CASE REPORT

Use of prothrombin complex in patients with an intracerebral hemorrhage who are on oral anticoagulants

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The use of oral anticoagulants is increasing, leading to a rise in the number of complications emergency health services must cope with. A review of the literature showed that prothrombin complex is an important therapeutic option when emergency reversion of anticoagulation is required, as it acts more quickly and completely than fresh frozen plasma. In this case report we review the use and indications of prothrombin complex in patients on oral anticoagulants, noting that rapid onset of effect is particularly important in cases of intracerebral hemorrhage. [Emergencias 2012;24:130-133]

Key words: Oral anticoagulation. Vitamin K antagonists. Intracerebral hemorrhage. Prothrombin complex.

Introduction

Oral anticoagulants are indicated in the prevention of thromboembolic disease. Anti-vitamin K agents (AVK) (anticoagulants derived from coumarin) act as antagonists of vitamin K, necessary for the carboxylation of factors II, VII, IX and X and proteins C and S. Acenocoumarol, used most in our country, and warfarin, used in Anglo-Saxon countries, are the AVK drugs most widely used. The main differences between them are pharmacokinetic; the half-life of acenocoumarol is 2-3 days. Other anticoagulants (dabigatran, a direct thrombin inhibitor, and rivaroxaban and apixaban, inhibitors of factor Xa) can be used as alternatives to AVK.

The most serious complication in patients on AVK is intracranial hemorrhage (ICH) with a mortality rate of at least 50%. To reverse its effect, there are several treatment options: vitamin K, fresh frozen plasma (FFP), recombinant factor VII (rFVIIa) and prothrombin complex concentrate (PCC). Traditional methods (vitamin K or FFP) have been slow or ineffective so alternative treatments have been developed. The use of rFVIIa reverses the international normalized ratio (INR), but its clinical impact on decreasing bleeding is unclear. PCC is considered the most effective treatment for the urgent reversal of anticoagulation induced by AVK. We present the case of a patient treated with AVK in whom PCC was used as haemostatic treatment.

Case report

A 60 year-old man with a history of atrial fibrillation (AF) anticoagulated with acenocoumarol consulted for an episode of dizziness. He had vision loss and behavioral alterations. Physical examination showed blood pressure (BP) 190/117 mmHg, oxygen saturation 95%, antiarrhythmic heart rate 70 bpm and no murmurs. Neurologically he had a Glasgow coma score (GCS) of 15/15, was disoriented but the rest of the examination was normal. Additional tests showed an INR of 2.01, BP 29, and other parameters within the range of normality. The ECG showed atrial fibrillation (AF) at 74 bpm. Cranial CT showed a hyperdense lesion in the right posterior temporoparietal region corresponding to a hematoma 3.8 cm in diameter with minimal perilesional edema (Figure 1). After 45 minutes in the emergency department (ED), the patient developed generalized tonic-clonic seizure of approximately 2 minutes duration, and then his level of consciousness de-

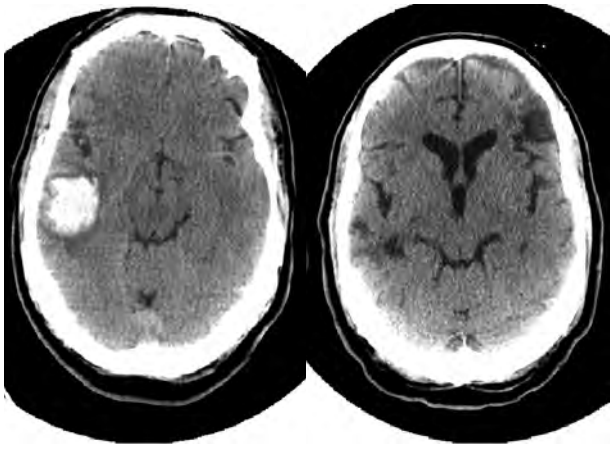

Figure 1. Left: Cranial CT scan showing hyperdense lesion (hematoma). Right: Cranial CT scan showing re-absorption of the hematoma.

clined with a GCS of 8 points and a heart rate of 160 bpm. Despite INR values within therapeutic range, we suspected re-bleeding and proceeded to isolate the airway and administer vitamin K iv (10 mg) and PCC (dose 30 IU / kg). At 6 hours he was extubated. At 48 hours CT angiography was performed and compared with the previous image: we observed evolving right temporoparietal hematoma with no evidence of vascular malformations or aneurysms. The patient was admitted to the department of neurology and evolved well. At discharge he was asymptomatic without neurological sequelae and prescribed antiplatelet therapy pending the reintroduction of oral anticoagulation (Figure 2).

