ORIGINAL ARTICLE

Cost-effectiveness of using prothrombin complex concentrate to prevent complications related to overdoses of anticoagulants in the emergency department

Manuel QUINTANA DÍAZ[1], Alberto M. BOROBIA[1], Santiago PÉREZ CACHAFEIRO[2], Cilia RODRÍGUEZ[3], José Antonio GARCÍA ERCE[4]

[1]Servicio de Urgencias, Hospital Universitario La Paz de Madrid, Spain. [2]I+D+i, Complejo Hospitalario de Pontevedra, Spain. [3]Grupo de Investigación USEES-URG, Spain. [4]Servicio de Hematología, Hospital San Jorge de Huesca, Spain.

Correspondence:
Manuel Quintana Díaz
Servicio de Urgencias
Hospital Universitario La Paz
Paseo de la Castellana, 261
28046 Madrid, Spain
E-mail: mquintana@gmail.com

Received:
20-9-2011

Accepted:
5-12-2011

Conflict of interest:
None

Background and objective: Prothrombin complex concentrates (PCCs) are currently used principally for rapid reduction of the anticoagulant effects of administering vitamin K in cases where acute bleeding develops or during emergency surgery. PCCs are a better choice than fresh frozen plasma in these situations. These drugs have become essential for reducing the risk of hemorrhage thanks to their composition, safety, and rapid restoration of hemostasis, specifically of the international normalized ratio (INR). This study aimed to assess the efficacy, in terms of incremental cost-effectiveness, of PCC use in restoring the INR in routine emergency department practice.
Study design: For the cost-effectiveness analysis we constructed a year-by-year decision-tree (Markov model) using spreadsheet software (Excel). The probabilistic simulation sampled 5% of all emergency department patients on oral anticoagulant therapy with antivitamin K and an elevated INR in each year for 10 years. Octaplex® was the PCC used in the model.
Results: Sensitivity analysis showed that PCC use had a more favorable incremental cost-effectiveness ratio than did other strategies for correcting the INR.
Conclusions: Use of PCCs in the emergency department would be cost-effective. [Emergencias 2012;24:113-120]

Key words: Prothrombin complex. Anticoagulants. Overdose.

Introduction

Rapid reduction of the anticoagulant effect produced by vitamin K antagonists (VKA) is essential in cases of acute hemorrhage or emergency surgery[1]. In addition, the reversal of anticoagulant therapy is indicated in patients with an international normalized ratio (INR) outside the therapeutic range without major bleeding (Table 1), which is a common clinical condition in the emergency department (ED).

To reverse the anticoagulant effects of VKA in cases of minor bleeding, the dose may be suspended or decreased, and vitamin K administered, but if rapid reversal is required, then fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) should be administered. PCC is currently a combination of high-purity derivatives of factor IX and recombinant factor IX, and active FFP-derived agents or recombinant factor VII[2,3]. Its rapid action and the absence of the volume overload effect produced by FFP make it the treatment of choice for the urgent reversal of the effects of VKA (Table 1) and for bleeding associated with trauma surgery[4-8].

At present, most formulations of PCC contain four vitamin K-dependent coagulation factors (II, VII, IX and X)[9]. Pathogen protection is provided by viral load inactivation and since PCC is nanofiltered and free of leukocytes, they are unlikely to

Table 1. Summary of recommendations on reversal of anticoagulation with vitamin K antagonists (VKA)[1]

1. For patients with an INR outside the therapeutic range but less than 5 and no significant bleeding:
   – Lower the dose or omit a dose, monitor INR more frequently and restart at a lower dose when the INR is at therapeutic levels (Grade 2C).
2. For patients with INR ≥ 5 but less than 9 and no significant bleeding:
   – Omit one or two doses, monitor INR frequently and restart treatment at a lower dose when INR is at therapeutic levels.
   – Another alternative is to omit a dose and administer vitamin K1 (1-2.5 mg) orally, particularly if the patient is at high risk of bleeding.
   – If necessary reverse quickly because the patient requires emergency surgery: vitamin K1 (≤ 5 mg) orally with the possibility of reducing the INR in 24 hours.
   – If the INR is still high, 2 mg of oral vitamin K1 must be added (Grade 2C).
3. For patients with INR ≥ 9 and no significant bleeding:
   – Suspend VKA and administer a high dose of oral vitamin K1 (5-10 mg), with the possibility of reducing the INR in 24-48 hours.
   – If necessary, monitor INR frequently and use additional vitamin K1. Treatment should be restarted at a lower dose when the INR is at therapeutic levels (Grade 2C).
4. In patients with major bleeding and elevated INR:
   – Discontinue VKA and administer vitamin K1 (10 mg) slow infusion with intravenous fresh plasma. PCCs or recombinant activated factor VII are useful according to the urgency of the situation. Vitamin K1 can be repeated every 12 hours (Grade1C).
5. In patients with life-threatening bleeding and elevated INR:
   – Discontinue VKA and administer PCC or recombinant activated factor VII or fresh plasma, supplemented with 10 mg of vitamin K1 in slow intravenous infusion.
   – Repeat the dose if necessary depending on INR (Grade 1C).
6. In patients with slightly or moderately elevated INR without major bleeding:
   – It is suggested that when needed, vitamin K should be given orally rather than subcutaneously (Grade 1A).
   – It should be remembered that in cases of excessive anticoagulation and major bleeding, the administration of vitamin K1 should not be the first or the only measure, since its maximum effect is only achieved at 12-24 hours.
   – In this situation, use of plasma or PCC is recommended.

