Danaparoid thromboprophylaxis in pregnant women with heparin-induced thrombocytopenia

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Case report 1

A 38 year old woman presented to the antenatal clinic at 36 weeks of gestation. She had received no antenatal care before this. In her previous nine pregnancies, she had four normal full term vaginal deliveries, two terminations of pregnancy, one miscarriage, one intrauterine death at 36 weeks of gestation and an emergency caesarean delivery at term (her last pregnancy). Nine days after her last delivery, she developed pulmonary embolism. During her treatment with intravenous heparin, she developed thrombocytopenia. Her platelet count decreased gradually from $266 \times 10^9/L$ on the second day of treatment to $112 \times 10^9/L$ on the fourth day. Platelet factor antibodies were present in her serum and a diagnosis of heparin-induced thrombocytopenia was made. She was anticoagulated with danaparoid (Orgaran-Durbin) and her platelet count recovered within three days. The woman continued anticoagulation with warfarin. Investigations for thrombophilia (protein C, protein S, fibrinogen, factor VIII, lupus anticoagulant, anticardiolipin antibodies, activated protein C ratio and antithrombin) were all negative. Her medical and family histories were otherwise normal. In her index pregnancy the history of heparin-induced thrombocytopenia excluded unfractionated and low molecular weight heparin as thromboprophylactic agents. Because of her past history of thromboembolism, age and multiparity, it was felt that aspirin alone was insufficient as thromboprophylaxis. Therefore, she was treated with aspirin antenatally and danaparoid (750 iu twice daily) was administered subcutaneously during labour and warfarin postnatally. The woman went into spontaneous labour and was delivered spontaneously. During the course of her treatment, she did not develop thrombocytopenia. Both mother and baby were discharged seven days following delivery. She did not breastfeed.

Case report 2

A 32 year old woman booked at nine weeks of gestation in her second pregnancy, her first pregnancy having resulted in a miscarriage. Three years before the index pregnancy she developed sagittal sinus vein thrombosis while taking the combined oral contraceptive pill. Treatment with heparin was complicated by the heparin-induced thrombocytopenia; this was confirmed by serum platelet factor four antibodies. Associated with the heparin-induced thrombocytopenia, she developed a thrombosis in the left femoral vein. She made a slow recovery over the next few months. Her maternal aunt suffered from deep vein thrombosis and she had relatives who had had strokes. However, thrombophilia studies, performed when she was not anticoagulated or pregnant, were negative. Because of her past and family history, it was again decided that aspirin alone would be insufficient as thromboprophylaxis. The alternatives were low dose warfarin with the risk of birth defects or danaparoid. After full discussion, she was given danaparoid prophylaxis (750 iu twice daily) by subcutaneous injection from nine weeks of gestation. The woman had an uneventful pregnancy and she was delivered of a baby girl at term. Postpartum warfarin was given, and danaparoid was continued until her international normalised ratio was $> 2.0$.

Discussion

Heparin-induced thrombocytopenia can be classified into two types: type 1 and type 2. Type 1 heparin-induced thrombocytopenia is a mild form of thrombocytopenia and is thought to be due to the direct effect of heparin on the platelet membrane. The thrombocytopenia is of little clinical significance and is usually not diagnosed. It does not require any treatment. Type 2 heparin-induced thrombocytopenia is an immune mediated destruction of platelets secondary to heparin where other causes are excluded.
Heparin-induced thrombocytopenia is 3%\(^1\). It can also occur with subcutaneous heparin-induced thrombocytopenia. The frequency of heparin-induced thrombocytopenia in women who is prescribed many drugs and who slowly develops thrombocytopenia. The usual clinical course is of a patient who is not pregnant, is in hospital with many clinical disorders, and a past history of heparin-induced thrombocytopenia. Danaparoid has a molecular weight of 7500–10000 daltons, and is coated with heparin\(^2\). The most serious complication of heparin-induced thrombocytopenia is thromboembolism, resulting in myocardial infarction, thrombotic strokes, recurrent pulmonary embolism, and venous and arterial thrombosis in limbs.

