Prothrombin complex concentrates (PCCs) containing coagulation factors II, IX, and X, with or without factor VII, have been used for years in the treatment of inherited coagulation factor deficiencies, particularly in factor IX deficiency [1, 2]. Furthermore, PCCs have been proposed as a substitution therapy in acquired coagulation factor deficiencies or as antagonists to warfarin-like anticoagulants [3–5]. With the widespread use of PCCs, an increasing amount of data on possible side effects has been published: the association with thromboembolic complications [6–8] and activation of the coagulation cascade [9–11] have led to a call for cautious use of PCCs. A survey of thromboembolic episodes during treatment with PCCs conducted by Jeanne Lusher on behalf of the International Society on Thrombosis and Hemostasis reported 72 cases between 1987 and 1990 [6]. Most of the data concerning thrombogenicity and activation of the coagulation cascade were based on laboratory experiments [12–14] or on small-scale clinical studies in hemophilia B patients [15–18]. Substitution of coagulation factors is a major concern in the intensive care setting. Critically ill patients frequently undergo invasive procedures while suffering from disturbances of plasma coagulation and are therefore at a higher risk of bleeding. Administration of PCCs seems more convenient than transfusion of fresh frozen plasma with regard to clotting time and to laboratory coagulation test values. However, the potential for thrombotic complications and activation of the coagulation cascade must be considered. A survey of thromboembolic episodes during treatment with PCCs conducted by Jeanne Lusher on behalf of the International Society on Thrombosis and Hemostasis reported 72 cases between 1987 and 1990 [6]. Most of the data concerning thrombogenicity and activation of the coagulation cascade were based on laboratory experiments [12–14] or on small-scale clinical studies in hemophilia B patients [15–18]. Substitution of coagulation factors is a major concern in the intensive care setting. Critically ill patients frequently undergo invasive procedures while suffering from disturbances of plasma coagulation and are therefore at a higher risk of bleeding. Administration of PCCs seems more convenient than transfusion of fresh frozen plasma with regard to clotting time and to laboratory coagulation test values. However, the potential for thrombotic complications and activation of the coagulation cascade must be considered.

**Abstract**

**Objective:** To evaluate thrombogenicity of prothrombin complex concentrates (PCCs) in critically ill patients.

**Design:** Prospective clinical study.

**Setting:** Medical intensive care unit at a university hospital.

**Patients:** 16 consecutive patients suffering from acquired deficiencies of coagulation factors and with either overt bleeding from any site or a planned invasive procedure.

**Interventions:** 2000 factor IX units of PCCs intravenously.

**Measurements and results:** Prothrombin time (PT), activated partial prothrombin time, fibrinogen, platelet count, plasma levels of coagulation factors II, VII, VIII, IX, X, antithrombin, protein C, thrombin-antithrombin complex (TAT), prothrombin fragment F1+2, and the fibrin degradation product D-dimer were measured prior to and 1, 3, and 24 h after administration of PCCs. PT as well as coagulation factors II, VII, IX, and X, TAT, and F1+2 showed a significant increase after administration of PCCs. All other parameters remained unchanged.

**Conclusions:** Administration of PCCs induces thrombin generation. No evidence for induction of disseminated intravascular coagulation in biochemical terms could be found. When rapid correction of acquired coagulation factor disturbances is warranted, the use of PCCs seems reasonable, but the elevated risk of intravascular thrombus formation should be kept in mind.

**Key words** Prothrombin complex concentrates · Thrombogenicity · Intensive care · Disseminated intravascular coagulation

