

Successful control of massive coumarol-induced acute upper gastrointestinal bleeding and correction of prothrombin time by recombinant active factor VII (Eptacog-alpha, NovoSeven) in a patient with a prosthetic aortic valve and two malignancies (chronic lymphoid leukaemia and lung cancer)

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Severe, life-threatening acute upper gastrointestinal bleeding may occasionally occur in patients receiving coumarol prophylaxis for prosthetic heart valves. These patients are exposed to two potential, serious risks: bleeding due to the severe blood loss induced by excessive anticoagulant effect or as a consequence of the cessation of anticoagulation subsequent thrombotic occlusion of the valve and loss of patency. Herein a short case report is presented. The elderly male patient had a prosthetic valve in the aortic position and also suffered from two malignant diseases: chronic lymphocytic leukaemia and a more recently developed lung cancer with metastatic spread into both lungs. The patient had a major gastrointestinal bleed, leading to a sudden fall of haematocrit (0.09), and to a collapse of peripheral circulation due to too excessive a coumarol effect (International Normalized Ratio > 8). An acute left ventricular failure developed during the early period of the emergency blood transfusion, so the correction of prothrombin time by fresh-frozen plasma (due to the large volume requirement) was not feasible. The patient received 50 µg/kg intravenous bolus of NovoSeven (recombinant active factor VII) in an almost desperate

situation. The International Normalized Ratio changed to 2.1 in 30 min; bleeding had stopped immediately. There was neither evidence of disseminated intravascular coagulation (in spite of the age and underlying diseases) nor loss of valve patency or infective endocarditis during follow-up. This modest report may call attention to the potential use of recombinant active factor VII in the coumarol-induced severe bleeding episodes of prosthetic heart valve patients. *Blood Coagul Fibrinolysis* 15:265–267 © 2004 Lippincott Williams & Wilkins.

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Herein a short case report is given about recombinant active factor VII (rFVIIa) (NovoSeven) administration to a severely bleeding elderly patient with a prosthetic aortic valve. To the authors' best knowledge there is so far no written report on using rFVIIa in bleeding patients with prosthetic valves [1–3].

The patient was a 66-year-old male. He received his first aortic artificial valve in 1979, due to advanced valvular heart disease along with infective endocarditis. The prosthetic valve had to be replaced three times (due to thrombotic events and to severe mechanical haemolysis). A B-cell chronic lymphoid leukaemia (stage Rai-III) had been diagnosed in the same year (1966, B-chronic lymphocytic leukaemia, based on characteristic peripheral blood and bone marrow specimen morphology and CD5/CD19-20 coexpression, etc.). A second tumour, lung cancer, had been diagnosed in December 2001. The cancer, in spite of

carboplatine-etoposide chemotherapy, showed metastatic spread into both lungs.

The patient received standard coumarol prophylaxis throughout these years. However, he had been transferred to our Bleeding Unit in severe shock and a critically bad condition due to acute, profuse haematemesis (2 February 2002). The patient's haemoglobin was 30 g/l, the haematocrit was 0.09 (suggesting an acute blood loss exceeding 2000 ml) and the International Normalized Ratio (INR) was above 8.0. Intravenous fluids and packed red blood cell transfusion had been immediately implemented, but soon an acute left ventricular failure developed. The life-threatening emergency situation and limited heart functions did not allow giving the necessary amount of fresh-frozen plasma to the patient. Therefore the patient received 50 µg/kg rFVIIa (NovoSeven) in a bolus injection. There was a quick shortening of the prothrombin time,

and 30 min following rFVIIa injection the INR was 1.95, which can be regarded as a safe value either in respect of bleeding or not leaving the artificial valve without protection. The patient's condition improved quickly, endoscopy (2 h later) revealing diffuse gastric erosions (no bleeding at the time of endoscopy). There was no further bleeding and the patient received 2×50 U/kg low molecular weight heparin (nadroparine) on the consecutive day, followed by standard anticoagulant prophylaxis. There was no evidence of disseminated intravascular coagulation (normal prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, platelet counts), thrombotic occlusion or endocarditis on the prosthetic aortic valves (echocardiography). The patient died in April 2002 due to the progression and further spread of his lung cancer (there were no signs of infective endocarditis or prosthetic valve thrombi at autopsy).

The most common cause of acute gastrointestinal bleeding in patients with prosthetic heart valves is antithrombotic, anticoagulant drug side-effect complication (coumarol, especially if combined with aspirin). Special care and experience are needed to stop bleeding and to avoid thrombotic occlusion of the valves at the same time [1,2]. The most important issue is to correct the INR quickly into a safe range in each respect.

To achieve the reversal of excessive coumarol effect the administration of vitamin K, prothrombin complex concentrates (PCCs) [factor IX (FIX) concentrates] or fresh-frozen plasma is the standard tool. Vitamin K has a rather slow onset of action, and INR correction may require hours, which is too long a time for reversal in serious internal bleeding [1,2]. Fresh-frozen plasma is safe but the infusion time is rather long due to the large volume, which may also be troublesome for patients with heart failure (as in our case).

PCC possesses fairly quick action [4,5]. The first PCCs were purified FIX concentrates, containing other factors of the prothrombin complex copurified with FIX (factor II, factor X, and some factor VII). The vitamin K-dependent clotting factors, because of their similar structures, tend to co-purify by most of the methods used to isolate them from plasma. The presence of this complexity and some 'activated forms' (as a consequence of the purification procedure itself) seems to be the cause of the occasionally life-threatening thrombotic complications, including deep vein thrombosis, embolism, myocardial infarction and disseminated intravascular coagulation [4,5]. Special precaution is recommended in liver failure, cancer patients, or if the PCC was used in high or multiple doses, and probably in patients with prosthetic heart valves [4]. The latest, highly purified, recombinant or plasma-derived (FIX-

based) PCCs are much safer; their use in neurosurgical cases, cerebral bleedings, and reversal of other warfarin overdose-induced emergency bleeding situations was successful [4–7]. However, PCC administration still needs great caution in bleeding patients with malignant diseases or with prosthetic heart valves.

There is a growing body of evidence, that rFVIIa (NovoSeven) has some therapeutic potential in the so-called 'off-label' indication group [3]. Bleeding due to loss of prothrombin activity is one of these relatively new areas [8,9]. There were some efforts to correct the INR in cirrhotic as well as in coumarol-treated patients [9,10]. The applied dose range was 5–80 µg/ml, relatively small as opposed to the dose used in standard indications (inhibitory or acquired haemophilia, special von Willebrand cases, etc.).

rFVIIa is probably much less thrombogenic, as it contains only a single (activated) clotting factor [3], and it acts at the sites of tissue factor exposure (i.e. sites of vascular injury). In addition, rFVIIa is also capable of activating platelets (via increased thrombin generation) at the site of vascular injury. There is no tissue factor or phospholipid on artificial surfaces, therefore rFVIIa cannot activate FIX or factor X on these surfaces. Further advantages are the small volume, the bolus injection route and a virtually immediate action.

The dramatic clinical situation, severe bleeding and excessive INR prolongation required immediate, effective, safe INR correction, which was achieved by 50 µg/kg NovoSeven in our patient. There was no further bleeding, no disseminated coagulation, or loss of patency on the artificial valves due to thrombotic events. This case report may call attention to the possible use of rFVIIa in prosthetic heart valve patients with severe acute bleeding due to the prolonged INR. The major advantages are: small volume (bolus injection), quick action [4], and the relative safety from thrombotic events (see our elderly patient with proven chronic lymphoid leukaemia and lung cancer).

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