INR: international normalized ratio, PCC: prothrombin complex concentrates.

cause pulmonary damage such as that associated with transfusion[1,9]. Within this group of drugs, three different compounds are marketed in Spain. Table 2 shows the characteristics and composition of each[10]. Several clinical trials have demonstrated their rapid and potent ability to reverse the anticoagulant effects of VKA (such as warfarin or acenocoumarol - Sintrom®) and ensure rapid correction of INR[11,12]. The appropriate dose depends on the INR before treatment and the target INR (Table 3)[10].

Historically, PCC has been associated with thrombotic complications[13], and this must be weighed against the need for effective reversal of the coagulopathy. PCC should be used according to CHADS-2[14-18] and HAS-BLED scores[19,20], and patient monitoring is recommended[21].

A recent meta-analysis by Sorensen et al[3] covering various studies carried out between 1988 and 2010 concluded that, although thrombotic complications have been associated with PCC, the causes remain uncertain; the evidence suggests that factor II plays an important role in thrombogenicity[3]. In contrast, other authors have concluded that the administration of PCC carries a low risk of thromboembolism and could still be more effective than other treatments at reversing the anticoagulant effects of VKA[22-26], which raises the possibility of its use even in the presence of major bleeding.

These seemingly contradictory results and the absence of methodologically well-designed clinical trials with comparative designs highlight the need to continue the analysis of PCC use and effectiveness. The aim of this study was to evaluate the incremental cost-effectiveness ratio (ICER) of PCC to normalize INR in routine clinical practice of hospital EDs, in patients with altered INR regardless of the complaint.

Methods

We performed a cost-effectiveness study, with sensitivity analysis (univariate and probabilistic), on the benefit of using PCC compared to the alternative conservative approach which involves no treatment to normalize the INR of patients admitted. We used an Excel® Markov simulation model with a time span of ten years, based on a decision tree (Figure 1) that simulates the natural and probable evolution of a patient with elevated INR and takes into account the possibility of their suffering an episode of minor bleeding (epistaxis), major bleeding (gastrointestinal bleeding) or critical bleeding (intracranial hemorrhage), as well as death or neurological sequelae after bleeding or as a complication of PCC use. The probability of these events varies according to INR normalization with PCC. Since three PCC formulations are marketed in Spain, each with different characteristics, composition and price (Table 2), we selected the PCC used in our ED (Octaplex®), hereinafter referred to as PCC-1, and based our pharmaco-economic model on it. The dose of PCC-1 in the model was 3-6 units per patient.

The Spanish Agency of Medicinal Products (Agencia Española del Medicamento) states that the dose of PCC-1 for perioperative bleeding and

Table 2. Prothrombin complex concentrates available in Spain and drug characteristics*

Laboratory	Baxter	Octapharma	CSL Behring
License date:	01-10-1980	12-11-2004	13-06-2008
Name	Prothromplex-T®	Octaplex®	Beriplex®
Presentation	Prothromplex® T 600 IU/20 ml, powder & solvent for solution for injection. 1 vial of 600 IU + 1 vial water 20 ml	Octaplex®, powder & solvent for solution for infusion, 1 vial of powder + 1 vial of water 20 ml	Beriplex®, 500 IU, powder & solvent for solution for injection
Price	Lab: € 217,49; Retail: € 273,94	Lab: € 194,5 Retail: € 271,35	Retail: € 271,35
Composition			
Factor II	30 IU ml^{-1}	11-38 IU ml^{-1}	20-48 IU ml^{-1}
Factor VII	25 IU ml^{-1}	9-24 IU ml^{-1}	10-25 IU ml^{-1}
Factor IX	30 IU ml^{-1}	25 IU ml^{-1}	20-31 IU ml^{-1}
Factor X	30 IU ml^{-1}	18-30 IU ml^{-1}	22-60 IU ml^{-1}
Protein C	Minimum, 20 IU ml^{-1}	7-31 IU ml^{-1}	15-45 IU ml^{-1}
Protein S	–	7-32 IU ml^{-1}	13-26 IU ml^{-1}
Total proteins	15-37 mg ml^{-1}	13-41 mg ml^{-1}	6-14 mg ml^{-1}
FIX activity	–	0,6 IU mg^{-1}	2,5 IU mg^{-1}
Excipients	Heparin Antithrombin III Citrate	Heparin Citrate Sodium	Heparin Antithrombin III Albumin

