, there are some factors identified by pharmacogenetics, which studies how genetic differences influence the variability in patients'responses to drugs (14). Most of genetic changes are common polymorphism and these influence drug metabolism by modifying the function of drug-metabolizing enzymes, or by affecting its binding capacity to target proteins as carriers or receptors, drug absorption, distribution, excretion or targeting to the site of action (15) (16) (17). Patients with the same CYP2C9 genotype have a great standard deviation to the mean maintenance dose and it is now well established that common polymorphism in regulatory regions of the vitamin K epoxide reductase (VKOR) gene correlate strongly with VKA response. However, it is still necessary to determine with high quality evidence whether pharmacogenetic testing is worthwhile or which patients would better benefit by this strategy (18) (18) (19).

But probably, the most decisive factors are the intensity of the anticoagulation therapy and how properly the lifestyle indications and coagulation controls are being performed, as shown by the fact that almost all major bleedings occur in patients with long coagulation times (20) (21) (22). Warfarin treated patients have a risk of bleeding that increases as the INR rises, particularly if the INR exceeds 4. Studies have also demonstrated that the rate of bleeding is highest during the first month of treatment and then fell to a stable rate over the next 2 months (11) (12) (13), like in this case where the patient had started the treatment just a month ago. The risk of a second adverse event is highest once an event has occurred (23).

Among major bleeds, spontaneous intra-parietal hematomas and hemoperitoneum are very unusual, with a study reporting an incidence of 1 case of intra-parietal hematoma in every 2500 anticoagulated patients (24). Apparently, all of these cases are warfarin related and the vast majority show very high coagulation times, with the INR ranging from 6 to 16 in some studies and reports (21) (22) which, as stated above, may result from inappropriate assessment or education. These patients may present with hemoperitoneum and intramural hematoma simultaneously, some also have intraluminal bleedings and in very rare cases, intestinal obstruction may appear due to any of these phenomena (25).

Most of these patients present mild to moderate abdominal pain, although some, such as the one presented in this report, may have severe pain with peritoneal irritation sings that mimic other more frequent acute abdomen causes, mainly appendicitis (21).

Patients with severe bleeding must be admitted to hospital, have their TP measured immediately, and begin treatment without delay so INR returns to a normal value (<1.5) as fast as possible. Bleeding surgical control is necessary in some severe cases and this must be decided on the basis of individual evaluation. In all cases, VKA is discontinued and prothrombin complex concentrate (PCC) containing blood clothing factors II, VII, IX and X, as well as protein C and S, may be administered plus 10 mg vitamin K supplement either orally or intravenously (2). PCC brings the INR between 1.2 and 2 within 10 min in 79% to 100% of cases, without a clear dose-effect relationship for doses from 25 to 50 U/kg (26). Fresh frozen plasma contains all of the vitamin K dependent coagulation factors and has been the mainstay for reversing the effect of VKA. Nowadays it is used when PCC is not available since the latter is more effective (27) and bears less adverse effects (2). Besides, red cell packs may be used to control hemorrhage when needed. INR is measured within 30 minutes of PCC administration and every 6 to 8 hours while the situation remains critical and then daily (2) (28).

It is also important to protect patient against thrombosis in most clinical situations, so if indication for a VKA still stands, therapeutic doses of unfractioned heparin or low molecular weight heparins should be given together with VKA resumption, which should take place in hospital under

clinical and biological monitoring. Patients with mechanical heart valve should have a bridging period from 1 to 2 weeks. Thrombotic risk with mitral valves is greater than aortic valves (2).

CONCLUSION

It is important that patients be warned against taking any new drugs without the knowledge of their attending physician, and it is prudent to monitor the INR more frequently when any drug (including natural compounds or food supplements) is added or withdrawn from their regimen. The first month of anticoagulant therapy is especially problematic because the therapeutic dose is empirically assessed, and further adjustment is made on the basis of a trial-and-error strategy. This adjustment leads to the risk of over-anticoagulation with potential bleeding complications or under-anticoagulation with potential thrombotic events. For warfarin-treated patients, the risk of bleeding increases as the INR rises, particularly if the INR exceeds 4. The dose-response relationship to warfarin therapy varies widely between individuals and, therefore, the dose must be carefully monitored to prevent overdosing or under-dosing.

This case highlights the need to strengthen measures directed at improving surveillance and prescription quality, and educating patients in safe drug use, focusing especially on older patients and narrow therapeutic index drugs.

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