A short half-life of the administered factor XIII (FXIII) concentrates after the first replacement therapy in a newborn with severe congenital FXIII deficiency

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Dear Sirs,

Factor XIII (FXIII) is a fibrin-stabilising factor which crosslinks fibrin monomers among themselves as well as to α2-plasmin inhibitor and fibronectin, and thus contributes to haemostasis, wound healing, and maintenance of pregnancy (1–3).

Congenital FXIII deficiency is a rare haemorrhagic disorder. Umbilical bleeding in the neonatal period is characteristic and the most frequent symptom (4, 5). Intracranial haemorrhage is less frequent but the leading cause of death at all ages. Plasma-derived FXIII concentrates are available for the treatment of congenital FXIII deficiency. The response to infused FXIII is mostly excellent to get a good control of bleeding (6). Regular replacement therapy with FXIII concentrates is recommended for prophylaxis of bleeding (6–9). However, an appropriate interval of FXIII administration is not known in the neonatal period, because to our best knowledge no report has ever been published on the half-life of FXIII during this stage of a patient’s lifetime.

Here, we report that the half-life of the administered FXIII concentrates was markedly shortened in a male neonate with severe congenital FXIII deficiency.

A Japanese male baby was born after 36 weeks and six days of gestation with a birth weight of 2,446g by normal vaginal delivery. He has no family history of bleeding disorders, and his parents are non-consanguineous. He had hypoglycaemia after birth and received intravenous drip infusion of glucose. He had no problems with haemostasis after venipuncture such as intravenous drip infusion. However, excessive umbilical bleeding occurred on day 5. Umbilical bleeding stopped temporarily after applying pressure, AgNO3, or suturing, but, every time, a large amount of blood was seen on a covering gauze within 12–24 hours after haemostasis. Blood clots were gelatinous and fragile. There were oozing without application of pressure.

Laboratory examinations on day 5 revealed that platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, fibrinogen/fibrin degradation products, antithrombin, factors VIII, IX, and von Willebrand factor were within the normal ranges (see Figure 1). Noriko Fujii et al.suppl. Table 1, available online at www.thrombosiss-online.com).

Umbilical stump bleeding recurred intermittently (Fig. 1), and the patient developed severe anaemia (haemoglobin; Hb, 5.8 g/dl), and was thus transfused with red blood cell concentrate at 10 ml/kg on day 15. His FXIII activity was only 4% on day 12. Accordingly, he was diagnosed to have FXIII-A deficiency, which was confirmed by an amine incorporation assay, ELISA, and fibrin-crosslinking test (data not shown). In addition, Western blot analysis showed virtually no FXIII-A antigen in the patient’s plasma (see Figure 1). Dot blot analyses using recombinant FXIII-A and FXIII-B (10) demonstrated negative results for anti-FXIII antibodies (data not shown).

He was injected with FXIII concentrates at 80 U/kg on day 15 immediately after receiving the FXIII result. His umbilical bleeding stopped promptly. Thereafter, he did not show any sign of bleeding, judging by any measure including magnetic resonance imaging, ultrasonography as well as

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Figure 1: Clinical course of and FXIII levels in the proband. Gray-shadowed peaks (top left) show the severity/degree of umbilical bleeding. Solid circles indicate actual FXIII activities (% of normal), while open circles show theoretically calculated FXIII activities (% of normal) after the injection of FXIII concentrates (FXIII Conc.) on day 15. Hb levels (Hb conc. in g/dl) are depicted by solid triangles. Open arrows indicate the administration of FXIII concentrates at 240 U. Both FXIII activity and Hb conc. are shown on the logarithmic scale. A small arrow stands for the infusion of red blood cell concentrate (RCC). Numbers next to markers represent values of FXIII activities and Hb levels.
extensive physical inspection and examinations.

On day 40 (four weeks after the first replacement therapy), his FXIII activity decreased again to less than 3% (less than the detection limit of a commercial ammonia release assay; Berichrome FXIII, Dade Behring AG, Marburg, Germany). Therefore, a half-life of the administered FXIII in the patient was estimated to be as short as about four days after the first replacement therapy using plasma-derived FXIII concentrates (►Fig. 1). Accordingly, thereafter the patient was started on regularly FXIII concentrate application at 12.5 U/kg every three weeks. No bleeding has occurred in the 15 months since then. He kept a trough of FXIII activity at 4% about six months after birth. It is noteworthy that his FXIII activity increased to 14% by a dose of 25 U/kg three weeks after the last prophylactic replacement at 15 months of age, suggesting that a half-life of the administered FXIII became longer.

A family study revealed that his father’s and mother’s FXIII activities were 48% and 38% of normal, respectively. An uncle and a grandfather of the father’s side as well as a grandmother of the mother’s side had moderately reduced FXIII activities (see ►Suppl. Fig. 2, available online at www.thrombosis-online.com), suggesting that they are all heterozygotes of FXIII deficiency.

Gene sequencing analyses and genetic diagnoses of F13A confirmed that the proband was a compound heterozygote of Tyr204Stop and Ser708Arg mutations, and that family members of his father’s and mother’s sides have Tyr204Stop and Ser708Arg, respectively. These mutations likely bring about structural changes in the variant FXIII-A molecules (paper in preparation by MS). Recently a German group has stated that heterozygotes of FXIII deficiency can manifest bleeding symptoms upon various stress/challenge, such as trauma and major surgery (5). In contrast, none of the carriers of the two mutations in this patient’s family showed excessive bleeding, suggesting that they did not have such stresses/challenges and/or that these mutations may cause only minor haemos tatic defects.

Neonates are physiologically in an enhanced fibrinolytic state, because anti-fi brinolytic ability decreases and bleeding symptoms occur at a high rate especially when FXIII activity decreases (11–13). Therefore, patients with congenital FXIII deficiency usually develop umbilical bleeding during the neonatal period (4, 5). It is important to diagnose such patients early enough, in order to implement haemostasis immediately by urgent supplement with FXIII concentrates. This is also true for early diagnosis and early prophylaxis (14).

Prophylactic therapy is recommended using plasma-derived FXIII concentrates at a dose of 10–20 U/kg every 4–6 weeks (4, 9, 15, 16). This long injection interval for adult patients (4, 6, 8, 17, 18) is based on the half-life of plasma-derived FXIII, about 10 days (17–19). There has not been any report on the half-life of FXIII in a neonate, which could be used as a basis for a dose and an interval of FXIII replacement therapy for neonatal FXIII deficiency. Nevertheless, his physician needed to inject FXIII concentrates every three weeks because the half-life of the administered FXIII was very short in our neonate patient. It is consistent with the fact that dosage regimens vary widely depending upon patient’s response and pharmacokinetics (16).

Therefore, this novel finding will contribute to the consideration of an optimal regimen of FXIII substitution for a new neonate case of this disease. This is consistent with a general concept that the rational interval of replacement therapy must be relevant to the half-life of each drug.

In summary, we propose that determination of the half-life of FXIII in neonatal cases with congenital FXIII deficiency is important for physicians to decide an interval of replacement therapy with FXIII concentrates individually for each neonate case. This may be also applied to recombinant FXIII-A products (20). FXIII supplementation may increase clot firmness (21).

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Conflict of interests

None declared.

References