Factor XI Kinetics after Plasma Exchange in Severe Factor XI Deficiency

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Key Words

Factor XI deficiency
Plasma exchange therapy
Factor XI kinetics

Abstract

Plasma exchange in a patient with factor XI deficiency allowed the determination of the factor XI disappearance time. The decay curve showed a biphasic pattern with a $t_{1/2}$ of 12.3 h during the first 3 days, followed by a slower decay with a $t_{1/2}$ of 121 h. After a loading dose by means of plasma exchange with fresh frozen plasma (FFP) up to a factor XI level of 65%, administration of 0.5 liter FFP every 12 h was necessary to maintain the factor XI concentration between 40 and 60%. The clearances of factor XI, calculated from the results of plasma exchange and from the maintenance dose, correlated very well and showed that the $t_{1/2}$ of factor XI did not change after surgery. The patient underwent major surgery uneventfully but ultimately died 3½ weeks after operation from cerebral damage due to cardiac arrest, which occurred on the 2nd postoperative day.

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Introduction

Factor XI deficiency was described the first time in 1953 by Rosenthal et al. [1]. Ten years later already 200 cases had been detected [2]. The vast majority of patients recognized have been Ashkenazi Jews [3, 4], although factor XI deficiency may occur also in other races [5–9]. It is a hereditary disorder, transmitted as an autosomal-recessive trait with variable expression [10]. Patients with severe factor XI deficiency ($F_{XI} < 20\%$) can present with epistaxis, hematuria, gastrointestinal bleeding, menorrhagia or obstetric hemorrhage [10–12]. Spontaneous joint bleedings have not been reported. Post-surgical hemorrhage has been described, mainly after tooth extractions and prostatectomy [4, 10, 13–15]. The hemostatically effective level of factor XI is supposed to be 20–30% at minor surgery and 40–60% at major surgery. To obtain the required level of factor XI the patients have to be treated with administration of fresh plasma or fresh fro-

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Fig. 1. Two-compartment fit of the factor XI decay curve after 3 liters of plasma exchange. zen plasma (FFP) or with supernatant of cryoprecipitate. Exact data about the factor XI kinetics are not available. Horowitz and Fujimoto [16] observed a half-life time of 10 h; Nossel et al. [17]

and Rosenthal and Sloan [18] described half-life times of 60 and 40–84 h respectively. This paper reports additional data about the kinetics of factor XI after plasma exchange in a patient with severe factor XI deficiency.

Case Report

A 53-year-old male of Ashkenazic origin with cervical spondylolisthesis was referred preoperatively by the orthopedic surgeon because of a history of easy bruising and bleeding after small injuries. His medical history revealed a substantial bleeding for several days after a nail extraction. His mother died at the age of 50 years from a gastrointestinal bleeding. His father, brother and his 2 sons never showed unusual bleeding. The patient's medical problem was ankylosing spondylitis since the age of 38 years, resulting in ankylosis of the cervical spine and listhesis between the 4th and 5th cervical vertebra with impending danger of sub-luxation and spinal cord compression. Coagulation studies revealed that the bleeding tendency in this patient was due to a severe factor XI deficiency. To substitute the factor XI deficiency and to avoid circulatory overload during and after the operation, plasma exchange of 3 liters FFP was performed. During the procedure a skin rash occurred, which faded after administration of an antihistaminic drug. The operation was cancelled but the plasma exchange offered us the opportunity to measure the rate of decay of factor XI (fig. 1).

The patient was treated several months palliatively with a 'Somi collar' without any improvement and finally it was decided to perform a surgical spondylod-esis. Preoperatively plasma exchange was again per-

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Fig. 2. Factor XI rise after plasma exchange (a) and the effect of maintenance therapy with infusion of 500 ml FFP every 12 h. o = Before infusion; ■ = after FFP infusion.

formed with 3 liters of FFP under prophylactic protection with antihistaminics and corticosteroids because of the previous allergic reaction after plasma administration. The operation was uneventful. Maintenance treatment was given with 500 ml (7 ml/kg) FFP twice daily to keep the factor XI level postoperatively between 40 and 60% (fig. 2). The 2nd postoperative day, several hours after removal of the tracheal tube, an acute respiratory obstruction occurred due to glottis edema. Reintubation was difficult and was complicated by a cardiac arrest. After defibrillation and rein-stitution of artificial respiration the patient remained unconscious and ultimately died from decerebration, 3½ weeks after operation. obtained by centrifugation (15 min at 3,000 g). The coagulation studies were performed according to the methods described by Biggs [19]. All factor assays were conducted by one-stage assays using either artificial deficient substrate plasma (II and X) or congenital deficient plasma samples (V, VII, VIII, IX, XI, XII). The factor XI-deficient plasma was obtained from George King Biomedical (Kans., USA).

