

Case report

Open Access

Emergency correction of coagulation before major surgery in two elderly patients on oral anticoagulation

Marzia Angelo¹, Bernhard Gutmann¹, Michele Adami¹, Bernd Zagler¹, Anton Zelger¹, Christoph Pechlaner² and Christian J Wiedermann *¹

Address: ¹2nd Division of Internal Medicine, Department of Internal Medicine, Central Hospital of Bolzano, Bolzano, Italy and ²Division of General Internal Medicine, Department of Internal Medicine, Medical University of Innsbruck, Innsbruck, Austria

Email: Marzia Angelo - marzia.angelo@asbz.it; Bernhard Gutmann - bernhard.gutmann@asbz.it; Michele Adami - michele.adami@asbz.it; Bernd Zagler - bernd.zagler@asbz.it; Anton Zelger - anton.zelger@asbz.it; Christoph Pechlaner - christoph.pechlaner@uibk.ac.at; Christian J Wiedermann* - christian.wiedermann@asbz.it

* Corresponding author

Published: 10 January 2007

Thrombosis Journal 2007, 5:1 doi:10.1186/1477-9560-5-1

This article is available from: <http://www.thrombosisjournal.com/content/5/1/1>

© 2007 Angelo et al; licensee BioMed Central Ltd.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Received: 14 November 2006

Accepted: 10 January 2007

Abstract

Recommendations for urgent reversal of oral anticoagulation with vitamin K₁ antagonists are largely derived from case series employing empirical dosing regimens with vitamin K₁ and prothrombin complex concentrates. Data on the use of prothrombin complex concentrates in this indication are scarce in the elderly who are at high risk of both hemorrhagic and thrombotic complications. The two cases presented here describe patients older than 75 years who underwent rapid International Normalized Ratio (INR) reversal with prothrombin complex concentrates for surgical treatment of a bleeding ruptured spleen and for emergency surgery of a dissecting aorta. Both patients had their INRs rapidly corrected to ≤ 1.6 and underwent operation without complications. Evidence on treatment of patients who present with elevated INR and who have major bleeding or need to undergo emergency surgery is based mainly on observational studies. The two elderly patients presented here underwent successful emergency surgery after their INRs had been corrected with the intravenous use of vitamin K₁ in combination with prothrombin complex concentrate that was administered according to current guideline recommendations.

Background

For "over-anticoagulation" associated with major bleeding or in the case of reversal for emergency surgery in patients orally anticoagulated with coumarin or related vitamin K₁ antagonists, administration of vitamin K₁ is inadequate, since its full effect occurs after 12 to 24 hours. The volume of plasma required for reversal is almost invariably too large to be infused safely, whereas prothrombin-complex concentrates (PCC) are effective and convenient [1,2]. These products are virally inactivated and therefore safer than plasma with respect to the trans-

mission of viral diseases, but a thrombogenic effect has occasionally been reported; as bleeding complications are more prevalent in orally anticoagulated elderly patients, a lack of published data on the clinical use of PCC in the elderly may even be more relevant regarding its safety [3-5]. Some randomised controlled studies on the safety of administering a PCC to urgently reverse the anticoagulant effects of vitamin K₁ antagonists to normalize INRs support the recommendations of consensus guidelines developed by various task forces and expert panels that PCCs

are the agents of choice for urgent vitamin K₁ antagonist reversal [3].

We describe our experience with two patients older than 75 years of age in whom PCC was used for immediate correction of their INRs before undergoing major cardiothoracic and abdominal emergency surgery.

Cases

Patient 1

A 80 year-old patient receiving coumarin for atrial fibrillation, arterial hypertension and diabetes mellitus was admitted to our hospital because of left-sided thoraco-abdominal pain. Initial evaluation ruled out coronary artery disease. An electrocardiogram on admission demonstrated atrial fibrillation at a rate of 145 beats per minute. There was no hematemesis or melena. Presence of low-grade fever and non-productive cough, and the physical examination suggested lower airway infection which was confirmed by chest radiography. Blood tests revealed anemia with hemoglobin 10.4 g/dL and hematokrit 31.4%, leukocytosis of 10,600 G/L and an elevated C-reactive protein of 14.9 mg/dL. Under long-term oral anticoagulation with coumarin an actual INR of 2.96 was determined. His pain presented with slow onset and was aggravated by respiration suggesting its pleural origin due to lower respiratory tract infection. As after 48 hours pain was continuously present and now independent of respiration, additional imaging studies were performed. Abdominal ultrasonography and computerized tomography identified splenomegaly with inhomogenous parenchymal structure compatible with splenic hemorrhage. Hemodynamically stable his hemoglobin had dropped to 8.3 g/dL. Therefore PCC ("Uman Complex®"; Kedron Spa., Castelvecchio Pascoli, Italy) at a dose of 50 IU per kg body weight were administered i.v. in combination with 10 mg of vitamin K₁. At three and a half hours after PCC infusion, the INR was 1.5 and emergency splenectomy was performed. Surgical intervention and postoperative course were uncomplicated with no signs and symptoms of venous or arterial thromboembolism. The patient was discharged after oral anticoagulation had been reinstated.