**Introduction**

Prothrombin complex concentrates (PCCs) containing coagulation factors II, IX, and X, with or without factor VII, have been used for years in the treatment of inherited coagulation factor deficiencies, particularly in factor IX deficiency [1, 2]. Furthermore, PCCs have been proposed as a substitution therapy in acquired coagulation factor deficiencies or as antagonists to warfarin-like anticoagulants [3–5]. With the widespread use of PCCs, an increasing amount of data on possible side effects has been published: the association with thromboembolic complications [6–8] and activation of the coagulation cascade [9–11] have led to a call for cautious
to volume overload and speed of administration. On the other hand, the fear of inducing thrombotic complications or consumption coagulopathy has led many intensivists to adopt a cautious attitude toward substitution of coagulation factors. In vivo data on the use of modern PCC preparations in patients suffering from acquired coagulation factor deficiencies are limited; prospective studies investigating the effects of PCCs on coagulation activation in critically ill patients especially are missing. We therefore conducted a prospective study on the influence of PCCs on coagulation parameters in critically ill patients suffering from coagulation factor deficiency due to inadequate hepatic synthesis, in whom overt bleeding or the necessity of invasive procedures made substitution of coagulation factors necessary.

Patients and methods

The study was performed between November 1997 and June 1998 according to the guidelines of the local ethical review board. Patients were eligible if the prothrombin time, expressed as a percentage of normal, was < 50% of a normal plasma pool (thromboplastin time) and bleeding from any site was present or an invasive diagnostic or therapeutic procedure involving the risk of bleeding, i.e., implantation of intravascular catheters or a biopsy, was planned. The exclusion criteria were planned surgery during the study period, heparin therapy, and clinically overt disseminated intravascular coagulation (DIC). Since molecular markers to diagnose DIC rapidly are not part of the hospital routine yet, we chose a definition of DIC based on clinical judgment and routine laboratory parameters for inclusion: presence of a clinically apparent thrombohemorrhagic disorder and a decrease in platelet count of more than $40 \times 10^{9}$/l and/or fibrinogen of more than 50 mg/dl within 24 h.

Sixteen consecutive patients admitted to the intensive care unit (10 males, 6 females, median age 57 years, range 23–67 years) were enrolled in the study. Baseline laboratory data were collected from routine laboratory testing on the day of inclusion and Acute Physiology and Chronic Health Evaluation III scores were calculated after admission to the intensive care unit by using the worst available values during the first 24 h in the unit according to Knaus et al. [19]. Hemoglobin levels were kept above 8.0 g/dl by transfusion of packed red blood cells. None of the patients received heparin, derivatives from human blood plasma, or inhibitors of fibrinolysis, like aprotinin, during the study period. Additional therapy consisted of mechanical ventilation in 14 patients, substitution of crystalloid fluid in all patients, broad-spectrum antibiotic therapy in 12 patients, and vasopressor therapy in 5 patients. None of the patients underwent extracorporeal circulation during the study. Patients' characteristics and baseline laboratory findings are given in Table 1.

First, 2000 factor IX units (i.e., four packages) of a commercially available PCC (Beriplex P/N, Centeon, Marburg, Germany) were reconstituted from the lyophilisate according to the manufacturer's guidelines. In this preparation, virus elimination is provided by pasteurization and nanofiltration [20]. According to the manufacturer, a package contains 640 IU of coagulation factor II, 340 IU of factor VII, 500 IU of factor IX, 760 IU of factor X, 600 IU of protein C, 8–40 IU of heparin, 4–30 IU of antithrombin, 40–80 mg human albumin as well as sodium chloride and sodium citrate. The preparation was administered over 60 min via a perfusor syringe. Blood samples were drawn prior to administration, immediately afterwards, and 3 and 24 h later. All blood samples were drawn from separate venous puncture sites. For coagulation tests, blood was collected into trisodium citrate, for platelet counting into ethylenediaminetetraacetic acid. Blood was centrifuged immediately after being drawn at 3000 U/min for 30 min at 4 °C and then stored at −70 °C until work-up. The following parameters were assessed at all time points: prothrombin time (PT), partial prothrombin time (aPTT), fibrinogen, platelet count, plasma levels of coagulation factors II, V, VII, VIII, IX, X, antithrombin, protein C, thrombin-antithrombin complex (TAT), prothrombin fragment F_1+2, F_2, and D-dimer. PT (Normotest, Nycomed, Oslo, Norway) and aPTT (PathoTest, Behring, Marburg, Germany) were measured using a KC-10 coagulometer (Amelung, Liemle, Germany). The patient sensitivity index of the thromboplastin used for PT determination was 0.89, the correction factor was 0.10. Coagulation factors II, V, VII, VIII, IX, and X were measured using factor-deficient plasmas [21] (Behring, Marburg, Germany for coagulation factors II, V, VII, and X; Immuno, Vienna, Austria for coagulation factors VIII and IX). Antithrombin levels were determined by a chromogenic method (Bierichrom, Behring, Marburg, Germany), protein C levels were assessed by enzyme-linked immunosorbent assay (ELISA) (Asserachrom Protein C, Roche, Vienna, Austria). TAT, F_1+2, and D-dimer were assessed by ELISA using commercially available kits (Behring, Marburg, Germany for TAT and F_1+2, and Boehringer, Mannheim, for D-dimer). Fibrinogen was assessed according to the Clauss method, platelets were counted in a counting chamber. To correct for the dilution of plasma by citrate, the values obtained for plasma protein activities were recalculated after correction for the hematocrit according to the following formula proposed by Seligsohn et al. [22]:

