Emergency reversal of anticoagulation: from theory to real use of prothrombin complex concentrates. A retrospective Italian experience

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Background. Prothrombin Complex Concentrates (PCC) are administered to normalise blood coagulation in patients receiving oral anticoagulant therapy (OAT). Rapid reversal of OAT is essential in case of major bleeding, internal haemorrhage or surgery.

The primary end-point was to evaluate whether PCC in our hospital were being used in compliance with international and national guidelines for the reversal of OAT on an emergency basis. The secondary end-point was to evaluate the efficacy and safety of PCC.

Materials and methods. All patients receiving OAT who required rapid reversal anticoagulation because they had to undergo emergency surgery or urgent invasive techniques following an overdose of oral anticoagulants were eligible for this retrospective observational study.

Results. Forty-seven patients receiving OAT who needed rapid reverse of anticoagulation were enrolled in our study. The patients were divided in two groups: (i) group A (n=23), patients needed haemostatic treatment before neurosurgery after a head injury and (ii) group B (n=24), patients with critical haemorrhage because of an overdose of oral anticoagulants. The International Normalised Ratio (INR) was checked before and after infusion of the PCC. The mean INR in group A was 2.7 before and 1.43 after infusion of the PCC; in group B the mean INR of 6.58, before and 1.92 after drug infusion. The use of vitamin K, fresh-frozen plasma and red blood cells was also considered. During our study 22 patients died, but no adverse effects following PCC administration were recorded.

Discussion. In our study three-factor-PCC was found to be effective and safe in rapidly reversing the effects of OAT, although it was not always administered in accordance with international or national guidelines. The dose, time of administration and monitoring often differed from those recommended. In the light of these findings, we advocate the use of single standard protocol to guide the correct use of PCC in each hospital ward.

Keywords: prothrombin complex concentrate, oral anticoagulant therapy, reversal of anticoagulation guidelines.

Introduction

Prothrombin complex concentrates (PCC) contain coagulation factor II, factor IX, factor X and factor VII (this last being present in very low amounts in three-factor PCC and in normal amounts in four-factor PCC), which are vitamin K-dependent clotting factors, produced in the liver[1]. PCC were developed in the late 1950s for the treatment of patients with haemophilia B: nowadays they are mainly used to reverse the effects of oral anticoagulant therapy and to manage coagulation disorders[2,3]. Compared to fresh-frozen plasma (FFP), PCC have the advantage that their volume of infusion is small and that they rapidly reverse coumarin-induced anticoagulation. In Italy over 1,000,000 people receive oral anticoagulant therapy (OAT) and this number is increasing steadily, particularly because of increasing use among the elderly[4]. OAT, including the vitamin K-antagonists acenocoumarol and warfarin, is used for the prevention and treatment of thromboembolic complications, such as cardiac embolism in patients with cardiovascular diseases and atrial fibrillation,

and for secondary prevention of deep vein thrombosis, pulmonary embolism or stroke[5-7]. Anticoagulants delay the process of blood coagulation, prevent serious thrombotic and vascular diseases, and reduce the risk of thromboembolism. Oral anticoagulants are effective, safe and inexpensive, and moreover patients usually comply well with this therapy. However, in the elderly, the treatment of co-morbidities, such as hypertension, bronchitis, gastritis or depression, may be associated with OAT-drug interactions, causing bleeding or haemorrhagic shock[8]. To avoid these risks and to maximise the benefits of OAT, blood coagulation should be measured by the International Normalised Ratio (INR)[9]. In healthy people, the INR is about 1.0. A high INR means that the blood is clotting slowly and there may be a risk of uncontrolled bleeding and haemorrhages: worldwide the incidence of bleeding during OAT is stated to be between 2% and 13%[10]. The products that can be used to restore haemostatic parameters and to stop haemorrhage in the case of critical bleeding due to vitamin K antagonists include PCC, other agents such as FFP, and vitamin K[11].

International guidelines

French guidelines (2010)[12] suggest that patients with severe bleeding must be admitted to hospital. Besides discontinuing vitamin K antagonists, PCC should be administered immediately in association with 10 mg vitamin K supplement (grade C, level 3), and massive haemorrhage, if present, managed urgently. FFP should only be used when PCC are not available (grade B, level 2). The use of recombinant activated factor VII (rFVIIa) is not recommended (grade C, level 3).