Patient 2

A 77-year-old man without a particular family history but with a past medical history of peripheral arterial occlusive disease that was surgically treated including long-term oral anticoagulation with coumarin presented with sudden onset chest discomfort at rest. He was admitted to our hospital. Hemodynamics were stable. There were no rales or heart murmurs, except S4 of the heart sound. Electrocardiography showed sinus rhythm with non-specific ST-segment changes in leads I, II, aVL, aVF and V3–6. Arterial blood pressure was 130/100 mmHg on the right arm and

110/60 mmHg on the left. The chest pain initiated with a blow and then migrated toward the lumbar area over time. Chest X-ray was unremarkable but contrast computed tomography confirmed aortic dissection from the ascending aorta to the abdominal aorta. Stanford type A aortic dissection with a possible tear entry near the aortic arch was diagnosed. The patient was oliguric 8 hours after admission. No other symptoms suggesting cerebral, spinal or peripheral perfusion deficits or hematoma formation were present. Laboratory examination identified elevated D-dimer levels and an INR of 3.44; other blood tests including cardiac markers and renal function tests were normal. PCC at a dose of 45 IU per kg body weight were administered i.v. in combination with 10 mg of vitamin K₁. He was then transferred to Verona University Hospital approximately 10 h after the onset. Two and a half hours after intravenous administration of PCC the INR was 1.6. Emergency graft replacement of the ascending aorta was performed. Surgical therapy was performed without complication and the postoperative clinical course was uneventful. Renal other organ functions remained normal and unaffected, respectively. The patient was transferred to his home hospital in Germany on the 6th postoperative day in stable condition after oral anticoagulation with coumarin was again begun.

Discussion

The two cases presented here describe orally anticoagulated patients over 75 years of age whose prolonged INRs were corrected with PCCs for surgical treatment of a bleeding ruptured spleen and for emergency surgery of a dissecting aorta. Both patients had their INRs corrected to below 1.5 and underwent operation without excessive bleeding or thromboembolic events.

Limitations in the use of PCC for anticoagulant reversal include the elderly because many studies reported orally anticoagulated patients mainly <75 years of age who are at lower risk of both, bleeding as well as atherothrombotic complications [5]. Current recommendations for emergency anticoagulant reversal apply to adult patients independent of age [1–4]. In the two presented cases with patients of > 75 years of age, PCC was effective and safe in reversing oral anticoagulation.

As the INR increases with oral anticoagulation, it has been assumed that any approach to the normalization of increased INRs is equivalent to reversal of the anticoagulant effect and the re-establishment of normal hemostasis. Even though the various strategies and therapeutic agents available to achieve this goal have rarely been compared in head-to-head randomized controlled clinical trials, case series including reports like this one are in support of using INR as a valid surrogate marker for corrected hemostasis.

Table I: Management of elevated INR or bleeding in patients treated with vitamin K antagonists targeted at an INR range of 2.0 – 3.0*

| | |
|--|--|
| 3.0 < INR ≤ 3.5 (no bleeding) | No dose reduction may be required Monitor INR again before lowering the dose |
| 3.5 < INR ≤ 5.0 (no bleeding) | Omit dose Monitor daily and resume at lower dose when INR in therapeutic range |
| 5.0 < INR < 9.0 (no bleeding) | Omit dose Give oral vitamin K ₁ (phytomenadione) 1 – 2.5 mg. Monitor daily and resume at lower dose when INR in therapeutic range |
| INR ≥ 9.0 (no bleeding) | Hold vitamin K antagonist therapy Give oral vitamin K ₁ at higher dose (5 – 10 mg) with the expectation that the INR will be reduced substantially in 24 to 48 hours Monitor daily and give additional vitamin K ₁ if necessary Resume at lower dose when INR in therapeutic range Hospitalization may be considered if patient at higher risk of bleeding |
| Major bleeding at any elevation of INR | Hospitalization Hold vitamin K antagonist therapy and give prothrombin concentrate complex supplemented with vitamin K ₁ (10 mg by slow intravenous infusion) Monitor from the fourth hour after prothrombin complex concentrate |

* Modified after Ref. [2, 14]

Thrombotic episodes have been reported with PCC when they have been used to cover surgery in patients with haemophilia B and in patients with liver disease [6]. Evans et al., however, reported zero thrombotic events in 59 patients from three studies where PCCs were used to reverse warfarin and estimated the upper 95% confidence interval for thrombosis post-PCC treatment to be 6% or 1 in 16 [7]. As always, a risk benefit decision has to be made for each patient, but, in the presence of major bleeding or emergency surgery, the benefits are likely to always exceed the small risk of thrombosis. No evidence of thromboembolic complications were seen in the two patients reported with multiple risk factors for developing such adverse events.

