

Emergency Oral Anticoagulant Reversal: The Relative Efficacy of Infusions of Fresh Frozen Plasma and Clotting Factor Concentrate on Correction of the Coagulopathy

Mike Makris¹, Mike Greaves², Wendy S. Phillips¹, Steve Kitchen¹, Frits R. Rosendaal³,
F. Eric Preston¹

From the ¹University Department of Haematology, Royal Hallamshire Hospital, Sheffield, UK,
²Department of Medicine and Therapeutics, University of Aberdeen, UK and
³Department of Clinical Epidemiology, Leiden University Hospital, Leiden, The Netherlands

Summary

Haemorrhage, including intracranial bleeding, is a common, potentially lethal complication of warfarin therapy and rapid and complete reversal of anticoagulation may be life-saving. Fresh frozen plasma (FFP) and vitamin K are most frequently administered. Because of the variable content of vitamin K-dependent clotting factors in FFP, and the effects of dilution, the efficacy of this approach is open to doubt. We have therefore compared the effects of FFP and clotting factor concentrates on the INRs and clotting factor levels of orally anticoagulated subjects requiring rapid correction of their haemostatic defect. In many, the pre-treatment INR was considered to be dangerously above the target therapeutic range. In the 12 patients given FFP, the INR did not completely correct (range 1.6-3.8, mean 2.3) indicating an ongoing anticoagulated state in all. In contrast, the INR in 29 subjects given clotting factor concentrates was completely corrected in 28 (range 0.9-3.8, mean 1.3). Following treatment, marked differences were observed in clotting factor IX levels between the two groups. The median factor IX level was 19 u/dl (range 10-63) following FFP infusion and 68.5 u/dl (range 31-111) following concentrate. In FFP treated patients, poorer responses were also observed for each of the other vitamin K-dependent clotting factors but these were less marked than for factor IX, which was present in low concentrations in some batches of FFP. Thus, haemostatically effective levels of factor IX cannot be achieved, in most instances, by the conventional use of FFP in patients requiring reversal of their anticoagulant therapy. Clotting factor concentrates are the only effective option where complete and immediate correction of the coagulation defect is indicated in orally anticoagulated patients with life or limb-threatening haemorrhage.

Introduction

The therapeutic value of oral anticoagulants for the treatment of acute venous thromboembolism is well established. More recently, the demonstration of their value as thromboprophylactic agents has resulted in an expansion in use, especially for stroke prevention, in subjects with atrial fibrillation and in the secondary prevention of myocardial in-

farction. World-wide, the number of individuals receiving warfarin is increasing rapidly.

Optimal oral anticoagulant dosage regimens reflect a balance between the antithrombotic effects of these drugs and their unwanted haemorrhagic side effects. Haemorrhage is a common, important and potentially lethal complication of oral anticoagulant therapy (1-3). Logic dictates that rapid and complete reversal of the anticoagulant effect could be life-saving in the case of intracranial haemorrhage.

There are surprisingly few studies of the clinical and haematological efficacy of the various therapeutic options for the treatment of serious bleeding episodes in overanticoagulated patients, or where rapid reversal of oral anticoagulation is otherwise required, and there are no clearly validated guidelines for the management of these patients.

In this study we have attempted to provide a rational basis for the reversal of overanticoagulation with blood products by comparing the effect of fresh frozen plasma (FFP) and clotting factor concentrates on the clotting factor abnormalities of overanticoagulated patients who had serious haemorrhage, or in those in whom there was an urgent clinical requirement for reversal of the anticoagulated state.

Patients and Methods

Forty-one patients, 15 males and 26 females, aged 21-88 years were studied. All were admitted into the Royal Hallamshire Hospital, Sheffield during the period 1991-1994 for the management of haemorrhage directly attributable to, or complicated by, oral anticoagulants, or for urgent reversal of their warfarin therapy. In all instances, immediate reversal of oral anticoagulant therapy was considered necessary by the admitting clinical team. Clotting factor concentrates were administered to 29 patients considered to have life-threatening haemorrhage or who required urgent anticoagulant reversal. These comprised 16 cerebral/spinal bleeds, 5 gastrointestinal bleeds with shock, 4 intra-abdominal bleeds, and 4 others. Data were also available on 12 similar subjects who received fresh frozen plasma (FFP).

FFP was supplied by the Trent Regional Blood Transfusion Service. Patients allocated to receive this product were each given 4 units (approximately 800 ml) intravenously.

