Letters to the Editor

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RfVII for Pediatric Acute Intracranial Hemorrhage

To the Editor:

A recent interesting phase IIB randomized, double-blind, placebo-controlled, dose-ranging "proof-of-concept" trial on recombinant activated factor VII (rFVIIa) for acute intracranial hemorrhage in adult patients has been reported. A lack of similar experience in the pediatric population is noted. rFVIIa has been anecdotally reported as effective for profound bleeding episodes in children. In the pediatric literature, case reports have been made with apparent clinical improvement seen after the use of rFVIIa for acute life-threatening bleeding; however, there are limited data regarding its use in infants younger than 4 months of age, regardless of whether it is a congenital or acquired condition. Two to three

We report on a case of acute intracranial hemorrhage in a newborn with congenital factor VII deficiency treated with rFVIIa and given a prophylactic program during a follow-up of 36 months. A full-term newborn boy, the first child of nonrelated black parents, was born to his mother aged 29, and the father was 28 years old. The family history was unremarkable. The pregnancy was uneventful. Her birth weight was 2800 g, height was 47.0 cm, and cranial perimeter was 33 cm. Appgar scores were 5 and 6 at 1 and 5 minutes, respectively. Multifocal seizures occurred on the second day postpartum. The fontanelle was tense, and the cerebrospinal was bloody. Cranial CT did not show abnormal parenchymal images. Subarachnoid hemorrhage was diagnosed. Posthemorrhagic hydrocephalus occurred later, and she required shunt placement. Tests for coagulopathies revealed factor VII deficiency. rFVIIa was given 150 μg/kg. The patient received a prophylactic treatment with an infusion program every 3 days in which she received rFVIIa using multiple doses from a single reconstituted vial over a 72-hour period. Since then, coagulation has been tested every 3 months and 80 μg/kg intravenous rFVIIa is given if prothrombin time is <30%. At the age of 4 months, he was admitted because of increased intracranial pressure and a temporoparietal hematoma was identified on CT of the brain, with the prothrombin time being of 30%. After a follow-up of 30 months, rFVIIa was required twice according to this scheme. No further hemorrhagic complications have occurred, with no change in prophylactic program. Developmental retardation is present. At 36 months old, MRI shows residual parenchymal lesion. Family study was uneventful.

Factor VII deficiency is the least rare among uncommon congenital coagulation disorders. The majority of cases are isolated deficiencies. Curiously, we remark that subarachnoid hemorrhage in adults has been previously reported.

Some practical questions are raised. First, we report on rFVIIa treatment and prophylaxis of bleeding in congenital deficiency. However, conclusions and hypotheses can be drawn from it independently of the congenital or acquired bleeding condition. Recombinant FVIIa has been reported to provide effective hemostasis in patients of all ages and in a range of bleeding situations, including acute central nervous system/life-threatening bleeding episodes, non-life-threatening bleeding episodes, surgery, and childbirth. It may also promote hemostasis in patients with normal coagulation. rFVIIa acts locally at the bleeding site without activating systemic coagulation. Reports suggest that it may also be effective prophylactically. However, the risk of thrombosis in FVII-deficient patients treated with rFVIIa is unknown, as is the occurrence of inhibiting antibodies.

Second, we do not know exactly the doses for both treatment and prophylaxis. Nor do we know if doses for both congenital and acquired condition are the same. Effect was reached with all 3 doses that were tested (40, 80, and 160 μg/kg). A phase II trial comparing 20 and 80 μg/kg rFVIIa with placebo is now in progress. However, physiological differences in the hemostatic system between children and adults have been reported. The most commonly used dose is 90 μg/kg body weight rFVIIa as bolus, and, if necessary, followed by additional injections at intervals of 2 to 3 hours. In factor VII deficiency, lower dosages of 15 to 30 μg/kg body weight of rFVIIa are given every 4 to 6 hours, whereas higher doses of 150 to 200 μg/kg body weight are used in neonates.

We do not know the exact level of coagulability to guarantee a nonhemorrhagic diastasis condition in case of factor VII deficiency. In fact, a reported 65-year-old patient with congenital isolated factor VII deficiency and bleeding problems had not shown earlier bleeding problems, presumably because of compensation for the factor VII deficiency by enhanced activities of components of the extrinsic coagulation pathway, factors II, VIII, IX, and X.

Third, the use of rFVIIa in hemorrhagic shock in neonates and preterm infants is increasing. For instance, neonates with massive postsurgical hemorrhage after ileostomy, with severe pulmonary hemorrhage in the course of mechanical ventilation for meconium aspiration syndrome, with congenital heart disease. Also, during postoperative resuscitation after cardiac surgery for congenital heart disease in which multiple administration of rFVIIa (120 μg/kg per dose) and antifibrinolytic therapy, aminocaproic acid (100 mg/kg per dose), were successfully used.

Prevention of intraventricular hemorrhage and its potential long-term sequelae remain one of the major challenges in the early management of preterm infants. rFVIIa, a novel hemostatic agent with an ever-expanding list of potential applications, warrants consideration for use in this setting. The hypothesis that early prophylactic administration of rFVIIa to extremely preterm infants (<28 weeks) would reduce the incidence of severe intraventricular hemorrhage needs to be tested.

Finally, intracerebral hemorrhage causes severe disability and a staggering economic burden. Because rFVIIa is a very expensive therapy, possible strategies for optimizing its use in these settings in the pediatric population are particularly needed.

Disclosures

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