The plasma exchange of 3 liters FFP was performed with the use of a continuous-flow blood cell separator (Celltrifuge II, Fenwall Corp.). The blood samples for the plasma factor XI determinations were drawn at the end of the plasma exchange and during the next first 3 days at short intervals; thereafter, at longer intervals up to 14 days as indicated in figure 1.

Material and Methods

Blood was drawn from the antecubital vein using a 19-gauge needle. 9 parts of blood were mixed with 1 part of 3.8% sodium citrate. Platelet-poor plasma was

Factor XI Half-Life and Clearance

In order to analyze the data according to pharmacokinetic compartment models, plasmapheresis is considered as a continuous infusion of factor XI. The total volume of plasma exchanged is taken as the dose infused ($D = 3$ liters). The concentration of factor XI is

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expressed as percentage of normal. With these dimensions the data were analyzed according to a one- and a two-compartment open model [21] with the aid of a computer program for nonlinear regression [22].

Results

All coagulation studies were normal except the APTT: 107 s (normal range 30–40 s), and the factor XI activity: 3 % (normal range 70–150%). The APTT in the patient plasma was normalized by the addition of the normal plasma, excluding a circulating anticoagulant. We also had the opportunity to examine 2 sons of the patient. They exhibited factor XI levels of 55 and 38%, respectively. The plasma exchange of 3 liters FFP resulted in a rise of factor XI concentration up to 65%.

Factor XI Half-Life and Clearance The two-compartment model appeared to yield a better fit of the measured factor XI concentrations versus time than the one-compartment model. As shown in figure 1, there is some scattering of the experimental data around the drawn line, representing the best fitting curve. At least part of this scatter is caused by the error in the determination of factor XI activity. Nevertheless, the two-compartment computer fit results in a fairly reliable estimate of the operational half-lives of the two phases of the decay curve, namely 12.3 h ($\pm 23\%$) and 121 h ($\pm 10\%$).

For further, model-independent, calculation, the area under the factor XI plasma curve (AUC) was determined according to the trapezoidal rule. The AUC turned out to be 3,880 ($\% \times h$). With the aid of this, a 'plasma clearance' (Cl) of factor XI may be defined and calculated as:

$Cl = D/AUC = 7.73 \times 10^{-4} \text{ l} \cdot \text{h}^{-1} \cdot \text{kg}^{-1}$

Evidently this parameter has not the usual dimension of clearance (which is volume per unit of time), but in a functional sense it is equivalent. Therefore, Cl may be used for calculating the average steady level to be expected on repeated administration of factor XI. This steady-state level equals the dose flow (dose per unit of time) divided by the plasma clearance. For the patient under study it was calculated that daily administration of 1 liter of FFP would result in a factor level of 54%. Measurements during maintenance treatment confirmed this prediction.

Discussion

The plasma exchange offered us the possibility to administer a large volume of FFP without danger of circulatory overload and provided the opportunity to study the disappearance rate of factor XI in a factor XI-deficient patient. Replacement with 3 liters of FFP resulted in a rise of the factor XI level up to 65% in both instances. Factor XI showed a biphasic exponential decay; a first phase with $t_{1/2} = 12.3$ h and a second phase with $t_{1/2} = 121$ h. The initial phase $t_{1/2}$ of 12.3 h is similar to that reported by Horowitz and Fujimoto [16], but their particular observation was too short (20 h) to discriminate the second phase. Rosenthal and Sloan [18] measured factor XI $t_{1/2}$ of 40–84 h in 5 patients. But because of a too short observation period and a limited amount of measurements they too did not notice the biphasic decay. Nossel et al. [17] found the half-life of factor XI of 190 h which approaches the second phase $t_{1/2}$ of 121 h which we observed. They did not

observe the first equilibration phase, probably because of a too slow infusion rate of the FFP. From the measurements made after the first plasma exchange we could calculate that administration of 1,000 ml FFP/24 h should result in a plateau level of 54% factor XI activity. This is in complete accordance with the results of maintenance therapy, where 500 ml FFP twice daily appeared sufficient to maintain the factor XI level between 40 and 60%. This implies that the factor XI decay after operation does not differ essentially from the disappearance rate before operation. These findings do not support the suggestion of Nossel et al. [20], that the half-life of factor XI is shortened postoperatively due to wound repair or metabolic changes following surgery. The risk of circulatory overload during treatment with FFP is considerably less after plasma exchange than after loading up by daily administration of 15–20 ml/kg FFP. Nevertheless, circulatory overload may occur during the postoperative maintenance therapy (2X7 ml/kg FFP daily). Administration of diuretics, decrease of the amount of daily FFP or repeated plasma exchange may be necessary.

Acknowledgements

We wish to thank Mrs. C. Otero for the laboratory assistance and Mrs. L. Brinkman for typing the manuscript.

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