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# Rapid reversal of oral anticoagulation with warfarin by a prothrombin complex concentrate (Beriplex): efficacy and safety in 42 patients

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**Summary.** Beriplex, a prothrombin complex concentrate (PCC), was administered to 42 patients requiring immediate reversal of their oral anticoagulant therapy. The dose administered was determined using the pretreatment International Normalized Ratio (INR). Blood samples were obtained before treatment and at 20, 60 and 120 min after treatment. The following investigations were performed on all samples – INR, clotting factors II, VII, IX and X, coagulation inhibitors protein C (PC) and antithrombin (AT), and other markers of disseminated intravascular coagulation, plasma fibrinogen, D-dimer and platelet count. Immediate reversal of the INR, the vitamin K-dependent clotting factors and PC was achieved in virtually all patients. Reduced AT levels were present in 18 patients before treatment. Further slight AT reductions occurred in four patients, but other associated abnormalities of haemostasis were observed in only one of the four patients. One patient with severe peripheral vascular disease, sepsis and renal and cardiac failure died of a thrombotic stroke following leg amputation, 48 h after receiving Beriplex. No other arterial and no venous thromboembolic events occurred within 7 d of treatment. Beriplex is effective in rapidly reversing the anticoagulant effects of warfarin, including PC deficiency, without inducing coagulation activation. Caution should continue to be exercised in the use of these products in patients with disseminated intravascular coagulation, sepsis or liver disease.

**Keywords:** Beriplex, prothrombin complex concentrates (PCC), warfarin, overanticoagulation, oral anticoagulation.

For patients receiving oral anticoagulant therapy, there are a number of clinical circumstances that necessitate rapid anticoagulant reversal. The most important indications are spontaneous life-threatening haemorrhage, trauma, particularly when associated with head injury, and prior to emergency surgery. We have previously demonstrated that, in situations in which complete and immediate correction of the oral anticoagulant effect is indicated, clotting factor concentrates are the only effective therapeutic option (Makris *et al*, 1997). However, a potential disadvantage of the use of these products is their associated thromboembolic risk (Lusher, 1991). For this reason, prothrombin complex concentrates (PCC) should be used with caution.

In this study we have evaluated the efficacy and safety of Beriplex P/N (Aventis, UK), a PCC, in 42 patients requiring immediate reversal of their oral anticoagulation with warfarin.

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## PATIENTS AND METHODS

Forty-two warfarinized patients, 26 men and 42 women, aged 26–83 years (median 70 years) were studied. All were admitted into the Northern General or Royal Hallamshire Hospitals, Sheffield, during the period 1998–2001. A unified clinical and laboratory haematology service is provided for both hospitals. Each patient was considered by the admitting clinical team to require immediate reversal of his or her oral anticoagulant therapy. This was the only criterion for entry into the study. Patients were excluded if they were: (a) under 18 years of age; (b) pregnant; (c) had disseminated intravascular coagulation (DIC), evidenced by hypofibrinogenaemia, thrombocytopenia and elevated D-dimer; (d) known to be hypersensitive to plasma proteins; and (e) known to have hepatic dysfunction. Apart from the above exclusion criteria there was no selection of patients who were, wherever possible, entered consecutively into the study.

The clinical indications for oral anticoagulant reversal were: gastrointestinal haemorrhage (17), post head injury (5), subdural haematoma (5), miscellaneous spontaneous haemorrhage (5), emergency surgery (5), post trauma (2),

miscellaneous causes (3), acute pancreatitis (1), acute abdomen and suspected intracranial haemorrhage (1).

Ethical approval for the study was obtained from the Central Sheffield University Hospitals (CSUH) Trust. Written, informed consent was obtained from all patients who were able to provide this. The Ethics Committee provided written approval to include those patients too ill to give prospective consent and who ultimately died before consenting.

The PCC used in the study was Beriplex P/N (Aventis, UK). Beriplex P/N 250 contains clotting factors II (320 IU), VII (170 IU), IX (250 IU) and X (380 IU). It also contains protein C (300 IU). Viral inactivation and elimination is by pasteurization and nanofiltration. The dose of Beriplex was based on the factor IX content of the product and was determined according to the pretreatment International Normalized Ratio (INR), as indicated in Table I.

Twenty patients received 25 u/kg, 12 patients received 35 u/kg and 10 patients received 50 u/kg Beriplex. One patient with mechanical heart valves and with an INR > 6·0 received 35 u/kg Beriplex on account of concerns expressed by the cardiologists in respect of valve-related thrombosis.