In 2008, the American College of Chest Physicians published its guidelines[13] that recommend, for patients with life-threatening bleeding and elevated INR, withholding warfarin therapy and administering FFP, PCC, or rFVIIa supplemented with vitamin K 10 mg by slow intravenous infusion, repeated, if necessary, depending on the INR (grade 1C).

In 2004 the Australasian Society of Thrombosis and Haemostasis published consensus guidelines on warfarin reversal, indicating that the effects of oral anticoagulation can be reversed by vitamin K and that coagulation factors can be replaced by infusing PCC and FFP. It was also noted that the choice of each approach is based largely on clinical judgement, because no randomised trials have compared these strategies in terms of clinical outcomes[14].

Italian guidelines

In Italy, in September 2010, the Federation of Centres for the Diagnosis of Thrombosis and Monitoring of Antithrombotic Therapies (FCSA)[15] published guidelines for the emergency treatment of orally anticoagulated patients. Emergency treatment may be necessary in the case of spontaneous intracranial haemorrhage, post-traumatic brain haemorrhage, massive bleeding or when the patient requires immediate surgery that can not be postponed. These guidelines recommend the suspension of OAT and infusion of vitamin K, and discuss the use of FFP, rFVIIa and PCC.

The recommended dose of vitamin K is 10 mg intravenously, but, in the case of major haemorrhage, the administration of vitamin K is not sufficient as the only treatment and should always be associated with other procedures to restore the levels of coagulation factors.

The recommended dose of FFP is 15 mL/kg, but attention must be paid to the risk of volume overload, to the possibility of allergic reactions, to the variability of coagulation factors due to the dilution effect and finally to the fact that the concentration of factor IX is not always sufficient for complete reversal of anticoagulation. rFVIIa is not recommended. Reversal of anticoagulation is an "off-label" use of rFVIIa. This clotting factor is expensive, less effective than PCC in animal model studies and can cause thromboembolic events. The recommended dose of PCC depends on each patient's weight and INR value on admission. Given that PCC cost less than rFVIIa, that the volume of infusion is small and does not, therefore, lead fluid overload and that these concentrates have an immediate effect, PCC are considered the "*treatment of choice for rapid reversal of oral anticoagulation*".

Purpose of the study

The primary end-point of this study was to evaluate whether PCC in our hospital were being used in compliance with international and national guidelines for the reversal of anticoagulation on an emergency basis. The secondary end-point was to evaluate the efficacy and safety of PCC.

Materials and methods

Patients

All patients taking vitamin K antagonists who were referred to the University Hospital of Udine for rapid reversal of anticoagulation because they had to undergo emergency surgery or urgent invasive techniques following an overdose of oral anticoagulants were initially considered for this study.

Methods

The patients' data were retrieved from the clinical records in the archive of the University Hospital of Udine. All patients' vital signs were recorded on arrival at the hospital. The oral anticoagulants administered were warfarin (Bristol Myers Squibb, Srl) and acenocumarol (Novartis, S.p.A.). The INR was measured using an Electra 1800C Automatic Coagulation Analyzer (Hemoliance, Hemostasis from MLA and Ortho).

The PCC administered in our hospital during the study period was a three-factor concentrate: Uman Complex D.I. 500 IU, reconstituted solution (Kedrion S.p.A). Each vial provided factor II (in an amount equivalent to that delivered in 200-500 mL FFP), factor IX (200-500 IU) and factor X (in an amount equivalent to that delivered in 200-500 mL FFP).

Vitamin K (Konakion®, Roche S.p.A.) was given intravenously at a dose of 10 mg. Red blood cells were administered in the case of massive haemorrhage or when the haemoglobin concentration was less than 8.0 g/dL. FFP was used before surgery, if the patient was bleeding or after surgery to restore plasma volume.