*Data obtained from "Agencia Española del Medicamento"[10].

prophylaxis depends on pre-treatment INR and the target INR. Table 3 provides the approximate dose required and how it is calculated (ml / kg body weight of the reconstituted product) to achieve INR normalization (≤ 1.2 in 1 hour) starting from different initial INR levels.

For the probabilistic simulation of the model, we included a population of 14,000 patients receiving oral anticoagulant therapy with warfarin, of whom 5% were expected to present an elevated INR, according to population-based estimates made by the University Hospital La Paz, Madrid, in annual cycles, during 10 years.

We performed a systematic search of the literature to determine baseline probabilities for the model, to which we applied an inverted beta distribution. We reviewed all economic studies of PCC used to treat patients with severe bleeding or hemophilia included in Medline, the Cochrane Library and the ISI Web of Science Citations during the past 10 years.

The probabilities not found in the literature search were determined by qualitative techniques based on the consensus of an expert committee of specialists from the departments of intensive care and emergency medicine, University Hospital La Paz, Madrid (Table 4). Regarding health utilities, we assigned a quality of life score of 0.78 in anticoagulated patients and 0.35 in those with neurological sequelae. No discounts on quality of life were applied.

Costs are taken from the official bulletin of the Community of Madrid (Order 629/2009, 31 August), which publishes updated prices for the provision of services and activities in the Community of Madrid Health Center Network (BOCM, 10 September 2010), as shown in Table 5. These official data include all care costs except that of PCC-1, which was obtained from a computer database of medicinal drugs and checked with the Coordinator of the ED, University Hospital La Paz. The

Table 3. Calculating the dose of prothrombin complex concentrate (PCC) for urgent reversal of anticoagulation[16]

Step 1: Decide on target level of INR according to clinical situation:

Clinical situation	INR TARGET
Moderate bleeding & high risk of thrombosis	2.0-2.1
Major bleeding, moderate risk of thrombosis	1.5
Major bleeding, life-threatening risk of thrombosis	1

Step 2: Conversion of INR to PCC (expressed as % of normal plasma)

	INR	Approximate %
Excessive anticoagulation	> 5	5
	4.0-4.9	10
Therapeutic range	2.6-3.2	15
	2.2-2.5	20
	1.9-2.1	25
Sub-therapeutic range	1.7-1.8	30
	1.4-1.6	40
Complete reversal to normal	1.0	100

Step 3: Formula to calculate the dose
[target level as a percentage – present level as a percentage] x body weight in Kg = international units (IU) of PCC.

INR: international normalized ratio.