All patients received 2–5 mg of intravenous vitamin K given simultaneously with the Beriplex. Blood samples were taken before and 20, 60 and 120 min after treatment.

The following tests were performed on each sample: INR, clotting factors II, VII, IX and X, protein C (PC), antithrombin (AT), D-dimer, plasma fibrinogen, thrombin time and platelet count. Prothrombin times for INR determinations were performed using PT Fib HS-plus rabbit brain thromboplastin in combination with a Futura instrument (Instrumentation Laboratory Ltd, UK) and an instrument-specific International Sensitivity Index (ISI) and a locally derived mean normal prothrombin time. Standard one-stage clotting assays of factors II, VII and X were performed using PT Fib HS-plus. One-stage factor IX assays were performed using kaolin/platelet substitute (Diagnostic Reagents Ltd, Oxford, UK) with 5-min activation and 0·025 mol/l calcium chloride. All assays were determined with the ACL instrument using three dilutions of test plasma and human-deficient plasma (Precision Biologic, Canada). Assays were calibrated using three dilutions of a commercial reference material calibrated against World Health Organization (WHO) International Standards. Protein C was determined by chromogenic assay using Protac (Pentapharm, Switzerland) as an activator of PC. AT was determined by its' ability to inhibit bovine thrombin in the presence of excess heparin in a chromogenic assay (Dade-Behring, Milton Keynes, UK). Both AT and PC assays were calibrated using multiple dilutions of the 8th British Standard for Blood Coagulation Factors (NIBSC, Potters Bar, UK) and determined using a CA6000 coagulometer (Sysmex, Milton Keynes, UK). D-dimer was determined by agglutination of latex beads coated with antibody to D-dimer.

**Table I.** Beriplex dosage and factor IX content determined by pretreatment Internationalized Normal Ratio (INR).

| INR | Dose (u/kg factor IX) |
|---|---|
| 2·0–3·9 | 25 |
| 4·0–6·0 | 35 |
| > 6·0 | 50 |

All infusions were completed within 10 min.

The Haemostasis Laboratory participates satisfactorily in the UK National External Quality Assessment Scheme (UKNEQAS) in respect of all investigations reported in this study.

When the study was initially conceived, the primary aims were to determine the rate of correction of the warfarin-induced coagulopathy and to establish whether there was associated coagulation activation and DIC. Following completion of the study, but before clinical events had been analysed, it was decided to include arterial and venous thrombovascular events. A decision was taken to report arterial thrombovascular events which occurred within 48 h of treatment with Beriplex and within 7 d for mortalities and venous thrombovascular events. The information was derived from inspection of the clinical records and also hospital discharge letters, death certificates and autopsy findings.

## RESULTS

### *Inr*

The median (range) pretreatment INR was 3·98 (2·0–27·6). Complete INR correction (< 1·3) was achieved in 20 min in 33 patients. The remaining nine patients had INRs of 1·30–1·90, 20 min after receiving Beriplex. The INR responses to the three-dosage regimens are presented in Fig 1.

### *Factor II*

The median (range) pretreatment factor II was 0·08 iu/ml (0·01–0·32). The 20-min post-treatment levels were 0·84 iu/ml (0·34–1·18).

### *Factor VII*

The median (range) pretreatment factor VII was 0·15 iu/ml (0·03–0·49). The 20-min post-treatment levels were 0·43 iu/ml (0·25–1·05).

### *Factor IX*

The median (range) pretreatment factor IX was 0·23 iu/ml (0·04–0·86). The 20-min post-treatment levels were 0·80 iu/ml (0·44–1·37).

### *Factor X*

The median (range) pretreatment factor X was 0·08 iu/ml (0·02–0·23). The 20-min post-treatment levels were 0·98 iu/ml (0·38–1·5).

### *Protein C*

Normal PC concentrations were achieved at 20 min in 36 of the 42 patients. The median (range) pretreatment PC was