Screening for viral infections was performed using tests to detect hepatitis B surface antigen (Cobas Core HbsAg EIA, Roche Diagnostics), antibodies to hepatitis C virus (Cobas Core Anti HCV EIAII, Roche Diagnostics) and antibodies to human immunodeficiency virus-1/2 (Cobas Core HIV Combi, Roche Diagnostics).

Results

This retrospective study evaluated the use of PCC in 47 patients (Table I) divided into two groups: (i) group A, consisting of 23 patients who needed haemostatic treatment prior to neurosurgery after a head injury; and (ii) group B, comprising 24 patients with critical haemorrhage due to an overdose of oral anticoagulants.

Infusion of prothrombin complex concentrates

Group A consisted of 23 patients receiving OAT who were hospitalised following a serious head trauma that caused life-threatening bleeding and who were treated with PCC. The mean INR of this group of patients upon their arrival at hospital and before treatment was 2.7 (range, 1.56-4.67). Twenty patients (87%) were given a single dose of PCC (mean dose, 17.8 IU/Kg; range, 6.4-37.8 IU/Kg), whereas for three patients (13%), the physicians considered it appropriate to administer a second dose of PCC. Subsequent monitoring of the INR showed the values decreased, reaching a mean of 1.43 (range, 1.04-1.83). The mean time to INR monitoring after PCC infusion, was 46 minutes. Neither venous complications (deep vein thrombosis or pulmonary embolism) nor arterial complications (myocardial infarction, ischaemic stroke, any other arterial occlusion) were observed by the treating physicians.

Group B consisted of 24 patients hospitalised and treated with PCC because of ingestion of excessive doses of oral anticoagulants that had caused intracranial haemorrhage in 17 cases, acute gastrointestinal bleeding in four cases and retroperitoneal haemorrhage in three cases. At hospital admission and before medical intervention,

Table I - Baseline characteristics of the patients.

Group	N. of pts	Sex (M/F)	Mean age (years)	Atrial fibrillation	Ischaemic Cardiopathy	Idiopathic VTE	Acenocoumarol	Warfarin
A	23	14/9	77	14 (60.9%)	5 (21.7%)	4 (17.4%)	14 (60.9%)	9 (39.1%)
B	24	9/15	74	15 (62.5%)	4 (16.7%)	5 (20.8%)	14 (58.4%)	10 (41.6%)
Total	47	23/24	76	29 (61.8%)	9 (19.1%)	9 (19.1%)	28 (59.6%)	19 (40.4%)

the mean INR of these patients was 6.58 (range, 1.73 - not coagulable). Twenty-one patients (87.5%) were given a single dose of PCC (mean dose, 21.3 IU/Kg; range, 7.4-42.6 IU/Kg) and three patients (12.5%) with severe intracranial haemorrhage received a second dose. Subsequent monitoring of INR showed a decrease of the mean value to 1.92 (range, 0.91-4.33). The mean time to INR monitoring, after PCC infusion, was 55 minutes. No venous or arterial complications were observed in these patients. Three patients died during the medical treatment: in these cases, the INR after PCC administration was not checked because of the sudden death.

Other treatments

Twelve patients (25.5%) with severe bleeding and INR >4.0 (6 in group A and 6 in group B) received a single dose of vitamin K 10 mg intravenously. Seventeen patients (36.2%) (9 in group A and 8 in group B) were given FFP to restore plasma volume: the mean dose was 1073 mL (range, 600-2,400 mL). Three patients (6.4%) with critical intracranial haemorrhage (1 in group A and 2 in group B) received an emergency infusion of vitamin K 10 mg intravenously and FFP (mean, 1,080 mL; range, 600-1,800 mL), before PCC infusion. Twelve patients (25.5%) (2 in group A and 10 in group B) with major bleeding and a haemoglobin concentration less than 8.0 g/dL were given red blood cell transfusions on arrival at hospital. Six patients (12.8%) (2 in group A and 4 in group B) needed red blood cell transfusions after surgery in order to restore a target haemoglobin value.

Acenocumarol versus warfarin

The characteristics of the patients treated with acenocumarol and those treated with warfarin are shown in Table II.