Correction factor = (hematocrit + 11.1)/hematocrit.

All data are shown as mean ± SD except when indicated otherwise. Difference over time course and between single time points were

### Table 1

| Patient characteristics. Values are number of patients and mean ± SD (ARDS: adult respiratory distress syndrome, CPR: cardiopulmonary resuscitation) |
|---|
| **Diagnoses** | |
| Peritonitis | 1 |
| CPR | 3 |
| Sepsis | 2 |
| Hepatic failure | 4 |
| Major thoracic surgery | 1 |
| ARDS | 1 |
| Pneumonia | 4 |
| **Indication for substitution** | |
| Gastrointestinal bleeding | 4 |
| Postoperative bleeding | 4 |
| Dialysis catheter implantation | 5 |
| Transbronchial biopsy | 2 |
| Intracranial bleeding | 1 |

| **Baseline characteristics** | |
| Age (years) | 48 ± 16 |
| Body weight (kg) | 72 ± 44 |
| APACHE III admission score | 46 ± 28 |
| Fibrinogen (mg/dl) | 399 ± 236 |
| Platelet count (× 10⁹/l) | 156 ± 116 |
| Hemoglobin (g/dl) | 9.5 ± 1.9 |
| Albumin (g/l) | 27 ± 8 |
| Bilirubin (mg/dl) | 2.7 ± 2.8 |

Note: Table 1 includes patient characteristics and baseline laboratory findings.
Table 2 Laboratory findings. (Values are mean ± SD. Values in parentheses are hematocrit corrected (PT prothrombin time, aPTT partial thromboplastin time, Hb hemoglobin, AT antithrombin, F coagulation factor, TAT thrombin-antithrombin complex, F$_{1+2}$ prothrombin fragment F$_{1+2}$))