Discussion

The risk of bleeding in anticoagulated patients increases with surgery and trauma, and over-anticoagulation (INR $\geq$ 4.5), although complications can occur when INR is within the therapeutic range[4,5], as in our case. FFP is a method used for reversal of the anticoagulant effect. Is obtained from donors or human plasma and must be frozen rapidly within a few hours. It is available in several forms: inactivated FFP and quarantined or secured FFP. The main adverse effects after administration are: allergic reactions, infectious complications, hemolysis, fluid overload, acute lung injury and immunosuppression[6]. The usual dose of plasma is 15 ml / kg, but the optimal dose has not been established. FFP must be thawed before use, which can delay treatment[7].

The use of rFVIIa has not yielded the results expected. In placebo-controlled trials, high-dose rFVIIa significantly increased the risk of arterial thromboembolic events, especially in the elderly[8], but it may be effective in patients under 70 with intra-cerebral bleeding less than 60 ml when administered in the first 2.30 hours of onset of symptoms[9].

PCCs are plasma concentrates of vitamin K-dependent coagulation factors (II, VII, IX and X), although in some formulations the content of factor VII is zero or very low. The indication in the treatment and prevention of bleeding due to over-anticoagulation is well defined in different clinical practice guidelines10. The optimal dose is established, typically 15 to 50 IU / kg[3]. Some authors suggest a particular dose while others suggest the dose should depend on the INR[11]. Compared with alternative treatments, PCC achieves faster INR reversal, but the response is less sustained over time. The half-life of each factor is different, hence, to avoid the "rebound effect", vitamin K should be given. PCC are currently indicated for various patient groups[12,13]: 1) patients with acquired or congenital deficiency of vitamin K-dependent factors, 2) anticoagulated patients requiring urgent AVK reversal, and 3) control and prevention of acute bleeding episodes in critical patients or those with severe liver disease. Its main adverse effect is venous or arterial thrombosis, especially in patients with liver disease, neonates or those requiring high or repeated doses[11,12]. Some measures to reduce its thrombogenicity include the addition of heparin and antithrombin and/or protein C7. It is contraindicated in patients with disseminated intravascular coagulation (DIC)[11]. The advantages of PCC versus FFP are shown in Table 1.

For years there has been general enthusiasm about the use of FFP. In fact, its use has been accepted without being subjected to critical clinical research normally required to demonstrate effecti-

Table 1. Advantages of using prothrombin complex concentrate (PCC) versus fresh frozen plasma (FFP)

1. PCC has shown greater efficacy than PFC to correct INR.
2. PCC is associated with a reduction in the incidence and degree of hematoma development compared to PFC.
3. PCC has a lower risk of viral disease transmission (eg. hepatitis and HIV).
4. PCC has been shown to provide faster and more complete correction of vitamin K dependent coagulation factors.
5. PFC needs more time to prepare (30 minutes thaw time), and may even require cross-matching.
6. PCC requires lower infusion volumes: PFC volumes of 15 ml / kg are needed versus about 1-2 ml / kg of PCC, thus minimizing hemodynamic problems.
7. PFC is associated with increased risk of acute lung injury associated with transfusion, a major cause of death after transfusion.

INR: international normalized ratio.