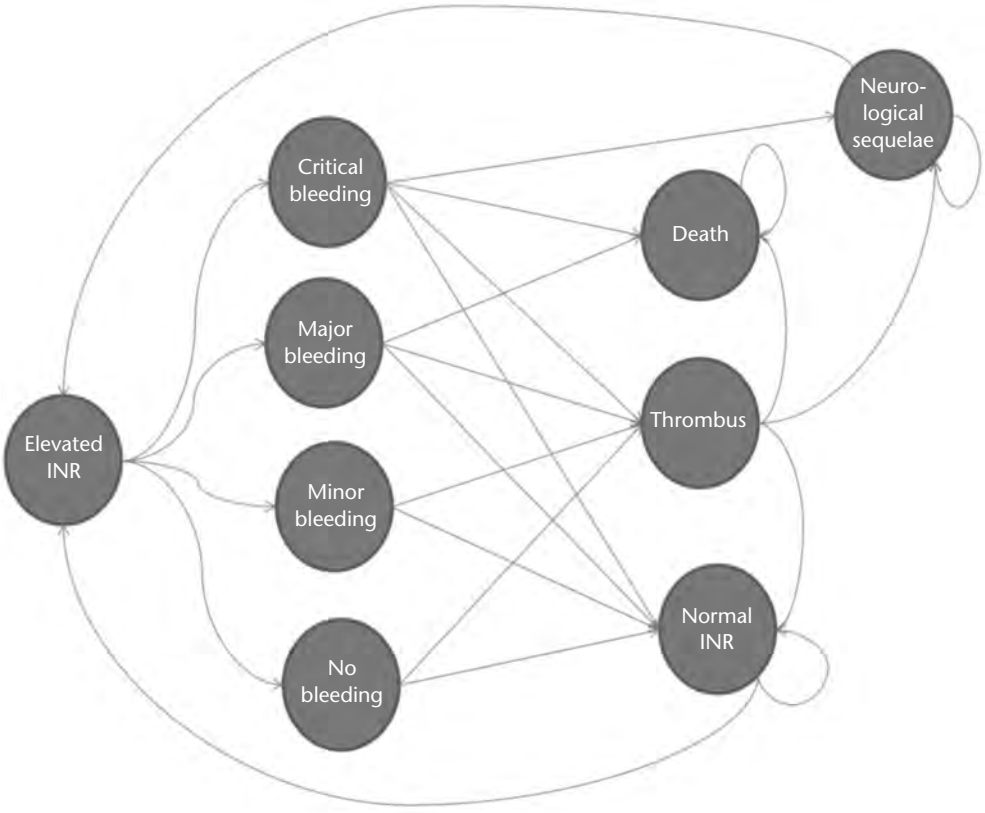

Figure 1. Markov model.

cost of neurological sequelae was estimated on the basis of four visits by primary care physicians and nurses per year and complementary tests performed as a result of one such visit. Our cost analysis was performed from the perspective of ED management, over a time span of 10 years, with a cost discount rate of 5% per year. In the model shown in Figure 1 we introduced each year a population of 700 patients with elevated INR (5% of the estimated 14,000 patients treated with anticoagulants in the reference area of our General University Hospital La Paz, Madrid), for whom PCC-1 would be indicated.

The results were expressed as euros per year adjusted for quality of life (QALY), which is the health index that takes into account years of life and the quality thereof.

Sensitivity analyzes were performed to assess the influence of parameter uncertainty (efficacy, dropout rates, costs and clinical complications) in the results of the study and to validate its robustness. Univariate analysis was used in the baseline case for different discount rates (0%, 3% and 10%). Likewise, we performed a univariate analysis in which all critical complications required intracranial intervention, which substantially increases the cost of this arm. Finally, we performed a probabilistic sensitivity analysis in which the probabilities, being natural events, were considered to follow a normal distribution while costs, being health costs, were considered to follow a triangular distribution with a standard deviation equal to one quarter of the mean cost.

Table 4. Annual probabilities used in the model

Type of complication	%
Critical complications without treatment	0.60
Major complications untreated	1.10
Minor complications without treatment	25.00
No complications untreated	73.30
Untreated neurologic sequelae if critical complications	50
Critical complications with PCC-1	0.30
Major complications with PCC-1	0.55
Minor complications with PCC-1	12.50
No complications with PCC-1	86.65
Neurological sequelae with PCC-1 if critical	50.00
Neurological sequelae with PCC-1 if thrombus	25.00
Chance of thrombus with PCC-1	0.05
Probability of death (critical complication)	40.00
Probability of death (major complication)	15.00
Probability of death (minor complication)	0.00
Probability of death (thrombi)	10.00

PCC-1: Octaplex®.

Table 5. Costs introduced in the model

Concept of the model	Code BOCM	Cost (€)
ED visit (applicable to whole population)	E 03.1.1.2.2.1	122
Epistaxis (minor complication)	E03.1.1.1.55	2,400
Gastrointestinal bleeding (major complication)	E03.1.1.1.160	3,460
Intracraneal bleeding (critical complication)	E03.1.1.1.628	6,383
Neurological sequelae		246
– PC consultation with tests (1 visit)	E 03.1.3.2	57
– PC consultation without tests (3 visits)	E 03.1.3.1	39
– Nurse consultation (4 visits)	E 03.1.3.3	18
Thrombosis (ictus with infarction)	E03.1.1.1.11	5,027
Intracranial vascular procedures with main diagnosis of bleeding (used in sensitivity analysis)	E03.1.1.1.649	31,894
Prothrombin complex (Octaplex®, per unit)	Personal communication	215

PC: primary care

Results

The economic evaluation was based on the incremental cost-effectiveness ratio (ICER), which is the ratio of the change in costs to incremental benefits of a therapeutic intervention or treatment, obtained using the formula:

$$ICER = \frac{C_A - C_B}{E_A - E_B}$$

where C_A and E_A are the cost and effect in the intervention or treatment group and where CB and EB are the cost and effect in the control care group receiving the alternative standard treatment.