Safety

In our study no adverse events related to PCC infusion were reported by treating physicians or reported in the patients' medical records. All patients underwent cerebral computed tomography scanning on arrival at the emergency department and the examination was repeated during hospitalisation. Six patients underwent a chest X-ray. No allergic reactions, thromboembolic events, or viral infections were found. All tests for viral infections such as HBV, HCV or HIV performed during hospitalisation and a fortnight after discharge were negative.

Deaths

Three patients (6.4%) died during emergency surgery. These deaths were due to haemorrhagic shock that caused severe, sudden hypotension. Nineteen patients (40.4%) died in hospital following the emergency treatment, after a mean of 4.5 days (range, 1-14 days).

The causes of death are shown in Tables III and IV. Instrumental and diagnostic tests such as computed tomography scans revealed no complications following the administration of PCC. The high mortality rate in this study was due mainly to the old age of the patients (the mean age of the patients who died was 78.5 years) associated with a clinical situation compromised by the severity of the

Table II - Treatment characteristics between patients receiving acenocoumarol or warfarin.

	Acenocoumarol (group A, 14/23 pts)	Warfarin (group A, 9/23 pts)	Acenocoumarol (group B, 14/24 pts)	Warfarin (group B, 10/24 pts)
INR at admission: mean (range)	2.81 (2.19-4.67)	2.52 (1.56-4.09)	6.45 (1.83-N.C.)	5.78 (1.73-N.C.)
INR after PCC: mean (range)	1.44 (1.04-1.83)	1.43 (1.15-1.83)	1.99 (1.27-3.13)	1.81 (0.91-4.33)
Single administration of PCC	14//14 (100%)	6/9 (66.7%)	12/14 (85.7%)	9/10 (90%)
Two administrations of PCC	0/14 (0%)	3/9 (33.3%)	2/14 (14.3%)	1/10 (10%)
Patients treated with vitamin K	5/14 (35.7%)	1/9 (11.1%)	4/14 (28.6%)	2/10 (20%)
Patients treated with FFP	5/14 (35.7%)	4/9(44.4%)	6/14 (42.8%)	1/10 (10%)
Patients treated with FFP + Vit K	1/14 (7.1%)	1/9 (11.1%)	1/14 (7.1%)	0/10 (0%)
Patients needing RBC before PCC	0/14 (0%)	2/9 (22.2%)	7/14 (50%)	3/10 (30%)
Patients needing RBC after PCC	1/14 (7.1%)	1/9 (11.1%)	3/14 (21.4%)	1/10 (10%)

N.C.: not coagulable.

Table III - Cause and day of death.

Patients	Group	Cause of death	Day of death after PCC
01	A	Cardiopulmonary arrest	5
03	B	Severe hypotension during surgery	0
06	A	Cardiopulmonary arrest	14
07	B	Severe hypotension during surgery	0
08	B	Cardiopulmonary arrest	6
09	B	Acute myocardial infarction	3
10	B	Irreversible coma, followed by cardiopulmonary arrest	3
12	B	Cardiopulmonary arrest	7
17	A	Heart failure	2
18	A	Irreversible coma, followed by cardiopulmonary arrest	9
19	B	Severe hypotension	1
20	B	Heart failure	3
21	A	Irreversible coma, followed by cardiopulmonary arrest	3
24	A	Cardiopulmonary arrest	12
27	A	Irreversible coma, followed by cardiopulmonary arrest	3
30	A	Cardiopulmonary arrest	5
31	B	Heart failure and gastrointestinal sepsis	1
36	B	Irreversible coma, followed by cardiopulmonary arrest	1
38	B	Severe hypotension and sepsis in patient with respiratory insufficiency	2
44	A	Sudden cardiopulmonary arrest	3
46	B	Severe hypotension during surgery	0
47	A	Irreversible coma, followed by cardiopulmonary arrest	2

Table IV - Deaths and bleeding.

Group	Deaths related to bleeding	Deaths not related to bleeding	Alive patients
A	4 (17.4%)	6 (26.1%)	13 (56.5%)
B	5 (20.8%)	7 (29.2%)	12 (50%)
Total (A+B)	9 (19.1%)	13 (27.7%)	25 (53.2%)

haemorrhage, which did not allow recovery of normal vital functions, and to delayed haemostatic treatment.