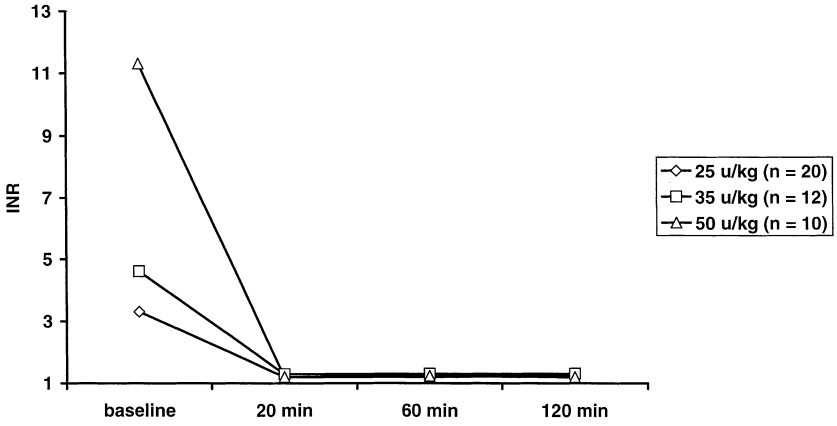


**Fig 1.** Correction of the International Normalized Ratio (INR) by three different doses of Beriplex.

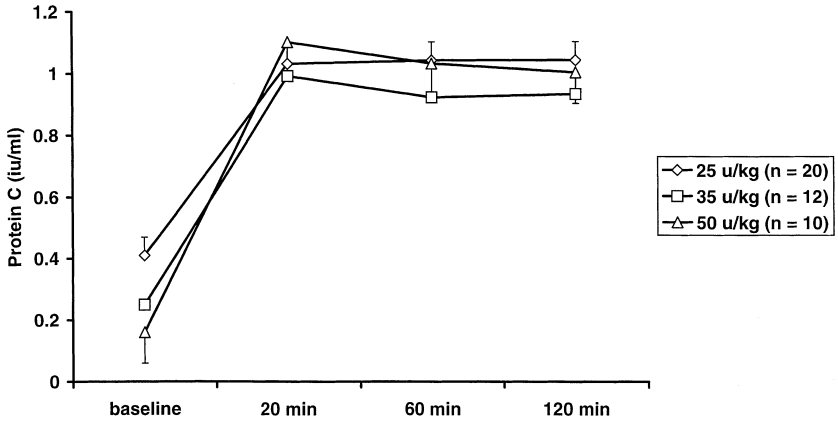


**Fig 2.** Increase in Protein C following three different doses of Beriplex.

0·30 iu/ml (0·01–0·80). The 20-min post-treatment levels were 1·04 iu/ml (0·44–1·86). The protein C responses to the three-dosage regimens are presented in Fig 2.

*Antithrombin*

On admission and before treatment with Beriplex, AT levels were below the lower limit of the reference range for our laboratory (< 0·84 iu/ml) in 24/42 patients. Following treatment, AT levels remained unchanged in 38/42 patients at all time points. The median (range) pretreatment AT was 0·80 iu/ml (0·36–1·17). At 60 min the levels were 0·78 iu/ml (0·34–1·08) and at 120 min 0·76 iu/ml (0·36–1·18).

In four patients, pretreatment AT levels fell from 0·78, 0·72, 0·80 and 0·77 iu/ml to 0·63, 0·57, 0·53 and 0·57 iu/ml at 120 min post treatment respectively. For three of these patients, the reduction in AT level was not accompanied by a corresponding fall in platelet count or in plasma fibrinogen concentration and there was no increase in D-dimer. In the fourth patient, the reduction in AT concentration from 0·77 iu/ml to 0·45 iu/ml was recorded 20 min after treatment with 25 u/kg Beriplex and this was accompanied by a fall in plasma fibrinogen from 3·16 to 1·81 g/l. At that time, both platelet count and D-dimers were normal, but at 120 min the platelet count fell slightly from 194 to 168 $\times 10^9$/l and the D-dimer concentration rose slightly from < 200–375 ng/ml. This patient was also receiving Hespan (hydroxyethyl starch) and there were no adverse clinical events.

With respect to the three doses of Beriplex, no differences were observed in AT levels at the different time points after treatment (Fig 3).

*D-dimer*

D-dimer levels remained unchanged for 120 min following treatment with Beriplex. The median (range) pretreatment D-dimer was < 250 ng/ml (< 200–3000). At 60 min the levels were < 250 ng/ml (< 250–4000) and at 120 min < 250 ng/ml (< 250–4000). Before treatment with Beriplex, five patients had D-dimer levels greater than 1000 ng/ml. These levels remained unchanged following treatment with Beriplex.

With respect to the three doses of Beriplex, no significant differences were noted in D-dimer levels at the different time points after treatment (Fig 4).