Clotting factor concentrates were obtained from two manufacturers. Before 1993, patients received a prothrombin complex concentrate (9A, BPL, UK, which contains factors II, IX, X) and also, a specific factor VII concentrate (BPL, UK). Subsequently, Prothromplex T (Immuno, Vienna), which contains clotting factors II, VII, IX and X, was used. Sixteen patients received Prothromplex T and 13 received the BPL products. The dose administered, for both 9A and Prothromplex T, was based on the factor IX content of the product and was approximately 25-50 units factor IX/kg estimated body weight. This was

Correspondence to: Professor F. E. Preston, University Department of Haematology, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK - Tel.: +44 114 271 2062; FAX Number: +44 114 275 6126

Table 1 Changes in the vitamin K-dependent clotting factors and INR following the administration of approximately 800 ml FFP in warfarin-treated patients. All clotting factor values in iu/dl

Patient	Factor II		Factor VII		Factor IX		Factor X		INR	
	pre	post	pre	post	pre	post	pre	post	pre	post
1	3	12	5	12	4	12	0	20	15.3	2.8
2	1	14	18	42	17	32	2	20	6.2	1.8
3	4	21	0	26	0	21	0	23	20	2.3
4	17	33	33	47	47	63	13	27	2.9	1.7
5	2	14	7	15	6	10	9	17	11.1	2.0
6	3	12	3	9	12	19	6	18	17.1	3.4
7	11	16	24	27	22	36	10	24	3.4	2.0
8	30	29	65	59	62	62	10	22	3.1	1.9
9	8	19	2	9	9	13	18	29	10.1	3.8
10	3	17	5	25	10	20	2	15	7.8	2.5
11	1	19	5	19	6	13	1	18	22	2.0
12	-	-	-	-	-	-	-	-	3.7	1.6
Median	3	17	5	19	10	19	6	20	8.95	2.0
Range	1-30	12-33	0-65	9-59	0-62	10-63	0-18	15-29	2.9-22	1.6-3.8

predicted to elevate plasma factor IX level by 25-50 iu/dl. Patients treated with factor VII concentrate received 20-30 units/kg.

All patients received intravenous vitamin K, 1-5 mg. For the concentrate recipients this was administered simultaneously with blood product replacement. For those receiving FFP, vitamin K was given after administration of the FFP and simultaneously with sampling for the second INR estimation, i.e. 15 min after completion of the FFP infusion.

In all instances the INR was determined immediately before treatment and at approximately 15 min after completion of the replacement infusion.

In addition to the INR determinations, assays for the vitamin K-dependent clotting factors II, VII, IX and X were performed in 14 patients who received clotting factor concentrates and in 11 patients who received FFP. Standard one-stage methods were employed. Prothrombin times for INR determination were performed using a rabbit brain thromboplastin (Instrumentation Laboratory; ISI approximately 1.2).

The relationship between INR and factor IX levels was studied in 25 patients who received either FFP (n = 11) or clotting factor concentrates (n = 14). Only pre-treatment values were included. In order to examine the relationship in greater detail, factor IX levels were also determined in an additional 19 plasma samples from anticoagulated patients attending an anticoagulant clinic.

The association between INR determination and factor IX level was assessed by linear regression, with factor IX level as the dependent (y-axis) and INR as the independent (x-axis) variable. A possible difference between the two groups of patients, i.e. those who did not receive FFP and those who did, was studied by entering group (0, 1) as a second independent variable. The results of the regression analysis are expressed in the regression coefficients, with 95% confidence intervals and significance tests based on the standard errors of these coefficients.

Finally, the concentrations of factors II, VII, IX and X were determined in 20 different batches of FFP, supplied by the Trent Regional Blood Transfusion Service.

Results

Coagulation Responses to FFP

The mean pre-treatment INR of the 12 patients who received FFP was 10.2 (range 2.9-22.0). Fifteen min post FFP infusion the mean INR was 2.3 (range 1.6-3.8).

The vitamin K-dependent clotting factors II, VII, IX and X were determined before and after treatment in 11 FFP recipients. Median pre-treatment values were 3.0, 5.0, 10.0 and 6.0 u/dl respectively. Corresponding values after treatment with FFP were 17.0, 19.0, 19.0 and 20.0 u/dl. Full details are presented in Table 1.

Coagulation Responses to Clotting Factor Concentrates

The mean pre-treatment INR of the 29 concentrate recipients was 5.8 (range 2.2-20). Fifteen min post-infusion the mean INR was 1.3 (range 0.9-3.8). Clotting factors II, VII, IX and X were also determined before and after treatment in 14 concentrate recipients. Median pre-treatment values were 15.0, 23.0, 35.5 and 14.5 u/dl respectively. Corresponding values after treatment with clotting factor concentrates were 50.0, 74.0, 68.5 and 72.0 u/dl. Full details of the responses are presented in Table 2.