Discussion

OAT is an effective, safe and inexpensive method used in the prevention and treatment of thromboembolic complications in patients with cardiovascular diseases[5]. Because this therapy prolongs the time for clotting to occur, the risk of haemorrhage and bleeding increases in patients on OAT, especially in the elderly[8,9,16,17]. Reduced synthesis of vitamin K-dependent coagulation factors, along with massive bleeding due to the OAT, causes an acquired deficiency of prothrombin complex factors, which prevents normal haemostasis. Although the American College of Chest Physicians guidelines[13] recommend the use of rFVIIa and some studies have demonstrated the effectiveness of this drug in the treatment of critical bleeding[18,19], for the management of patients taking vitamin K antagonists with spontaneous or trauma-induced bleeding, other published guidelines do not recommend its routine use due to "insufficient safety data and lack of information on appropriate dose"[16].

French[12] and Italian[15] guidelines consider PCC the most appropriate product to reverse the effects of vitamin K antagonists. These concentrates provide prompt restoration of haemostasis and the start of coagulation[12,20]. As shown in some studies, both PCC and rFVIIa reverse warfarin anticoagulation, but only PCC restore overall thrombin generation and are more effective than rFVIIa in restoring haemostasis[21,22].

All PCC contain coagulation factors II, VII, IX and X, but if the amount of FVII is very low, the concentrates are considered as three-factor PCC; conversely if the amount of FVII is normal these products are considered as four-factor PCC. Published studies have been conducted on both these types of concentrates. The efficacy and safety of three-factor PCC shown by Imberti *et al.*[23] was contradicted by the study by Holland *et al.*[24] The major difference between the two studies was the patients' baseline INR, which was moderately elevated in the Italian study (mean,

3.5), but very high in the Canadian study (mean, 8.6). This might suggest that three-factor PCC are not very effective in the case of high INR, although our study, albeit with some limitations, showed that even in the case of high baseline INR, such as in the group B patients (mean, 6.58), a three-factor PCC was effective in stopping bleeding and restoring haemostasis. Pabinger[10], Schick[25], Bruce[8], Roddie[26] and their colleagues reported the efficacy of four-factor PCC, but also described four cases of venous thromboembolism. Can it be assumed, therefore, that four-factor PCC are less safe than three-factor PCC? The four cases of venous thromboembolism reported in literature occurred in patients at high risk of venous thromboembolism after a high dose of PCC (40-100 IU/Kg). Therefore, as also affirmed by Makris *et al.*[27], it is impossible to correlate, with absolute certainty, the occurrence of a thrombotic event with the type of PCC infused. Comparative studies between three- and four-factor PCC are needed to determine whether there are differences in efficacy and safety between the tywo types.

In our study, in accordance with guidelines and published studies, physicians who decided to reverse excessive anticoagulation used three-factor PCC. In this study data from 47 consecutive patients were collected over the last 2 years. The baseline characteristics of the patients in this study were similar to those of the studies reported by Imberti *et al*.[23] and Tran *et al*.[28], but the mean age was higher than that of the patients in the studies by Schick *et al*.[25] and Bruce *et al*.[8] The number of patients enrolled in our study was comparable to the number in several other studies,[23,28] although our cohort was larger than that in the study by Bruce *et al*.[8] Most of the patients in our study were being treated with OAT for atrial fibrillation; other treatment indications were heart diseases (mechanical valve or ischaemic cardiomyopathy) and previous venous thromboembolism. The INR and vital signs were checked before treatment and were monitored during the post-operative course.