As mentioned in Methods, in the baseline case 700 people visit the ED annually with elevated INR, where a discount of 5% is applied and it is assumed that no cases of bleeding would require surgery. In this case, the ICER using CCP-1 versus no treatment would be € –3,859 per QALY. Table 6 shows the results of the sensitivity analysis where the discount rate varies between 0 and 10% and it is assumed that all critical bleeding would require intracranial surgery.

Figure 2 shows the results of the probabilistic analysis, where costs were made to vary according to the triangular distribution and the prevalence of bleeding according to normal distribution. In total, 2,000 simulations were performed, which provided a median incremental cost effectiveness of € 6,357 per QALY (interquartile range from € 20,412 per QALY to € 37,445 per QALY).

Discussion

Currently, the increase in indications for VKA therapy in a large spectrum of diseases, together with better knowledge and control of possible adverse effects such as bleeding or INR elevation, has extended the use of this therapy to a wide population which includes the elderly, and patients consulting the ED are often VKA users[27,28].

In emergency and intensive care medicine, PCC has proved an excellent choice of therapy to reverse the anticoagulant effects of VKA compared with the alternatives such as FFP or recombinant FVIIa, due to its effectiveness, rapid normalization of INR, control of bleeding and few adverse effects[29,30]. In the case of PCC-1, the safety profile is high regarding the risk of thrombosis and transmission of viruses.

With the assumptions made in our model, CCP-1 showed that it could be effective in the general population visiting the ED, provided the percentages of complications considered in this study are not exceeded, especially thrombotic complications.

The results of the sensitivity analysis (Table 5) showed that the ICER of using PCC-1 compared to other treatments to normalize INR favored the use of PCC-1. We observed a negative correlation between effectiveness and incremental cost, which means that the greater the incremental effectiveness of PCC use, the lower the expected incremental costs associated with such use. A large percentage of independent estimates of incremen-

Table 6. Baseline case and univariate analysis of sensitivity

	QALY			Costs			
	No treatment	Treatment with PCC-1	Difference	No treatment	Treatment with PCC-1	Difference	ICER
Baseline case	108,289	108,743	455	€ 18,015,547	€ 16,259,982	€ –1,755,566	€ –3,859
Discounts							
0%	108,289	108,743	455	€ 22,284,114	€ 20,087,125	€ –2,196,989	€ –4,829
3%	108,289	108,743	455	€ 19,544,836	€ 17,631,455	€ –1,913,381	€ –4,206
10%	108,289	108,743	455	€ 14,978,079	€ 13,534,581	€ –1,443,497	€ –3,173
Surgery	108,289	108,743	455	€ 22,153,001	€ 18,328,709	€ –3,824,292	€ –8,406

PCC-1: octaplex®; ICER:incremental cost effectiveness ratio QALY: quality adjusted life years.

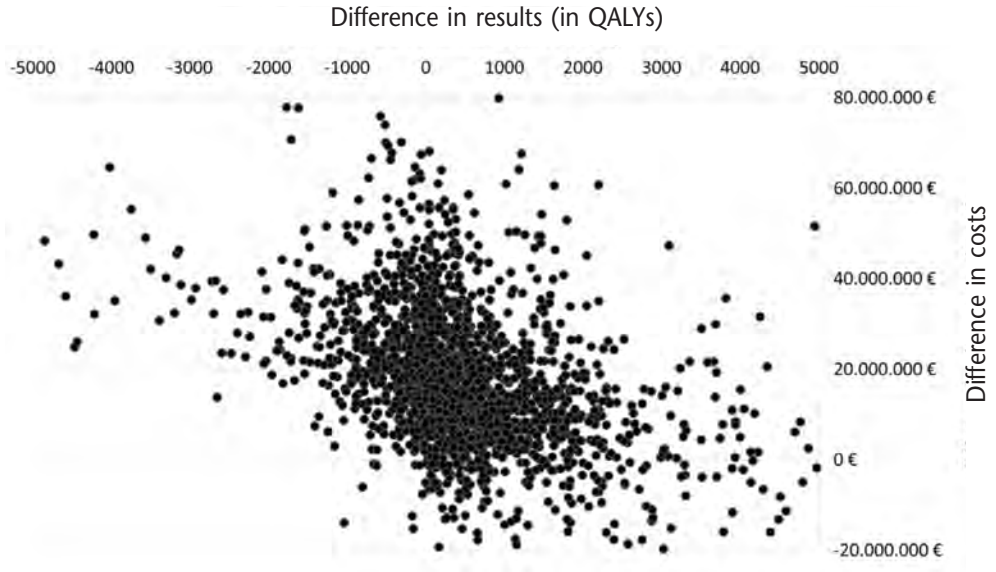

Figure 2. Results of probabilistic analysis of sensitivity. QALY: quality adjusted life years.