|                      | Time point |               |               |               | Sig. *          |
|----------------------|------------|---------------|---------------|---------------|----------------|
|                      | 0          | 1             | 3             | 24            |                |
| PT (s)               | 35 ± 8     | 26 ± 5 b      | 27 ± 5 b      | 29 ± 6        | p < 0.0001     |
| aPTT (s)             | 44 ± 7     | 38 ± 7        | 46 ± 7        | 37 ± 8        | NS             |
| Platelets (× 10^9/l) | 156 ± 116  | 154 ± 104     | 149 ± 116     | 161 ± 124     | NS             |
| Hb (g/dl)            | 9.5 ± 1.9  | 9.1 ± 2.3     | 9.6 ± 1.5     | 9.4 ± 1.6     | NS             |
| Fibrinogen (mg/dl)   | (590 ± 200)| (590 ± 210)   | (590 ± 310)   | (590 ± 330)   | NS             |
| AT (%)               | 57 ± 36    | 57 ± 32       | 56 ± 40       | 54 ± 44       | NS             |
| Protein C (%)        | (80 ± 51)  | (82 ± 52)     | (80 ± 54)     | (68 ± 44)     |                |
| F II (%)             | (50 ± 14)  | (110 ± 42) b  | (88 ± 24) b   | (56 ± 18) b   | p < 0.0001     |
| F VII (%)            | (32 ± 8)   | (61 ± 20) b   | (54 ± 16) b   | (44 ± 12) b   | p < 0.0001     |
| F VIII (%)           | (45 ± 14)  | (86 ± 28) b   | (74 ± 24) b   | (65 ± 25) b   |                |
| F IX (%)             | (14 ± 12)  | (15 ± 12)     | 12 ± 8        | 10 ± 4        | NS             |
| F X (%)              | (20 ± 18)  | (21 ± 20)     | (17 ± 14)     | (18 ± 11)     |                |
| F VII (%)            | (32 ± 48)  | (43 ± 32) b   | (40 ± 36)     | 19 ± 12       | p < 0.001      |
| F XII (%)            | (44 ± 63)  | (60 ± 42) b   | (54 ± 46)     | (45 ± 39)     |                |
| F VIII (%)           | (81 ± 40)  | (94 ± 44)     | 81 ± 40       | 83 ± 64       | NS             |
| F IX (%)             | (112 ± 56) | (132 ± 58)    | (110 ± 55)    | (111 ± 65)    |                |
| F X (%)              | (83 ± 74)  | (125 ± 86) b  | (99 ± 61)     | (93 ± 42)     |                |
| TAT (ng/ml)          | 19.4 ± 18.0| 28.2 ± 21.6 b | 29.2 ± 23.6 b | 24.8 ± 36.4 b | p < 0.001      |
| F$_{1+2}$ (nmol/l)   | 2.5 ± 1.6  | 10.3 ± 6.4 b  | 6.3 ± 4.8 b   | 3.8 ± 1.6 b   | p < 0.0001     |
| D-dimer (µg/ml)      | 5.9 ± 7.6  | 6.3 ± 8.8     | 6.6 ± 10.0    | 8.9 ± 10.0    | NS             |

a p values denote statistically significant differences over time course calculated by Friedman ANOVA.

b Statistically significant differences compared to baseline calculated by a one-way nonparametric repeated measures test (Friedman analysis of variance). A p value < 0.05 was regarded as statistically significant.

Results

All patients completed the study. Bleeding, indicated by hemoglobin levels, ceased in all cases. No bleeding complications occurred during any of the invasive procedures. No further substitution of human blood plasma derivatives, coagulation factors, or inhibitors of fibrinolysis like aprotinin was necessary during the study period. Three patients received 2 units of packed red blood cells each. In none of the patients were clinically overt thromboembolic events observed. The laboratory findings are listed in Table 2. PT, protein C, as well as coagulation factors II, VII, IX, and X, showed a significant increase after administration of PCCs. Moreover, TAT and F$_{1+2}$ increased significantly after administration of PCCs. All of these parameters decreased toward baseline within 24 h. aPTT, fibrinogen, platelet count, hemoglobin levels, antithrombin levels, coagulation factors V and VIII, and D-Dimer levels did not change significantly. The statistical results remained unchanged after correction for plasma dilution (Table 2).

Discussion

In our study, a dose of 2000 factor IX units of a PCC (mean of 30 U/kg body weight) was sufficient to normalize PT by raising the plasma levels of coagulation factors II, VII, IX, and X in patients with moderately reduced coagulation activity. We used a fixed dose of 2000 factor IX units as a very practical therapeutic approach. Based upon the calculations provided by the manufacturer, a dose of 1 IU/kg body weight of PCCs should raise the PT by 1% in terms of percent of normal. The PT decreased from a mean of 35 s to 26 s, i.e., an increase from 46 to 77%. The expected mean increase in our patients with a mean weight of 72 kg would have been 28%, the measured mean increase was 31%. Thus, the increase in PT very closely approached the ex-
performed rapidly. The separation and administration of PCCs is easy and can be performed rapidly. Patients suffering from cardiac failure. In contrast, preparation and administration of PCCs is easy and can be performed rapidly.

