Intraoperative defect in haemostasis in a child receiving valproic acid

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This report describes the development of an intraoperative defect in haemostasis which occurred during surgery for lengthening of the heel cords and release of hip contractures in a patient receiving valproic acid. A review of the literature failed to find any other cases of a valproic acid-induced bleeding disorder occurring under anaesthesia and surgery. While recognized in the non-surgical literature, this case reports the first in which the development of a valproic acid-induced haemostatic defect occurred under anaesthesia. The subsequent course is discussed and some pathophysiological mechanisms are presented. It is suggested that for patients receiving valproic acid preoperative education should include PT/PTT, platelet and fibrinogen counts and bleeding time so that abnormal coagulation states can be recognized.

Nous avons rencontré un problème d'hémostase intraopératoire lors d'une ténoplastie bilatérale des hanches et des talons chez un enfant qui prenait de l'acide valproïque. Quoique les effets de ce dernier sur la coagulation soient connus, il s'agit du premier cas de déficit hémostatique se manifestant lors d'une intervention chirurgicale. Nous discutons du cas et suggérons entre autres que l'évaluation pré-opératoire de ceux qui prennent de l'acide valproïque, comprenne une mesure du taux de fibrinogène plasmatique, des temps de Quick, de céphaline activée et de saignement en plus d'un décompte plaquettaire.

Key words

BLOOD: coagulation;

BRAIN: convulsions, valproic acid;

HAEMORRHAGE: coagulopathy, platelet.

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Numerous medications are known to alter intraoperative haemostasis by interfering with steps in the coagulation cascade. These include heparin, coumadin, aspirin and numerous anti-platelet drugs. Recently, the association between sodium valproate, an anti-convulsant, and alterations in the coagulation cascade have been suggested. The case of a 12-yr-old retarded child who received a therapeutic dose of valproic acid for a refractory seizure disorder and subsequently developed serious bleeding during a normally bloodless operation is presented. A review of the literature is presented, the pathophysiological mechanism described and a preoperative management plan is suggested for patients receiving valproic acid.

Case report

A 12-yr-old, 28 kg severely retarded male child with cerebral palsy presented for bilateral percutaneous lengthening of the heel cords and open adductor tendon hip releases. He had a severe seizure disorder controlled with phenytoin, phenobarbital, and valproic acid, and had had no seizure activity within the last three months. There was no history of surgery. There were no known allergies. His physical examination was remarkable only for the contractures, which were to be corrected. Haematocrit was 35%, platelet count was $150,000 \cdot \text{dl}^{-1}$, and prothrombin (PT) and partial thromboplastin times (PTT) were within normal limits.

The child received no pre-medication. Anaesthesia was induced with $\text{N}_2\text{O}/\text{O}_2$ (60/40) and halothane, and an iv line was started when he was obtunded. Release of the hip adductor tendon contractures was performed and brisk bleeding was noted from all cut surfaces. The groin incisions were explored for arterial bleeding, which was not identified. With continued oozing from the entire wound, blood loss became excessive. No definitive site was identified. The wounds were packed and pressure was applied. Type and cross-match for packed red blood cells was performed and blood for PT, PTT, and platelet count was sent. After 30 minutes of direct pressure, bleeding was greatly reduced and the wounds were closed over drains. Bleeding from heel cord releases was controlled with pressure and this procedure was uneventful. Estimated blood loss was 600 ml. One unit of packed

red blood cells was transfused for persistent tachycardia, mild hypotension, and a haematocrit of less than 25%. The PT, PTT and platelet count were normal. No other component therapy was administered. Postoperative recovery was uneventful without further diagnostic evaluation or evidence of bleeding and the child was discharged on the second postoperative day.

Discussion

This case demonstrates considerable intraoperative bleeding probably as a result of valproic acid-induced alteration in the coagulation system. Until this case, we were unaware of the association between valproic acid and an abnormality of the coagulation system and a review of the anaesthesia literature did not reveal a previous report. Although bleeding is recognized as a complication of valproic acid administration in the medical literature increased intraoperative risk is not widely recognized.