Particular attention was paid to the control of possible adverse reactions caused by the administration of PCC[29]. Three cases of thrombosis after the use of PCC were reported by Roddie *et al*.[26]; Pabinger *et al*.[10] described only one case of venous thromboembolism, but in these studies a high dose of PCC (40-100 IU/Kg) was administered to patients with multiple risk factors for thrombosis. The dose of PCC in our study, like that of Viguè *et al*.[30] in which patients were treated at hospitalisation with a bolus of PCC 10 IU/Kg, as in our study, was very low compared to the dose used in the study by Imberti *et al*.,in which patients received a dose of 35-50 IU/Kg, stratified according to initial INR[23]. In our study the risk of venous thromboembolism led physicians to use a low dose of PCC, but we do not think that this was the main cause of the high mortality. Computed tomography scanning performed after treatment showed resolution of cerebral haemorrhages and laboratory tests confirmed, in most patients, a satisfactory recovery of haemostasis. The deaths occurred due to a sudden worsening of the clinical and neurological state in elderly patients in whom treatment had not been prompt. Published guidelines recommend monitoring the INR within 30 minutes after the administration of PCC, but in our study, because the first measurement of INR after treatment was performed at different times for each patient, it was not possible to determine correlations among INR decrease, amount of PCC used and efficacy.

Hanslik *et al.*[31] confirmed the recommendations of international guidelines, establishing that the administration of intravenous vitamin K 10 mg is the first step to take to reverse the effects of oral anticoagulants in patients with massive haemorrhage and a high INR, but in our case, only 25.5% of patients received this therapy, a value that differs substantially from that in other studies[10,24,30], in which vitamin K was infused into 52% to 88% of patients. In the study performed by Imberti *et al.*[23] all patients received vitamin K, but that was a prospective study, unlike our retrospective, observational study.

The present study revealed that, in the absence of a shared protocol, the guidelines are not always applied correctly and consistently, and that variability in treatment often depends on the clinical experience of each physician. If bleeding does not stop and haemostasis is not restored, the guidelines recommend administered FFP or PCC. FFP is often used in such cases, but the ideal dosage to obtain a significant result is unknown[32] and the possibility of volume overload, especially in the elderly, must be considered. In our study 34% of the patients received FFP, but all patients receiving FFP also needed PCC to reverse

anticoagulation. Only 6.4% of patients required administration of vitamin K, FFP and PCC. In the case of major haemorrhage or when the haemoglobin concentration is below 8.0 g/dL, it is recommended that red blood cells are administered: 25.5% of our patients were give red blood cell transfusions at hospitalization.

In this study no significant differences were found between patients treated with acenocoumarol or warfarin.

The mortality rate in other published studies ranged between 10% and 28%[23,28,33]. In our study 46.8% of the patients died, similar to the rate in the study by Bruce *et al*.[8] In most cases, death was caused by serious head trauma, which produced fatal intracranial bleeding, or by severe spontaneous intracranial haemorrhage, which induced a state of irreversible coma in the anticoagulated elderly patients and subsequent cardiopulmonary arrest. A delay in the administration of therapy, underdosing of PCC and incorrect use of vitamin K may also have been factors contributing to the high number of deaths.

In our retrospective study we observed a discrepancy between the published guidelines on the management of patients on vitamin K antagonists with critical haemorrhage and the actual use of PCC in the different wards of our hospital. The management of these patients was often based only on the experience of the treating physicians rather than on the application of local protocols. In this way, the patients' management becomes subjective, leading to inappropriate therapeutic variability.

Conclusions

In our retrospective, observational study PCC were effective and safe in rapidly reversing OAT and remain an important medical opportunity for the clinicians, although their use did not always follow international or national guidelines. Indeed, the dose, time of administration and INR monitoring were often different from those recommended. In the light of the findings of this study, we suggest that an internal protocol for the correct use of PCC should be produced and delivered to all wards.

Given that the sample of patients was small and did not allow us to make a comparison with a control group, we also suggest that further comparative studies with more subjects are necessary to determine the real efficacy and safety of PCC in several branches of medicine.

Limitations

In this retrospective study we had some difficulty in recovering all data: the medical records often lacked information, such as a full medical history, family history or cause of death. A post-mortem examination was performed in only four patients (18.2%), while in several cases death was reported as due to cardiopulmonary arrest.

Another limitation of our study concerns the time of the first INR monitoring after administration of PCC. Although we can certainly state that the use of PCC is very important for lowering the INR into the range of normality, the lack of INR monitoring at fixed intervals after the beginning of a PCC infusion prevented us from determining variations of INR over time and the rate of change of INR values.

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Received: 16 March 2011 - Revision accepted: 4 May 2011
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