The effect of normalizing plasma coagulation, as indicated by PT, was still observed after 3 h and values had returned close to baseline within 24 h. The finding that a “time window” of more than 3 h after administration of PCC allows interventions under the condition of a normalized plasma coagulation seems to be important to clinicians for scheduling invasive procedures. Interestingly, aPTT, which was marginally elevated at baseline, normalized after infusion of PCCs but returned to baseline within 3 h. The kinetics of factors VIII and IX do not explain this observation; ongoing fibrinolysis can be excluded by stable levels of D-dimer. As the time course of aPTT did not reach statistical significance, the observed differences might as well have occurred by chance.

Our data on the correction of abnormal laboratory parameters suggest that the substitution of coagulation factors in patients suffering from acquired coagulation factor deficiencies seems to be an easy and effective way in emergency situations. However, both venous and arterial thromboembolic events have been attributed to the use of PCCs [6, 8, 23–26]. Moreover, induction of DIC was associated with administration of PCCs [11]. The exact causes of thrombogenicity associated with PCC therapy are not completely understood. Concentrates may contain activated coagulation factors and coagulant-active phospholipids, which might lead to an imbalance between procoagulant and anticoagulant pathways of hemostasis in the plasma [28–31]. Repeated high doses of PCCs could lead to supranormal values of not deficient coagulation factors, thus contributing to a hypercoagulable state [29, 32]. Modern PCC preparations like the one used in our study contain only small amounts of activated coagulation factors, especially factors VIIa and IXa, which seem to be important mediators of PCC-associated thrombogenicity [16, 33]. In a comparison of various PCC preparations, the one used in our study was found to contain relatively small amounts of activated factor VII [34]. No thromboembolic episodes were observed in our patient population; however, our study had far too few patients and was not designed to assess clinical endpoints as the incidence of thromboembolic complications. Most complications were reported in association with repeated high doses of PCCs and concomitant risk factors like major surgery or crash injuries, and the use of aprotinin [35–37].

With respect to laboratory findings on activation of plasma coagulation, we observed a significant increase in F1+2 and TAT. F1+2 is a measure of the cleavage of prothrombin by activated factor X being released from the amino-terminal portion of the molecule during its conversion to thrombin. Elevated levels, therefore, indicate intravascular thrombin formation. The same is true for TAT, which is formed by inhibition of thrombin by antithrombin in the case of thrombin formation [38]. Although the elevated levels of F1+2 after infusion of PCCs were in part attributed to a certain amount of F1+2 present in reconstituted PCCs [18], the amount of the increase observed in our study and the concomitant increase in TAT levels make the exogenous administration of a large amount of F1+2 unlikely [17]. The observed increase in both TAT and F1+2 thus indicates in vivo thrombin generation and the presence of a prethrombotic state. A prethrombotic state can be defined as an imbalance in hemostasis with a tendency to hypercoagulability due to an activation of enzymes of the coagulation cascade without clinical signs of thrombosis or laboratory evidence of fibrin deposits [39, 40]. In biochemical terms, an increase in the enzymatic activity of factor Xa in thrombin formation (reflected by the elevation of F1+2 and TAT levels) defines a prethrombotic state [40].

Since the coagulation cascade obviously was activated by infusion of PCCs, does this resemble DIC? According to the definition of DIC as a dynamic process involving thrombin and fibrin formation, DIC consists of (1) consumption coagulopathy leading to depletion of coagulation factors enhancing the risk of bleeding complications, (2) fibrinolysis, which could further aggravate bleeding, and, on the other hand, (3) hypercoagulopathy [41, 42]. Consumption coagulopathy and fibrinolysis may be present to different extents and do not necessarily parallel hypercoagulopathy. Thus, hypercoagulopathy without evidence of coagulation factor consumption and/or fibrinolysis may be a prodromal state of DIC, but in many cases resembles a prethrombotic or hypercoagulable state [41]. In our patients, a short peak of elevated markers indicating activation of the coagulation system leading to thrombin formation was observed, but neither prolonged consumption of thrombin nor a parallel increase in fibrinolytic activity could be found. D-dimer, a neoantigen formed as the result of plasmin digestion of cross-linked fibrin [43], had increased, though not significantly, after 24 h but did not change during the hours following the peak of TAT and F1+2. Moreover, neither consumption of an inhibitor (antithrombin) nor consumption of not substituted coagulation factors or platelets could be observed. Therefore, our results resemble the definition of a prethrombotic state rather than DIC, and we cannot derive induction
of DIC by PCC infusion from our data. These findings are consistent with the results of previous work comparing the thrombogenicity of PCCs with highly purified factor IX concentrates in hemophilia B patients [15, 17, 18].