Sussman¹ and Monet² reported a direct, dose-related hepatotoxicity, manifested by an abnormality of clotting factors, decreased fibrinogen concentration, decreased platelet count, and prolonged bleeding times in response to valproate therapy. Monet² reported one death from fulminant hepatic failure. Loiseau³ also reported abnormality of clotting factors and platelet function, and like Sussman¹ noted a return to baseline with either a decreased dose or after stopping valproic acid therapy.

Thrombocytopenia^{1,4-10} without clinical bleeding or abnormal bleeding time has been reported. Abnormal bleeding times with a normal platelet count,^{2,4,5} platelet antibody,^{11,12} isolated decrease in fibrinogen levels,¹³ and decreased clotting factors have also been reported,^{4,5} but there are no reports of intraoperative bleeding. However, Paworth⁸ reported a 9 × 10 cm lower abdominal haematoma postoperatively after emergency appendectomy and there were several reports of spontaneous bleeding,^{1,2,4,5,8} including a 5 × 12 cm spontaneous scalp haematoma.⁸ Dale¹³ discovered decreased fibrinogen concentration in preparation for surgery in a patient receiving valproic acid. The valproate was withdrawn and fibrinogen level returned to normal. Valproate was re-instituted and the fibrinogen concentration decreased again to below normal limits. Valproate was withheld for ten days and surgery was uneventful. Loiseau³ recommended a full clotting profile prior to elective surgery.

Von Voss¹⁴ and Keenan¹⁵ postulated a membrane disruption, manifested by decreased malonyldialdehyde production, as the aetiology of the platelet dysfunction. Richardson¹⁶ measured decreased malonyldialdehyde as a specific defect *in vitro* in the secondary phase of platelet aggregation, as an indicator of this dysfunction.

The possibility that other agents used before or during this operation may have contributed to bleeding must

also be considered. Mills¹⁷ demonstrated suppression of human platelet aggregation secondary to numerous membrane active drugs including antihistamines, local anaesthetics, tranquilizers and antidepressants. Both phenytoin and phenobarbital have membrane stabilizing properties. Gotta¹⁸ confirmed this with local anaesthetics, but at concentrations not clinically obtainable. Dalsgaard-Nielsen¹⁹ demonstrated decreased platelet aggregation and increased bleeding time during halothane anaesthesia, but demonstrated no clinical bleeding. Walter²⁰ demonstrated induction of adenylylase activity leading to increased c-AMP which inhibited platelet function. Lichtenfeld²¹ and Gotta²² suggested that this alteration of platelet aggregation is clinically insignificant and Gotta confirmed this by demonstrating normal thromboelastograms. Simpson²³ reported a tendency toward fibrinolysis under prolonged general anaesthesia with inhalation agents and narcotics, but this was not considered to be clinically important. Engquist²⁴ correlated the fibrinolysis with elevated cortisol levels which were indicative of stress or prolonged surgery. While any of these mechanisms could have contributed to the outcome in this case, it is unlikely that any were the primary cause for the massive bleeding encountered.

This patient did not have thrombocytopenia or deficient clotting factors as measured by platelet count and PT/PTT. Decreased fibrinogen concentration was neither suspected nor evaluated so that an abnormal platelet function was the most likely aetiology. A bleeding time was not performed, but this would have identified the lesion. Gardner⁶ suggested that a thromboelastogram would have been diagnostic. Direct pressure was undoubtedly the appropriate therapeutic manoeuvre in this case, since packed red blood cell therapy would not affect platelet count, function, or fibrinogen level significantly.

In summary, we report a dramatic bleeding intraoperatively during a normally bloodless surgical procedure in a child taking valproic acid. Review of the literature revealed numerous defects in the clotting cascade attributed to valproate, as well as a possible aetiology (platelet membrane abnormality). Caution for elective surgery in patients on valproate is suggested and full laboratory evaluation of hemostatic components, including PT/PTT, platelet and fibrogen count as well as clinical bleeding time, would seem prudent.

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