Thromboembolism occurs in 5%–10% of patients with heparin-induced thrombocytopenia\(^3\). Heparin-associated thromboses are likely to be underdiagnosed because of lack of awareness of the condition. The mortality of patients with heparin-induced thrombocytopenia who have thromboembolic complications is approximately 30%, with an additional 20% risk amputation of a limb\(^4\). With early recognition the mortality and morbidity may be reduced. Once heparin-induced thrombocytopenia is suspected or diagnosed, all heparin therapy must be withdrawn. The thrombocytopenia will generally resolve within several days to a week.

Heparin is used increasingly for treatment and the prevention of thromboembolism, which is the leading cause of maternal mortality in the UK. Heparin is also used to improve the poor fetal outcome in thrombophilia.

Alternative anticoagulants that can be used in pregnant women with heparin-induced thrombocytopenia are:

1. Aspirin: For some women at risk of thromboembolism aspirin alone may be insufficient.
2. Warfarin: This is associated with teratogenesis.
3. Low molecular weight heparin: This cross-reacts with unfractionated heparin and can itself cause heparin-induced thrombocytopenia\(^3\).
4. Danaparoid (Orgaran).

Sodium danaparoid is an antithrombotic agent derived from mucous membranes of pigs. It is a sulphated glycosaminoglycan heparinoid consisting of heparan sulphate (84%), dermatan sulphate (12%) and chondroitin sulphate (4%). Danaparoid is different from unfractionated heparin and from low molecular weight heparin. Danaparoid has a lower degree of sulphation and a lower charge density, which are thought to be important to the pharmacological effects of danaparoid. Danaparoid inactivates factor Xa and to a lesser extent, factor IIa.

Danaparoid reacts little with the heparin-associated antibodies that mediate heparin-induced thrombocytopenia. Danaparoid will react with heparin-associated antibodies in 0%–20% of cases of heparin-induced thrombocytopenia, compared with 25%–100% with low molecular weight heparins\(^5\). Danaparoid does not appear to impair the formation of a haemostatic plug of platelets, and therefore does not result in increased loss of blood during delivery\(^7\).

Danaparoid is supplied in ampoules or pre-filled syringes containing 750 antiXa units. For thromboprophylaxis in women weighing 55kg–90kg the recommended dose is 750iu danaparoid twice daily subcutaneously. The dose of danaparoid can be adjusted by measurement of antifactor Xa activity, but with prophylaxis this is not required. The molecular weight of danaparoids is about 6000 daltons and so it should not be excreted in breast milk; besides, danaparoid is inactivated in the gastrointestinal tract, and so the risk to a nursing infant from ingestion of danaparoid from breast milk should be negligible. At the doses recommended for thromboprophylaxis no case of osteoporosis has been recorded. Contraindications to danaparoid include severe hypertension, severe haemorrhagic disorders, uncontrollable active bleeding, haemorrhagic stroke in the acute phase, diabetic retinopathy, acute bacterial endocarditis, severe renal insufficiency and sensitivity to sulphite or danaparoid. Apart from the last two, these contraindications are not specific to danaparoid but apply to all anticoagulants.

A literature search using MEDLINE identified only one paper where, in the four women who received danaparoid in pregnancy, no antifactor Xa activity was demonstrated in fetal cord blood. In animal studies danaparoid did not cross the placenta or induce teratogenicity. The manufacturers recommend that danaparoid should be used in pregnant or lactating women only if no other alternative treatment is available. In the settings of current or previous heparin-induced thrombocytopenia, this would be justifiable.

Heparin-induced thrombocytopenia is an important complication of treatment with heparin. We describe two cases in whom danaparoid seemed to be a useful alternative to heparin in pregnancy. There is, however, little information on danaparoid in pregnancy. The cost of danaparoid is high (£18 per 750 antiXa units ampoule\(^8\)), but the risk of fatal thromboembolism in women with heparin-induced thrombocytopenia justifies this cost.

References


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