Prophylactic administration of antithrombin has been proposed to avoid thromboembolic complications after administration of PCCs [37]. This approach, however, cannot yet be substantiated by prospectively acquired data. Since antithrombin has not been shown to exert clear-cut positive effects in other disease entities like DIC or perioperative prophylaxis of thrombosis [44], we do not think that it can be recommended yet as standard therapy.

Modern PCCs contain protein C in various amounts – in our preparation, 600 IU per package – thus patients received 2400 IU of protein C. Protein C is a natural anticoagulant and has been found to exert positive effects in patients suffering from severe consumptive coagulopathies, especially in DIC induced by meningococcal infections [45, 46]. The dose administered in those studies was considerably higher than that given to our patients, nevertheless protein C levels were raised to normal or supranormal levels in nearly all patients. We cannot tell from our data to what extent protein C as a component of PCCs can prevent thromboembolic complications. Although most reported complications with the use of PCCs occurred with the older preparations containing no or small amounts of protein C, some sporadic case reports on thromboembolic events involving “modern” PCC preparations containing anticoagulants suggest that these complications cannot be prevented completely by these ingredients [37]. Since studies comparing PCC preparations containing different amounts of protein C or antithrombin are lacking, the protective effect of such ingredients cannot be quantified yet.

To our knowledge, our data represent the results of the first prospective study on thrombogenicity of modern PCCs in critically ill patients with acquired coagulation factor deficiencies. The administration of PCCs efficiently corrected the laboratory signs of the coagulopathy. On the other hand, administration of PCCs induced thrombin generation with the biochemical signs of a prethrombotic state, which could involve the risk of clinically relevant intravascular thrombin formation and ensuing thrombosis. No evidence for induction of DIC was found. In situations when a rapid correction of deficiencies in vitamin K-dependent coagulation factors is indicated and administration of fresh frozen plasma seems unreasonable due to volume overload or time loss, administration of PCCs can be an effective therapy. However, use of the lowest effective dose and use of preparations known to contain small amounts of activated coagulation factors could be particularly beneficial in the light of intravascular thrombin formation. Knowledge about dosing, indications and possible risks associated with the use of PCCs, as well as careful monitoring of the patient to detect any thromboembolic episodes, should be mandatory.