tal cost-effectiveness are in the quadrant corresponding to positive incremental cost and effectiveness, corroborating the trend shown in the ICER estimate. We would also note that, in the baseline scenario, the PCC-1 program was not associated with negative incremental costs, i.e. it is cost-saving. The benefits of intervention are not economic, but must be seen in the context of the number of deaths avoided with INR normalization. In this regard, the effectiveness of PCC-1 may exceed 80% when costs are equal or relatively equal to those assumed in the table of results of the univariate sensitivity analysis (Table 4).

These data are consistent with those of several international studies on PCC. In clinical trials to evaluate the efficacy of PCC-1, two have compared the effectiveness of the drug with the administration of vitamin K and FFP[25-31]. Despite the low number of clinical trials published, PCC has been shown to be more effective for rapid reversal of anticoagulation than vitamin K or plasma, which are also effective but require longer time periods, and time may be critically important in this type of patient.

Similarly, there are various systematic reviews on the efficacy of PCC. Lessinger et al[32] reviewed the results of 14 studies: three prospective, randomized, and controlled, four prospective non-randomized, one case-control study, and the remaining six were retrospective studies. The authors concluded that PCC is fast and specific at replacing vitamin K dependent factors, but more trials and evidence-based guidelines were needed. Another recent meta-analysis analyzed a total of 11 economic studies that evaluated the cost-benefit of activated PCC versus FVIIa-r for the treatment of bleeding in hemophilic patients. The conclusion was that they show similar efficacy and safety, although all the studies except one tended to favor the sponsor of the study, but in all cases efficacy, safety and cost-effectiveness of both agents was very good, thus demonstrating that prothrombin complexes are superior to plasma for the reversal of very severe warfarin-induced bleeding, especially in patients with significant deficit of vitamin K-dependent factors[26].

Makris et al.[10] describe the qualities of currently available PCC: a) 4-factor PCC which replaces all the coagulation factors in factor-deficient patients, b) 3-factor PCC containing little FVII, which has long been available for hemophilia B and for warfarin reversal, and which is less effective at correcting INR and coagulopathy; c) activated PCC (such as FEIBA), which is not for warfarin reversal and used only in hemophilia patients with FVIII / IX inhibitors[34]. Of course the best choice, if available, is 4-factor PCC, with presentations such as Octaplex ® (factors II, VII, IX, X, protein C and S). In order to clarify the indications for PCC, a consensus document has recently been published on the correct use of the drug, endorsed by the Ministry of Health, the Organization of Medical Colleges and British guidelines[35].

As regards the evaluation of safety, in pre-marketing studies, the most frequent severe adverse effects were disseminated intravascular coagulation and the risk of viral agent transmission, especially parvovirus B19 and hepatitis, but that risk is

reduced with the application of strict viral inactivation methods. In the 14 studies reviewed by Lessinger et al.[32], there was no clinical evidence of disseminated intravascular coagulation due to PCC, but 7 cases with thrombotic complications were recorded.

Regarding the allegedly higher cost of PCC, the cost of FFP is curiously not considered. Thus, for example in Catalonia, in 2009, the price of one unit of FFP inactivated with methylene blue was € 66.60 (€ 88.45 if purified). A patient weighing 80 kg would require between 1,600 and 3,000 mL of FFP (10-20 mL / kg), which at about 250-280 mL per unit is equivalent to 5 and 12 units of FFP, and the final price is between € 333 and € 1,061.

The total cost of treatment with PCC per individual is a small but non-negligible part of total pharmaceutical expenditure in the management of a critically ill patient, as demonstrated in this study. However, it would be advisable to rationalize expenditure and develop protocols with precise dosing and therapeutic indications adjusted to the clinical characteristics and coagulation parameters of each patient[23].

Finally, the limitations of this study should be taken into account. Other comparative economic analyses are required (e.g. PCC versus rFVIIa), or perhaps a clinical trial to further clarify the use of PCC and the cost-benefit of use in the EDs of our country. Importantly, we would emphasize the fact that there seems to be no systematic and controlled studies on the effect of CCP-1 in reversing the effects of acenocoumarol (the anticoagulant used in Spain), and most if not all studies have been conducted with warfarin, so both this work and the future research here proposed could be pioneers in their analysis and thus make a useful contribution to clinical practice in our EDs.