*Plasma fibrinogen*

The median (range) pretreatment plasma fibrinogen concentration was 3·97 g/l (1·4–8·0). At 60 min the median concentration was 3·5 g/l (1·3–7·31) and at 120 min it was 3·48 g/l (2·0–8·01). Before treatment, two patients had a plasma fibrinogen concentration that was below the lower

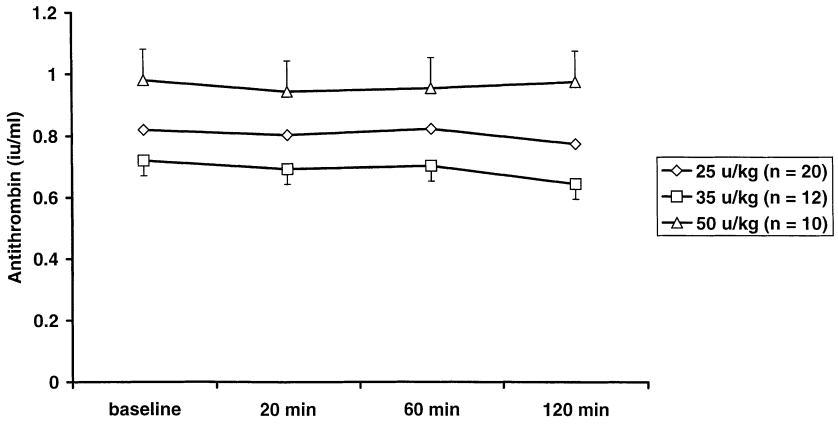


**Fig 3.** Antithrombin levels after three different doses of Beriplex.

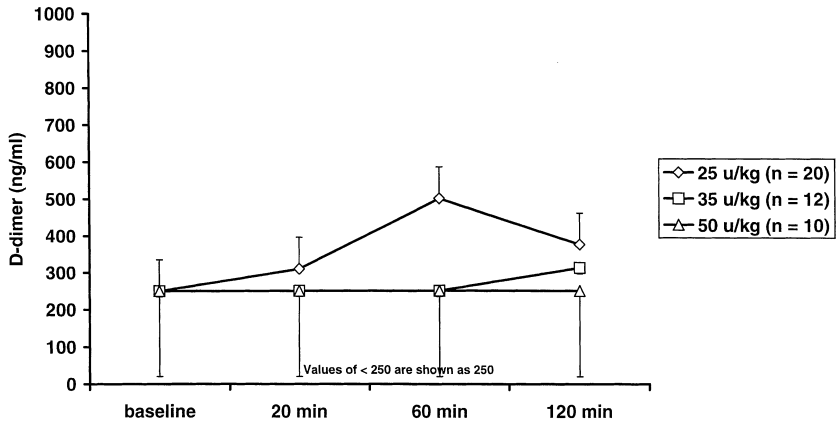


**Fig 4.** D-dimer levels after three different doses of Beriplex.

limit of our adult reference range (< 1·8 g/l). In these two patients the plasma fibrinogen levels remained unchanged following treatment with Beriplex. At 120 min, hypofibrinogenaemia was not observed in any of the patients.

With respect to the three doses of Beriplex, no differences were noted in plasma fibrinogen concentrations at the different time points after treatment.

*Platelet counts*

On admission and before treatment with Beriplex, the median platelet count was $251 \times 10^9$/l (111–573). Sixty minutes after treatment the median platelet count was $235 \times 10^9$/l (112–439) and at 120 min $224 \times 10^9$/l (108–479). When analysed with respect to the individual treatment regimens, a significant reduction ($P < 0{\cdot}01$) was observed in the median platelet counts at 60 and 120 min (260 and $258 \times 10^9$/l respectively) compared with the pretreatment value of $313 \times 10^9$/l, in patients treated with 35 u/kg Beriplex. Median platelet counts remained unchanged following treatment with 25 and 50 u/kg Beriplex.

Four patients had thrombocytopenia ($< 150 \times 10^9$/l) on admission. Further significant reductions in the platelet counts were not observed following treatment with Beriplex. At 60 min, four patients were mildly thrombocytopenic. In none of these was the platelet count $< 110 \times 10^9$/l and three of the four patients were mildly thrombocytopenic before treatment (platelet counts $111–145 \times 10^9$/l). No further reduction in these platelet counts was observed at 120 min and other tests for possible DIC remained unchanged.

*Clinical outcomes*

There was no clinical evidence of DIC in any of the patients treated with Beriplex. Eight patients died within 7 d of being treated with Beriplex. Clinical details are as follows:-

1. One man died of a thrombotic stroke 48 h after receiving Beriplex. The treatment was given to permit emergency leg amputation. At the time of treatment he also had severe sepsis and both cardiac and renal failure.