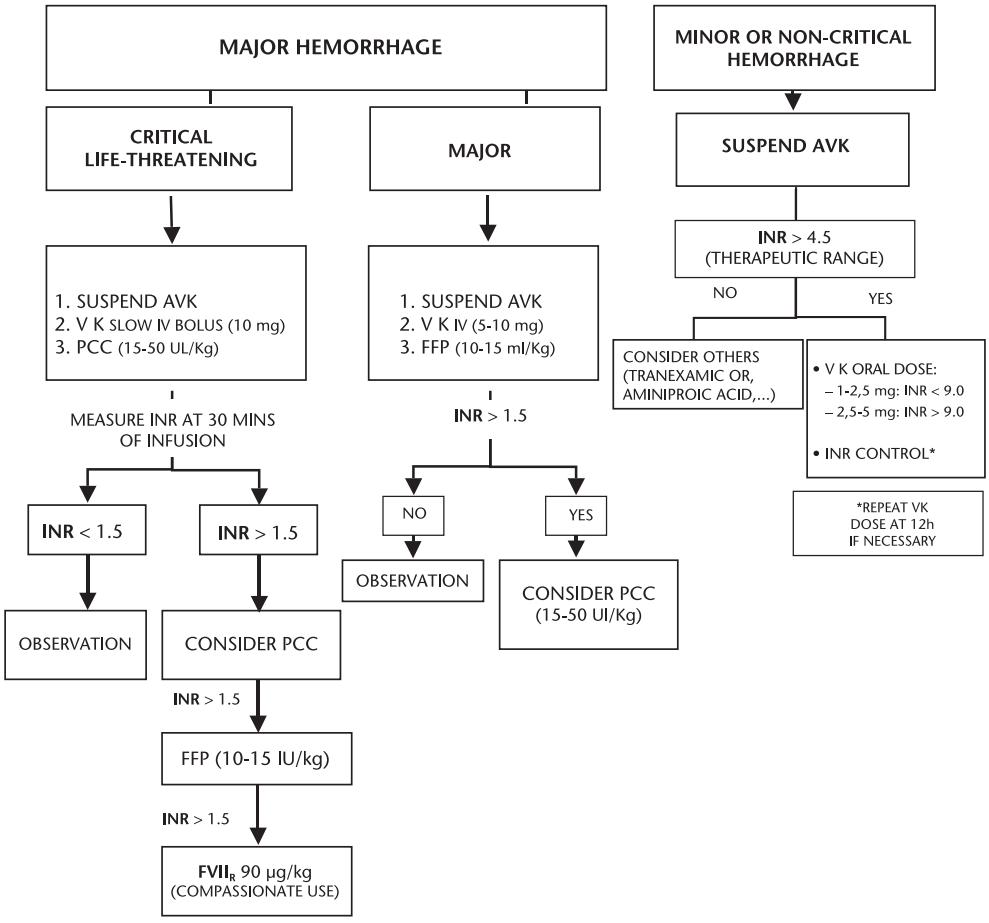

Figure 2. Algorithm for managing anticoagulated patients with critical hemorrhage affecting the central nervous system (CNS) or requiring urgent surgery or angiography. Major hemorrhage: potentially fatal, usually requiring hospitalization and transfusion (gastrointestinal, retroperitoneal, etc.). Minor hemorrhage: no need for further studies (gingival bleeding, epistaxis, hematomas, hematuria, hypermenorrhea and chemosis). PCC: prothrombin complex concentrate; AVK: anti-vitamin K, FFP: fresh frozen plasma; rFVII: recombinant factor VII, IV: intravenous, INR: international normalized ratio.

veness[14]. When reversal of anticoagulation is urgently required, the generally accepted approach remains administering FFP and vitamin K1. However, the delay due to thawing time and the adverse effects reported have led to the search for alternative approaches[7]. More recent studies have shown that PCC achieves anticoagulation reversal faster, safer and more completely than FFP, making it the treatment of choice in these cases[7,15]. Figure 3 shows an algorithm that may be useful in managing anticoagulated patients with hemorrhage.

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Uso del complejo protrombínico en pacientes anticoagulados que desarrollan hemorragia intracraneal

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El uso cada día más extendido de los anticoagulantes orales ha llevado al aumento del número de complicaciones con las que diariamente se enfrentan los servicios de urgencias (SU). El concentrado de complejo protrombínico (CCP) constituye una importante opción terapéutica cuando es urgente la reversión de la anticoagulación, ya que actúa de forma más rápida y completa que el plasma fresco congelado (PFC). A través del siguiente caso clínico, se revisa el uso e indicaciones del CCP en pacientes anticoagulados, y su utilización en procesos hemorrágicos intracraneales donde la rapidez de instauración del tratamiento es fundamental. [Emergencias 2012;24:130-133]

Palabras clave: Anticoagulación oral. Fármacos antivitamina K. Hemorragia intracraneal. Complejo protrombínico.

BIBLIOGRAPHIC NEWS

Title: Emergency Medicine Diagnosis and Management (6th Edition)
Authors: Anthony FT Brown, Michael D Cadogan
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The sixth edition of "Emergency Medicine: Diagnosis and Management" by Anthony FT Brown and Michael D Cadogan has just been published. It is a pocket handbook cited by some of the most prestigious journals in the field of accident and emergency medicine such as the Medical Journal of Australia or Emergency Medicine Australia, and aimed at students and physicians training in accident and emergency medicine. It is written and structured in a way that allows rapid consultation at the patient's bedside as well as the study of the essential features of any disease in the field of emergency medicine.

This new edition is an updated revised version of the handbook with numerous modifications. It includes some new sections, such as critical care, practical procedures, infectious disease and the traveler, tropical diseases, disaster medicine and multicasualty situations and starting out in the emergency department, while others have been expanded to include the latest evidence-based guidelines. The manual also includes an appendix detailing normal laboratory test values and doses of the drugs most commonly used in emergency medicine.

The whole work has been redesigned, revised and updated according to the latest evidence-based clinical guidelines and it includes a list of recommended reading material. Lastly, the manual offers electronic resources for in-depth information, clinical images and questions as well as free further reading material and additional resources.

The sixth edition of the manual is for everyday consultation and should be available to any physician working in the field of accident and emergency medicine, in order to help improve knowledge and provide the best possible attention for emergency patients.

Francisco Javier Martín Sánchez