There was no clinical or haematological evidence of disseminated intravascular coagulation in any of the treated patients.

Relationship between INR and Factor IX Levels

In patients treated with warfarin and who had not received replacement therapy (Fig. 1) the INR clearly predicted the factor IX concentration ($\beta = -2.80$, CI 95% -3.6 to -1.9) i.e. factor IX = 45.33 - 2.8 × INR. In patients who had received FFP we observed an association in the same direction ($\beta = -14.95$) which, however, was not significant ($p = 0.09$). After investigating INR as a predictor of factor IX in the two groups of patients separately we set up a regression model with both INR and patient group as predictor variables. This analysis allows us to assess, for a given INR, the association between patient treatment group and factor IX levels. When the patient group was entered into the analysis, this itself proved to be a significant predictor of the factor IX concentration ($p = 0.04$). The relationship between INR and factor IX levels for the two groups is therefore significantly different. The mean FIX level in patients prior to anticoagulant reversal was 26.45 u/dl and the mean INR was 6.73 compared to post-FFP treatment where the mean FIX was 27.36 u/dl and the mean INR was 2.38. Thus for almost identical factor IX levels in the pre and post-treatment patients the equivalent INRs were very different.

Patient	Factor II		Factor VII		Factor IX		Factor X		INR	
	pre	post	pre	post	pre	post	pre	post	pre	post
1	-	-	23	130	62	90	28	96	2.3	1.1
2	18	100	19	84	37	111	7	95	3.3	1.0
3	10	68	23	84	23	65	14	86	4.0	1.2
4	26	87	23	68	55	92	19	68	2.4	1.2
5	16	51	11	36	20	31	20	43	2.9	1.4
6	7	100	32	105	36	89	5	94	4.3	1.0
7	26	52	19	41	54	67	20	45	2.2	1.3
8	13	65	26	72	41	75	0	62	3.4	1.1
9	12	75	27	76	35	70	7	76	4.0	1.0
10	0	50	2	37	5	31	3	49	14	1.4
11	25	81	39	113	23	62	20	58	2.9	1.3
12	32	112	33	92	40	87	15	84	2.5	1.1
13	0	94	0	50	6	46	0	84	14	1.3
14	15	59	1	19	28	46	16	68	9.7	1.4
Median	15	50	23	74	35.5	68.5	14.5	72	3.35	1.2
Range	0-32	50-112	0-39	19-130	5-62	31-111	0-28	43-96	2.2-14.0	1.0-1.4

Table 2 Changes in the vitamin K-dependent clotting factors and INR following the administration of prothrombin complex concentrate to warfarin-treated patients. All clotting factor values in iu/dl

Clotting Factor Concentrations in FFP

The range and median concentrations of clotting factors II, VII, IX and X in 20 batches of FFP was 53-121 (82.5), 41-140 (92.0), 32-102 (61.0) and 61-150 (90.5) u/dl respectively. The median volume of the batches was 200 ml (range 150-237 ml). The factor IX concentration of 5 of the 20 batches of FFP was below the lower limit of the normal range for our laboratory (62 u/dl).

Discussion

There is a growing number of indications for oral anticoagulant therapy and more individuals are receiving these drugs. Antithrombotic benefits need to be considered against the risk of bleeding, since life-threatening haemorrhage, and particularly intracranial haemorrhage, is a frequent complication (4). This risk has recently been quantitated by van der Meer and his colleagues (3), in 6800 patients. Haemorrhagic complications occurred at a rate of 16.5 per 100 treatment-years. The frequency of major bleeds was 2.7 per 100 treatment-years. Haemorrhagic complications increased significantly with age and showed a relationship with increasing INR. More recently, in a case-control study designed to explore the rational use of oral anticoagulants, particularly in the elderly (4), the risk of intracranial haemorrhage was shown to rise dramatically when the prothrombin time ratio, expressed as an INR equivalent, exceeds 4.0. Based on these data, Hylek and coworkers (4) concluded that an INR greater than 4.0 carries an absolute risk of intracranial haemorrhage of 2% per year. It is not always appreciated that there is a markedly increased age-related sensitivity to oral anticoagulants (5, 6), and with increasing use of these agents in the elderly, one can confidently predict an increasing number of hospital admissions and a requirement for effective, rapid reversal of the coagulopathy.