2. A 79-year-old woman was admitted unconscious into hospital. She was receiving warfarin for atrial fibrillation and had sustained a head injury approximately 1 week before she was discovered unconscious in bed on the morning of her admission into hospital. A computerized tomography (CT) scan revealed a large subdural haematoma which was considered by Neurosurgeons to be not amenable to neurosurgical intervention. Warfarin was discontinued and its' effect reversed by Beriplex. She died 3 d later. At autopsy there was no evidence of arterial or venous thromboembolism.

3. A 76-year-old woman was admitted into hospital on account of back pain and haematuria. She was receiving

warfarin on account of having had an aortic and mitral valve replacement. On admission her INR was 11·1 and her haemoglobin was 8·6 g/dl. A retroperitoneal bleed was suspected and she was treated with Beriplex. She died 4 d after admission of congestive cardiac failure. At autopsy there was no evidence of arterial or venous thromboembolism.

4. A 61-year-old man was admitted into hospital on account of breathlessness and lethargy 4 weeks after undergoing aortic and mitral valve replacement. Five days after admission he became pyrexial with rigors. Blood cultures confirmed staphylococcal septicaemia. He failed to respond to antibiotic and other supportive therapy and, while on the coronary care unit (CCU), developed acute neurological deterioration. His INR was discovered to be 11·0 and this was reversed by Beriplex. He failed to recover and died approximately 24 h later. Death was certified as (1) staphylococcal septicaemia and (2) valvular disease of the heart (operated).

5. A 79-year-old man was admitted into hospital with a 3-d history of severe abdominal pain. He had two cardiac arrests in the ambulance and a further cardiac arrest in the Accident and Emergency Department. He was extremely ill with a blood pressure of 71/38. An abdominal CT scan revealed acute pancreatitis and his INR was discovered to be 7·7. He continued to deteriorate and died 5 h after admission of acute pancreatitis.

6. An 83-year-old man was admitted into hospital with severe gastrointestinal haemorrhage from a large duodenal ulcer. He was found to be in acute renal failure. Despite successful INR reversal and resuscitation, he died from acute renal failure 2 d after admission.

7. A 70-year-old woman with a prosthetic heart valve was admitted after a fall with head injury and haemarthrosis. She stabilized after INR reversal. Two days later she suffered an asystolic cardiac arrest. Autopsy confirmed severe coronary atheroma and a chronically scarred myocardium. There was no evidence of acute arterial or venous thromboembolism.

8. A 71-year-old man underwent carotid endarterectomy. Post-operatively while fully anticoagulated with warfarin, he developed severe hypertension and had a massive intracerebral bleed. Despite rapid reversal of his INR, his condition deteriorated and he died 4 d later of intracerebral haemorrhage.

## DISCUSSION

In recent years the clinical indications for oral anticoagulant therapy have increased and, worldwide, many more patients are now receiving coumarins for both therapeutic and thromboprophylactic purposes. Despite the widespread adoption of INR monitoring for oral anticoagulant control, bleeding continues to be a serious complication of coumarin therapy. van der Meer *et al* (1993) reported 16·5 bleeding complications per 100 patient years, including 2·7 major bleeds per 100 patient years. More recently, following a prospective cohort study in Italian patients, Palareti *et al* (1996) reported 7·6 bleeding complications per 100 patient years, including 1·1 major bleeds per 100 patient years. Both studies observed an increased risk of bleeding with increasing INR and higher bleeding rates with increasing age. Intracranial haemorrhage is a particularly serious complication of oral anticoagulant therapy and occurs in 0·25–1·1% of patients per year (Butler & Tait, 1998).

It is therefore clear that there is a need for effective therapeutic regimens for oral anticoagulant reversal, particularly when clinical circumstances demand a rapid response. In this respect, we have recently reported the inadequacies of fresh-frozen plasma and have demonstrated the potential value of prothrombin complex concentrates (PCCs) (Makris *et al*, 1997).

A potential and important drawback to the routine use of PCCs for oral anticoagulant reversal is their known association with thromboembolism (Lusher, 1991). Kasper (1973) reported postoperative thrombophlebitis, thrombosis and pulmonary embolism in patients with haemophilia B following treatment with PCCs and, in 1975, a Task Force of the International Society for Thrombosis and Haemostasis (ISTH) reported the occurrence of DIC pulmonary embolism and acute myocardial infarction in haemophilia B patients receiving PCC treatment (Kasper, 1975). More recently, and before the introduction of high purity factor IX concentrates for the treatment of haemophilia B, the number of reports of PCC-related thrombosis has declined. It seems likely that this relates to improved quality of the products (Prowse & Cash, 1981).