References

1 Riess HB, Meier-Hellmann A, Motsch J, Elias M, Kursten FW, Dempfle CE. Prothrombin complex concentrate (Octaplex) in patients requiring immediate reversal of oral anticoagulation. Thromb Haemost. 2007;98:790-7.

2 Key NS, Negrier C. Coagulation factor concentrates: past, present, and future. Lancet. 2007;370:439-48.

3 Sørensen B, Spahn DR, Innerhofer P, Spannagl M, Rossaint R. Clinical review: Prothrombin complex concentrates-evaluation of safety and thrombogenicity. Crit Care. 2011;15:201.

4 Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). Chest. 2008;133:160S-98S.

5 Baglin TP, Keeling DM, Watson HG. Guidelines on oral anticoagulation (warfarin). Br J Haematol. 2006;132:277-85.

6 Lorenz R, Kienast J, Otto U, Egger K, Kiehl M, Schreiter D, et al. Efficacy and safety of a prothrombin complex concentrate with two virus-inactivation steps in patients with severe liver damage. Eur J Gastroenterol Hepatol. 2003;15:15-20.

7 Coagulation Management in Trauma Related Massive Bleeding. (Consultado 6 Septiembre 2011). Disponible en: http://www.oegari.at/arbeitsgruppe.asp?id=116

8 Spahn DR, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, Gordini G, et al. Management of bleeding following major trauma: a European guideline. Crit Care. 2007;11:R17.

9 World Federation of Haemophilia Registry of Clotting Factor Concentrates. (Consultado 5 Septiembre 2011). Disponible en: http://www.wfh.org/2/docs/Publications/Treatment_Products/Monographs/FF6_Registry_8th_2008.pdf

10 CIMA: Centro de información online de medicamentos de la Agencia Española de Medicamentos y Productos Sanitarios. (Consultado 5 Septiembre 2011). Disponible en: http://sinaem4.agemed.es/consaem/fichasTecnicas.do?metodo=detalleForm&version=new

11 Demeyere R, Gillardin S, Arnout J, Strengers PF. Comparison of fresh frozen plasma and prothrombin complex concentrate for the reversal of oral anticoagulants in patients undergoing cardiopulmonary bypass surgery: a randomized study. Vox Sang. 2010;99:251-60.

12 Major J, Reed MJ. A retrospective review of patients with head injury with coexistent anticoagulant and antiplatelet use admitted from a UK emergency department. Emerg Med J. 2009;26:871-6.

13 Lusher JM. Thrombogenicity associated with factor IX complex concentrates. Semin Hematol. 1991;28:3-5.

14 Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285:2864-70.

15 Risk of Stroke with AF. VA Palo Alto Medical Center and at Stanford University: the Sports medicine Program and the Cardiomyopathy Clinic. (Consultado 5 Septiembre 2011). Disponible en: http://www.cardiology.org/tools/risk_of_stroke_AF.html. Retrieved 2007-09-14.

16 Karthikeyan G, Eikelboom JW. The CHADS2 score for stroke risk stratification in atrial fibrillation-friend or foe? Thromb Haemost. 2010;104:45-8.

17 Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137:263-72.

18 European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010;31:2369-429.

19 Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess one-year risk of major bleeding in atrial fibrillation patients: The Euro Heart Survey. Chest. 2010;18.

20 Lip GY, Frison L, Halperin JL, Lane DA. Comparative Validation of a Novel Risk Score for Predicting Bleeding Risk in Anticoagulated Patients With Atrial Fibrillation. The HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) Score. J Am Coll Cardiol. 2011;57:173-80.

21 Levi M, Eerenberg E, Kamphuisen PW. Bleeding risk and reversal strategies for old and new anticoagulants and antiplatelet agents. J Thromb Haemost. 2011;9:1705-12.

22 Majeed A, Eelde A, Agren A, Schulman S, Holmström M. Thromboembolic safety and efficacy of prothrombin complex concentrates in the emergency reversal of warfarin coagulopathy. Thromb Res. 2012;129:146-51.

23 van Aart L, Eijkhout HW, Kamphuis JS, Dam M, Schattenkerk ME, Schouten TJ, et al. Individualized dosing regimen for prothrombin complex concentrate more effective than standard treatment in the reversal of oral anticoagulant therapy: an open, prospective randomized controlled trial. Thromb Res. 2006;118:313-20.