Although serious and potentially life-threatening haemorrhage is a well recognised complication of oral anticoagulant therapy there are few studies which have compared the efficacy of methods of anticoagulation reversal and there are no universally acceptable guidelines for the emergency treatment of overanticoagulated patients. For this reason we have compared the effects of fresh frozen plasma and clotting factor concentrates on the INR and plasma levels of individual vitamin K-dependent clotting factors of patients admitted into hospital for reversal of their anticoagulant therapy. Although not a randomised study of clinical outcome, the mode of treatment was determined by the preference of the managing clinician in each case, thus allowing an analysis of the effects of the two treatments on blood coagulation.

The mean pre-treatment INR of the patients receiving FFP was greater than that of the group receiving concentrates because the latter group included patients whose anticoagulation control was initially satisfactory but for whom urgent anticoagulant reversal was required on account of head injury or unrelated emergency surgery. The infusion of FFP resulted in a significant reduction of the mean pre-treatment value of 10.2 to a mean post-treatment value of 2.3. In comparison, following the administration of clotting factor concentrates the mean pre-treatment INR of 5.8 was corrected to a mean value of 1.3. If complete correction of the coagulopathy is considered to be advantageous, clearly this is more likely to be achieved by the use of concentrates.

The INR system of monitoring oral anticoagulant control is based on the prothrombin time test, introduced by Quick in 1935 (7). This test is sensitive to reductions of the vitamin K-dependent clotting factors II, VII and X but not to a reduction of factor IX. We have demonstrated an inverse curvilinear relationship between INR (Fig. 1) and factor IX in warfarin-treated subjects with levels of factor IX falling below 40 u/dl

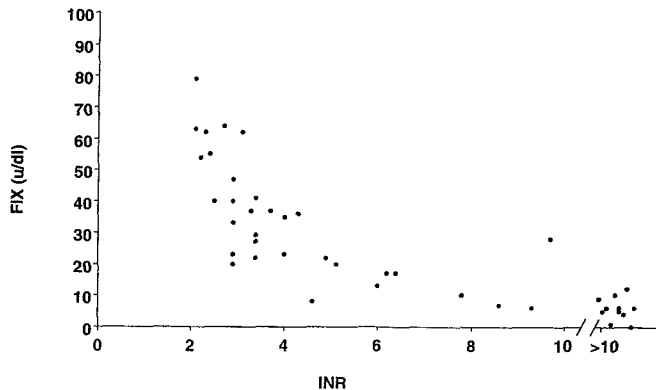


Fig. 1 Relationship between INR and factor IX levels in patients anticoagulated with warfarin

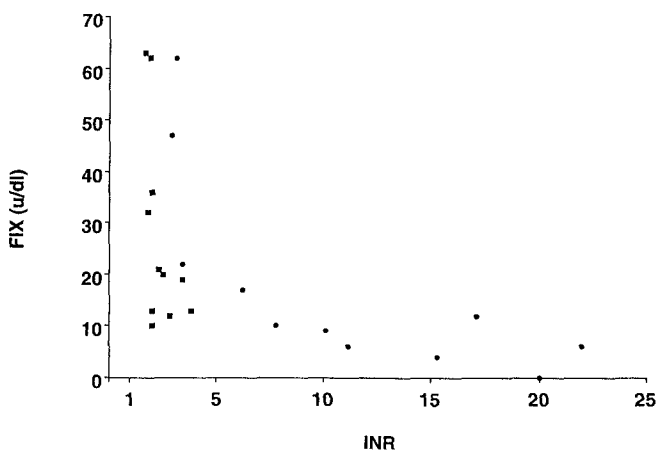


Fig. 2 Relationship between INR and factor IX levels in warfarin-treated subjects following treatment with FFP. Circles represent values prior to FFP administration and squares represent values following FFP

as the INR exceeds 3.0. Also, our data show that in anticoagulated patients, the INR predicts the plasma factor IX level. This relationship is significantly altered and the relationship no longer holds when patients are treated with FFP (Fig. 2). The INR system of reporting oral anticoagulant control is designed specifically for stably anticoagulated patients, and is an inappropriate test following replacement therapy with either plasma or clotting factor concentrates. Following the administration of plasma, the determination of an INR alone therefore provides an inadequate assessment of the haemostatic defect. This is clearly illustrated by this study in that the reasonably satisfactory correction of the INR, by plasma, was not accompanied by a similar correction of factor IX, further supporting the use of concentrates in this situation.