References

1. Menache D (1981) Prothrombin complex concentrates: clinical use. Ann N Y Acad Sci 370: 747–756
2. Seremetis SV, Aledort LM (1993) Congenital bleeding disorders-rational treatment options. Drugs 45: 541–547
3. Prowse CV, Cash JD (1981) The use of factor IX concentrates in man: a 9-year experience of Scottish concentrates in the South-East of Scotland. Br J Haematol 47: 91–104
4. Bick RL (1975) Prothrombin complex concentrate: use in controlling the hemorrhagic diathesis in chronic liver disease. Dig Dis 20: 741–749
5. Staudinger T, Locker GJ, Frass M (1996) Management of acquired coagulation disorders in emergency and intensive care medicine. Semin Thromb Hemost 22: 93–104
6. Lusher JM (1991) Thrombogenicity associated with factor IX complex concentrates. Semin Hematol 28 [Suppl 6]: 3–5
7. Blatt PM, Lundblad RL, Kingdon HS, McLean G, Roberts HR (1974) Thrombogenic materials in prothrombin complex concentrates. Ann Intern Med 81: 766–770
8. Fürth JH, Mahrer P (1981) Myocardial infarction after factor IX therapy. JAMA 245: 1455–1456
9. Campbell EW, Neff S, Bowdler AJ (1978) Therapy with factor IX concentrate resulting in DIC and thromboembolic phenomena. Transfusion 18: 94–97
10. Lusher JM, Shapiro SS, Palaseck JE, Rao AV, Levine PH, Blatt PM (1981) Hazards of prothrombin complex concentrates in treatment of hemophilia. N Engl J Med 304: 671–678
11. Cederbaum AI, Blatt PM, Roberts HR (1976) Intravascular coagulation with the use of human prothrombin complex. Ann Intern Med 84: 683–687
12. Morfini M, Longo G, Berntorp E, Cinotti S, Filiberti E, Messeri A, Nilsson IM, Rossi Ferrini P (1993) Pharmacokinetics, thrombogenicity and safety of a double-treated prothrombin complex concentrate. Thromb Res 71: 175–184
13. Prowse CV, Boffa MC, Guthrie C, Pepper DS (1980) In vitro thrombogenicity tests of factor IX concentrates. Thromb Haemost 42: 1368–1377
14. Menache D, Behre HE, Orthner CL, Nunez H, Anderson HD, Triantaphyllopoulos DC, Kosow DP (1984) Coagulation factor IX concentrate. Method of preparation and assessment of potential in vivo thrombogenicity in animal models. Blood 64: 1220–1227
15. Hampton KK, Preston FE, Lowe GDO, Walker ID, Sampson B (1993) Reduced coagulation activation following infusion of a highly purified factor IX concentrate compared to a prothrombin complex concentrate. Br J Haematol 84: 279–284
16. Philippou H, Adami A, Lane DA, MacGregor IR, Tuddenham EGD, Lowe GDO, Rumley A, Ludlam CA (1996) High purity factor IX and prothrombin complex concentrate (PCC): pharmacokinetics and evidence that factor IXa is the thrombogenic trigger in PCC. Thromb Haemost 76: 23–28
17. Thomas DP, Hampton KK, Dasani H, Lee CA, Giangrande PLF, Harmann C, Lee ML, Preston FE (1994) A crossover pharmacokinetic and thrombogenicity study of a prothrombin complex concentrate and a purified factor IX concentrate. Br J Haematol 87: 782–788
18. Mannucci M, Bauer KA, Gringeri A, Barzegar S, Bottasso B, Simoni L, Rosenberg RD (1990) Thrombin generation is not increased in the blood of hemophilia B patients after the infusion of a purified factor IX concentrate. Blood 76: 2540–2545
19. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A (1991) The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest 100: 1619–1636
20. Römisch J (1995) Erhöhte Kapazität zur Eliminierung von Viren. Krankenhauspharm 16: 504–507
21. Giddings JC (1980) Hereditary coagulation disorders, laboratory techniques. In: Thomson JM (ed) Blood coagulation disorders, laboratory techniques. Churchill Livingstone, Edinburgh pp 117–157
22. Seligsohn U, Kasper CK, Osterud B, Rapaport SI (1979) Fatal myocardial infarction following therapy with prothrombin complex concentrates in a young man with hemophilia A. Pediatrics 74: 279–281
23. Chavin SL, Siegel DM, Rocco DA Jr, Olson JP (1988) Acute myocardial infarction during treatment with an activated prothrombin complex concentrate in a patient with factor VIII deficiency and a factor VIII inhibitor. Am J Med 85: 245–249