The thrombogenicity of PCCs remains the subject of debate. There is evidence that this might relate to the presence of activated clotting factors in the products (Gray *et al*, 1995; Philippou *et al*, 1996), but imbalance between the procoagulant factors II and X on the one hand and inhibitors PC and PS on the other may be important (Köhler *et al*, 1990; Köhler, 1995).

In this study, and in order to detect clinically relevant coagulation activation, indicative of DIC, we elected to perform serial platelet counts, D-dimer, a specific marker of plasmin-mediated fibrinolysis of cross-linked fibrin, plasma fibrinogen and antithrombin assays.

A surprising observation was the occurrence of low AT activity, detected in 50% of patients in the study and before treatment with Beriplex. Acquired AT deficiency is usually a manifestation of hepatic dysfunction or DIC. On admission we did not perform detailed investigations of hepatic function, but it would seem highly unlikely that 50% of unselected warfarinized patients had clinically relevant liver disease. Although DIC is the more likely explanation for the low AT levels observed in this group of patients, the abnormal values were not accompanied by thrombocytopenia, hypofibrinogenaemia or elevated D-dimers, i.e. other laboratory markers of DIC. We are therefore unable to provide a convincing explanation for this observation.

Irrespective of the cause of the antithrombin deficiency, and apart from changes that occurred in a single patient, the administration of Beriplex was not accompanied by any further reductions in the AT levels, and plasma fibrinogen and D-dimer concentrations remained unchanged for the entire period of follow up.

In one patient, AT fell from a pretreatment level of 0·77 iu/ml to 0·45 iu/ml at 20 min. This was accompanied by a similar reduction in plasma fibrinogen but without an increase in D-dimer. We cannot exclude the possibility that these changes reflect genuine coagulation activation, but haemodilution is another possible explanation for the observed parallel reductions in AT and plasma fibrinogen levels as the patient was receiving intravenous hydroxyethyl starch at the time of testing.

Although treatment with 35 u/kg Beriplex resulted in a significant fall in the platelet count, the post-treatment counts remained within the normal range and were unaccompanied by other laboratory markers of DIC. Importantly, platelet counts remained unchanged in patients treated with the other two doses of the concentrate, including those treated with the higher dose of 50 u/kg. We were unable to detect evidence of coagulation activation following any of the three doses of Beriplex used in this study.

One possible explanation for the apparent lack of coagulation activation by this product is its' high concentration of protein C (PC). PC is a vitamin K-dependent protein and, consequently, all patients had reduced levels before anticoagulant reversal. Following treatment with Beriplex, normal PC levels were achieved at 20 min in 36 of the 42 patients. PC, through its' activated form APC, is an important natural anticoagulant with extensive anti-inflammatory properties. In the coagulation system, APC reduces thrombin and therefore fibrin formation by inactivating the clotting factors Va and VIIIa. Serial studies of PC and its' plasma inhibitor in patients with DIC provide compelling evidence for a major modulatory role for PC in DIC (Marlar *et al*, 1985). The possibility exists therefore that, in the patients described in this report, PCC-induced coagulation activation was reduced or suppressed by the simultaneous correction of the acquired PC deficiency.

Many of the patients described in this study were both elderly and extremely ill when admitted into hospital. This is reflected by the eight deaths which occurred shortly after admission. A thrombotic event was observed in only one of these. We cannot exclude the possibility that in this patient Beriplex was a contributory factor, but he also had severe arterial thrombovascular disease, necessitating emergency leg amputation, severe sepsis and both renal and cardiac failure. An autopsy, performed in three of the remaining seven patients, failed to demonstrate either arterial or venous thromboembolism.

We believe that these results provide good evidence that, in the patient group described here, rapid reversal of the haemostatic effects of warfarin was achieved by treatment with Beriplex and that this was unaccompanied by laboratory evidence of coagulation activation and, more importantly, clinical thrombovascular disease. Caution should continue to be exercised in the use of this and similar products in patients known to have DIC, liver disease or other risk factors for thrombovascular disease.

The increased use of prothrombin complex concentrates for the reversal of oral anticoagulation will depend not only on their reduced thrombogenic potential but also on their viral safety. Although this study was not designed to assess viral safety, this has improved immeasurably over the past 15 years and the risk of viral transmission by these products currently approaches zero.

## ACKNOWLEDGMENT

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