The optimal method for returning the INR to the desired range depends upon its degree of initial elevation and whether or not clinically significant bleeding is present. Recommendations have been elaborated by the American College of Chest Physician Consensus Conference and others [1,2] which are based on studies that use the elevated INR as a surrogate marker for the risk of bleeding. Most of the evidence has been obtained for anticoagulation with warfarin with evidence for phenprocoumon being less well established [2]. Evidence on treatment of patients who present with elevated INR and who have major bleeding are based mainly on observational studies. Treatment includes withholding oral anticoagulants, administering intravenous vitamin K, and transfusion of coagulation factor concentrates (Table 1). Coagulation factor replacement in combination with vitamin K therapy is currently recommended in patients with coumarin-associated major bleeding or with indication for immediate correction of their INR [2,5]. PCCs contain coagulant factors II, VII, IX, and X and can reverse the effect of coumarin more rapidly than fresh-frozen plasma in coumarin-related coagulopathy [10-14]. The PCC used in our patients (Uman Complex; Kedron Spa., Castelvecchio Pascoli, Italy) contains factors II, IX and X, and reversed the INR to levels allowing emergency surgery at about 1.5.

Other PCCs contain also factor VII (e.g. Beriplex P/N; ZLB Behring, Marburg) and may offer faster achievement of full anticoagulant reversal in even a smaller period of time.

In conclusion, vitamin K₁ antagonist-associated coagulopathy is commonly encountered and is particularly associated with bleeding in the elderly [4]. Avoiding over-anticoagulation and reducing periods of overdosing in the course of oral anticoagulant treatment may help to minimise the risk of bleeding. Evidence on treatment of patients who present with elevated INR and who have major bleeding are based mainly on observational studies. Randomized clinical trials that measure the usefulness of interventions by clinical mortality and morbidity (bleeding and thrombosis) endpoints are required and under way. Optimal treatment, including the use of oral vitamin K₁ in the asymptomatic patient, and intravenous vitamin K₁ in concert with coagulation factors in the bleeding patient, should reduce the mortality associated with this condition.

References

- Schulman S: **Clinical practice. Care of patients receiving long-term anticoagulant therapy.** *N Engl J Med* 2003, **349**:675-83.
- Dentali F, Ageno W, Crowther M: **Treatment of coumarin-associated coagulopathy: a systematic review and proposed treatment algorithms.** *J Thromb Haemost* 2006, **4**:1853-63.
- Kessler CM: **Urgent reversal of warfarin with prothrombin complex concentrate: where are the evidence-based data?** *J Thromb Haemost* 2006, **4**:963-6.
- Wilkerson VR, Sane DC: **Aging and thrombosis.** *Semin Thromb Hemost* 2002, **28**:555-68.
- Pautas E, Gouin-Thibault I, Debray M, Gaussem P, Siguret V: **Haemorrhagic complications of vitamin K antagonists in the elderly. Risk factors and management.** *Drugs Aging* 2006, **23**:13-25.
- Kohler M: **Thrombogenicity of prothrombin complex concentrates.** *Thromb Res* 1999, **95**:S13-7.
- Evans G, Luddington R, Baglin T: **Beriplex P/N reverses severe warfarin induced overanticoagulation immediately and completely in patients presenting with major bleeding.** *Br J Haematol* 2001, **115**:998-1001.
- Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E: **The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy.** *Chest* 2004, **126**(3 Suppl):204S-233S.

9. Lavenne-Pardonge E, Itegwa MA, Kalaai M, Klinkenberg G, Loncke JL, Pelgrims K, Strengers PF: **Emergency reversal of oral anticoagulation through PPSB-SD: the fastest procedure in Belgium.** *Acta Anaesthesiol Belg* 2006, **57**:121-5.
10. Bouliis NM, Bobek MP, Schmaier A, Hoff JT: **Use of factor IX complex in warfarin-related intracranial hemorrhage.** *Neurosurgery* 1999, **45**:1113-9.
11. Cartmill M, Dolan G, Byrne JL, Byrne PO: **Prothrombin complex concentrate for oral anticoagulant reversal in neurosurgical emergency.** *Br J Neurosurg* 2000, **14**:458-61.
12. Fredriksson K, Norrving B, Stromblad LG: **Emergency reversal of anticoagulation after intracerebral hemorrhage.** *Stroke* 1992, **23**:972-7.
13. Makris M, Graves M, Phillips WS, Kitchen S, Rosendaal FR, Preston EF: **Emergency oral anticoagulant reversal: The relative efficacy of infusions of fresh frozen plasma and clotting factor concentrate on correction of the coagulopathy.** *Thromb Haemost* 1997, **77**:477-80.
14. Yasaka M, Sakata T, Minematsu K, Naritomi H: **Correction of INR by prothrombin complex concentrate and vitamin K in patients with warfarin related hemorrhagic complication.** *Thromb Res* 2003, **108**:25-30.

Publish with **BioMed Central** and every scientist can read your work free of charge

"BioMed Central will be the most significant development for disseminating the results of biomedical research in our lifetime."

Sir Paul Nurse, Cancer Research UK

Your research papers will be:

- available free of charge to the entire biomedical community
- peer reviewed and published immediately upon acceptance
- cited in PubMed and archived on PubMed Central
- yours — you keep the copyright

Submit your manuscript here:
http://www.biomedcentral.com/info/publishing_adv.asp