24. Teitel JM, Bauer KA, Lau HK, Rosenberg RD (1982) Studies of the prothrombin activation pathway utilizing radioimmunoassays for the F2/F1+2 fragment and thrombin-antithrombin complex. Blood 59: 1086–1097
25. Sullivan DW, Purdy LJ, Billingham M, Glader BE (1984) Fatal myocardial infarction following therapy with prothrombin complex concentrates in a young man with hemophilia A. Pediatrics 74: 279–281
26. Agrawal BL, Zelkowitz L, Hletko J
27. Chavin SL, Siegel DM, Rocco DA Jr, Olson JP (1988) Acute myocardial infarction during treatment with an activated prothrombin complex concentrate in a patient with factor VIII deficiency and a factor VIII inhibitor. Am J Med 85: 245–249
28. White GC, Roberts HR, Kingdon HS, Lundblad RL (1977) Prothrombin complex concentrates: potentially thrombogenic material and clues to the mechanism of thrombosis in vivo. Blood 49: 159–170
29. Hultin MB (1979) Activated clotting factors in factor IX concentrates. Blood 54: 1028–1038
30. Seligsohn U, Kasper CK, Osterud B, Rapaport SI (1979) Activated factor VII: presence in factor IX concentrates and persistence in the circulation after infusion. Blood 53: 828–837
31. Giles AR, Nesheim ME, Hoogendorn H, Tracy PB, Mann KG (1982) The coagulant active phospholipid content is a major determinant of in vitro thrombogenicity of prothrombin complex (factor IX concentrates) in rabbits. Blood 59: 401–407
32. Magner A, Aronson DL (1979) Toxicity of factor IX concentrates in mice. Dev Biol Stand 44: 185–188
33. Römisch J, Bonik K, Diehl KH, Müller HG (1997) In vitro comparison of prothrombin complex concentrates. Kranenhauspharm 18: 124–127
34. Hellstern P, Beeck H, Fellhauer A, Fischer A, Faller-Stöckl B (1997) Factor VII and activated-factor-VII content of prothrombin complex concentrates. Vox Sang 73: 155–161
35. Lusher JM (1994) Use of prothrombin complex concentrates in management of bleeding in hemophiliacs with inhibitors – benefits and limitations. Semin Hematol 31: 49–52
36. Rösler P, Hellstern P, Lechner E, Überwalde M, Breitbach H, Faller-Stöckl B (1997) Factor VII and activated-factor-VII content of prothrombin complex concentrates. Vox Sang 73: 155–161
37. Köhler M, Hellstern P, Lechner E, Überwalde M, Breitbach H, Faller-Stöckl B (1997) Factor VII and activated-factor-VII content of prothrombin complex concentrates. Vox Sang 73: 155–161
38. Teitel JM, Bauer KA, Lau HK, Rosenberg RD (1982) Studies of the prothrombin activation pathway utilizing radioimmunoassays for the F2/F1+2 fragment and thrombin-antithrombin complex. Blood 59: 1086–1097
39. Müller-Berghaus G, ten Cate H, Levi MM (1998) Disseminated intravascular coagulation. In: Verstraete M, Fuster V, Topol EJ (eds) Cardiovascular thrombosis. Thromboembolism and thrombo-endotheliosis. Lippincott-Raven, Philadelphia, pp 781–799
40. Lechner K, Kytle PA (1995) Anti-thrombin III concentrates – are they clinically useful? Thromb Haemost 73: 340–348
41. Smith OP, White B, Vaughan D, Rafferty M, Steele L, Casey W (1997) Use of protein C concentrate, heparin, and haemodiafiltration in meningococcal disease. Lancet 350: 1590–1593
42. Rintala E, Seppala OP, Kotilainen P, Pettula V, Rasi V (1998) Protein C in the treatment of coagulopathy in meningococcal disease. Crit Care Med 26: 965–968
43. Carr JM, McKinney M, McDonald J (1989) Diagnosis of disseminated intravascular coagulation. Role of D-dimer. Am J Clin Pathol 91: 280–287
44. Lechner K, Kytle PA (1995) Anti-thrombin III concentrates – are they clinically useful? Thromb Haemost 73: 340–348
45. Smith OP, White B, Vaughan D, Rafferty M, Steele L, Casey W (1997) Use of protein C concentrate, heparin, and haemodiafiltration in meningococcal disease. Lancet 350: 1590–1593
46. Rintala E, Seppala OP, Kotilainen P, Pettula V, Rasi V (1998) Protein C in the treatment of coagulopathy in meningococcal disease. Crit Care Med 26: 965–968