Although it is generally acknowledged that major differences exist between the effective haemostatic concentrations of different clotting factors, for most, precise information on this is scanty. Exceptions are clotting factors VIII and IX, experience of which has been gained through treatment of patients with haemophilia A and B respectively. For both of these disorders, urgent restoration of the clotting factor defect to normal values is considered mandatory in life-threatening haemorrhagic situations (8). Clearly it is not logical to apply different therapeutic principles to acquired factor IX deficiency. In respect of factor IX, it is well established that a dose of 1 μ /kg body weight is required to elevate plasma factor IX levels by 1 u/dl (8). 800 ml of FFP

with a factor IX concentration of 61 u/dl would therefore yield 488 iu factor IX. The calculated increase in factor IX in a 70 kg adult would therefore be approximately 7 u/dl. This is close to the median increment of 9.0 u/dl which was observed in the eleven patients who received FFP. The results described here in patients receiving fresh frozen plasma are therefore similar to those based on calculations which apply to the recovery of factor IX in subjects with haemophilia B. If the same therapeutic principles are applied to overanticoagulated patients as to those with haemophilia B it is clear that the reversal of factor IX levels in overanticoagulated patients by fresh frozen plasma is not usually possible where the INR is greater than 5.0. An increase in the volume of FFP administered, in the emergency situation, could be unsafe and would not have an effect comparable to infusion of concentrate. The haemostatic response to FFP is influenced by plasma dilution and also by the clotting factor concentration of the infused plasma. It is noteworthy that the concentration of factor IX in each of the twenty different batches of FFP was the lowest of any of the four vitamin K-dependent clotting factors with a median factor IX concentration of only 61 u/dl. This compares with 82.5, 92.0, and 90.5 u/dl for the other vitamin K-dependent clotting factors.

Our results in anticoagulated patients are similar to those obtained by Mannucci and co-workers in 1979 (9), who compared the relative effects of fresh frozen plasma and prothrombin complex concentrates in correcting the haemostatic defect in patients with chronic liver disease. These workers also reported that a dose of 12 ml/kg body weight FFP was relatively ineffective in correcting the haemostatic defect and although they did not assay the factor IX concentration of the FFP, the recovery of this clotting factor, and also that of the other vitamin K-dependent factors was similar to that described by ourselves.

It could be argued that the concentrate-related clotting factor responses were influenced by vitamin K which was given simultaneously and approximately 20 min earlier than in the plasma-treated patients. Since effective correction of the coumarin effect by intravenous vitamin K is achieved only after some hours and since the measured clotting factor responses to concentrates were close to the predicted values, we believe that the influence of vitamin K on our findings has been negligible.

Although clotting factor concentrates are more effective than plasma in reversing the haemostatic defect of oral anticoagulants their use is not without potential hazard. Currently, prothrombin complex concentrates are being replaced by high purity factor IX products for the treatment of subjects with haemophilia B. The main impetus for this change is thromboembolism which is now recognised as a complication of these products (10). Although venous thromboembolism is an undoubted complication of prothrombin complex concentrates the magnitude of this risk remains to be established since in individuals with haemophilia B, the occurrence of thrombosis has been confined to situations where other mechanisms of coagulation activation are operating. These include major surgery and trauma. Over many years PCCs have been used extensively for the treatment of subjects with haemophilia B and apart from the above mentioned situations we are unaware of any reports of thrombosis complicating the routine use of these products.

We have demonstrated that the near correction of the INR in overanticoagulated patients by plasma is potentially misleading in that it

provides no information in respect of factor IX, the concentration of which is only minimally increased by this treatment. In clinical situations where reversal of the oral anticoagulant effect is an urgent priority, it is clearly not feasible to await results of individual clotting factor assays. In view of the very low levels of this clotting factor in subjects with an INR in excess of 5.0 it is clear that fresh frozen plasma is of extremely limited efficacy in the correction of the coagulopathy in overanticoagulated patients with serious bleeding necessitating reversal of anticoagulation. It therefore follows that, in the absence of data from a controlled trial with clinical outcome measures, in life-threatening situations the use of clotting factor concentrates, not plasma, is indicated. The advantage of complete and immediate reversal of the coagulopathy is likely to result in clinical benefit in this emergency situation. We would therefore recommend that all hospitals treating subjects with oral anticoagulants should retain stocks of appropriate clotting factor concentrates for emergency use. In view of the potential thrombotic risk of this material, we would advocate caution in the dose of product used. Although there has been a very great improvement in the viral safety of clotting factor concentrates, pharmacovigilance should be maintained.

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