24 Preston FE, Laidlaw ST, Sampson B, Kitchen S. Rapid reversal of oral anticoagulation with warfarin by a prothrombin complex concentrate (Beriplex): efficacy and safety in 42 patients. Br J Haematol. 2002;116:619-24.

25 Riess HB, Meier-Hellman A, Motsch J, Elías M, Kursten FW, Dempfle CE. Prothrombin complex concentrate (Octaplex®) in patiens requiring immediate reversal of oral anticoagulation. Thrombosis Research. 2007;121:9-16.

26 Pabinger I, Brenner B, Kalina U, et al. Prothrombin complex concentrate (Beriplex P/N) for emergency anticoagulation reversal: a prospective multinational clinical trial. J Thromb Haemost. 2008;6:622-31.

27 Navarro JL, Cesar JM, Fernádez MA, Fontcuberta J, Reverter JC, Gol-Freixa J. Morbilidad y mortalidad en pacientes con tratamiento anticoagulante oral. Rev Esp Cardiol. 2007;60:1226-32.

28 Quintana Díaz M, Carvalho M. Libro electrónico de Medicina Intensiva, Sección 27: Hematologia. (Consultado 5 Septiembre 2011). Disponible en: http://intensivos.uninet.edu/27/2701.html

29 Demeyere R, Gillardin S, Arnout J, Strengers PF. Comparison of fresh frozen plasma and prothrombin complex concentrate for the reversal of oral anticoagulants in patients undergoing cardiopulmonary bypass surgery: a randomized study. Vox Sang. 2010;99:251-60.

30 Major J, Reed MJ. A retrospective review of patients with head injury with coexistent anticoagulant and antiplatelet use admitted from a UK emergency department. Emerg Med J. 2009;26:871-6.
31 Lubestsky A, Hoffman R, Zimlichman R, Eldor A, Zus J, Kostenko V. Efficacy and safety of a prothrombin complex concentrate (Octaplex) for rapid reversal of oral anticoagulation. Thromb Res. 2004;113:371-8.
32 Lessinger C, Blatt P, Hoots W, Ewenstein B. Role of prothrobin complex concentrates in reversing warfarin anticoagulation: a review of the literature. Am J Hematol. 2008;83:137-43.
33 Hay JW, Zhou ZY. Systematic literature review of economics analysis on treatment of mild-to-moderate bleeds with aPCC versus rFVIIa. J Med Econ. 2011;14:516-25.
34 Makris M, van Veen JJ, Maclean R. Warfarin anticoagulation reversal: management of the asymptomatic and bleeding patient. J Thromb Thrombolysis. 2010;29:171-81.
35 Leal R, Alberca I, Asuero MS, Bóveda JL, Carpio N, Contreras E, et al. The Seville consensus document on alternatives to allogenic blood transfusion. Med Clin (Barc). 2006;127(Supl 1):3-20.

Estudio de coste-efectividad del empleo de concentrado de complejo protrombínico en urgencias para evitar las complicaciones de la sobredosificación de anticoagulantes

Quintana Díaz M, Borobia AM, Pérez Cachafeiro S, Rodríguez C, García Erce JA

Introducción: En la actualidad, los concentrados de complejos protrombínicos (CCP) son usados principalmente en la reducción rápida del efecto anticoagulante producido por la administración de antagonistas de la vitamina K (AVK) en los casos de aparición de hemorragia aguda o en cirugía de urgencia, y son la mejor elección frente al uso de plasma fresco congelado (PFC). Su composición, seguridad y acción rápida en la corrección de la hemostasia (ratio internacional normalizado-INR) y en la reducción del riesgo de hemorragia hacen de éste un fármaco esencial en la práctica de urgencias y en la cirugía hospitalaria. Este trabajo valora la eficacia (coste-efectividad incremental) del empleo de CCP para normalizar el INR en la práctica habitual de un servicio de urgencias.
Método: Se ha realizado un análisis coste-efectividad para el que se utilizó un modelo de simulación de Markov en Excel® (año-año), basado en un árbol de decisiones. Para la simulación probabilística se tomó el 5% del total de una población de pacientes con terapia anticoagulante oral con antivitamina K (AVK) e INR elevado en un servicio de urgencias, en ciclos anuales, durante 10 años. El CCP utilizado para el análisis ha sido Octaplex®.
Resultados: El análisis de sensibilidad ha demostrado que la razón coste-efectividad incremental (RCEI) de la administración de CCP frente al uso de otras terapias para la normalización del INR es favorable al uso del CCP.
Conclusiones: El uso de CCP en urgencias sería coste-efectivo. [Emergencias 2012;24:113-120]

Palabras clave: Complejo protrombínico. Anticoagulantes. Sobredosificación.