

HEPARIN

Use

Heparin can help maintain catheter patency, and is used during and after cardiovascular surgery. Low molecular weight heparins, such as enoxaparin (q.v.), are now generally used to prevent and manage venous thromboembolism but there is, as yet, little experience of their use in the neonate.

Pharmacology

Heparin is an acid mucopolysaccharide of variable molecular weight (4,000–40,000 Daltons) that was first obtained from the liver (hence its name) in a form pure enough to make clinical trials possible in 1935. While it has some thrombolytic action it is mostly used to prevent further blood clot formation rather than to lyse clots that have already formed. The higher molecular weight heparins also inhibit platelet activity. Heparin works *in vitro* by activating plasma antithrombin inhibitor, which then de-activates thrombin and factor Xa. It is metabolised by *N*-desulfation after IV administration and then rapidly cleared from the body. The half life of conventional unfractionated heparin is dose dependent, increasing as the plasma level rises. It averages 90 minutes in adults, but may be less at birth. Fractionated low molecular weight (4,000–6,000 Dalton) heparins, such as enoxaparin, have a much longer half life. They do not cause osteopenia during long term use, show much greater bioavailability when given subcutaneously, and are mostly excreted by the kidneys.

All products occasionally cause an immune-mediated thrombocytopenia, most commonly 5 to 10 days after the start of treatment. Because this can, paradoxically, cause a major thromboembolic event, the platelet count *must* be monitored. Stop treatment at once if thrombocytopenia develops, and do not give platelets. Heparin does not cross the placenta, is not teratogenic, and can be given with complete safety during lactation.

Women at high risk of thromboembolism because of immobility, obesity, high parity, previous deep vein thrombosis, or an inherited thrombophilia are now increasingly given enoxaparin during pregnancy and, more particularly, operative delivery and the early puerperium. Warfarin (q.v.) continues to be used to anticoagulate women with pulmonary vascular disease, and patients with an artificial heart valve or atrial fibrillation, but time may show that they, too, can be protected with low molecular weight heparin.

Indications for neonatal use

There is controlled trial evidence that even a small (0.5 unit/ml) dose of heparin can help sustain the patency of neonatal monitoring lines, especially when it is given as a continuous infusion, but there is no evidence that this reduces the risk of thromboembolism or arterial occlusion. Although one small study has suggested that full heparinisation may reduce the formation of arterial thrombi, the effect of any such approach on the risk of intraventricular haemorrhage remains uncertain. Three observational studies (one only reported in abstract) even suggest a correlation between total heparin exposure and the risk of intraventricular haemorrhage in babies of under 1.5 kg in the first week of life. However, this may merely mean that some babies got more heparin because they were already less well. No adequate sized trials have ever been done. However, while adverse effects of heparin are rare, heparinised babies can bleed unpredictably, so it is probably unwise to use heparin in babies with intracranial or gastrointestinal haemorrhage. Uncorrected thrombocytopenia ($<50 \times 10^9/l$) is also a contraindication, and intramuscular injections should not be given to any heparinised patient. Lumbar puncture can also be hazardous. Alteplase and streptokinase (q.v.) are almost certainly better at removing clots that have already formed.

Prophylactic strategies

Monitoring lines: Intravascular catheters are often used to monitor blood pressure and to make blood sampling possible without disturbing the patient. A steady 0.5 or 1.0 ml/hour infusion containing 1–2 units of heparin for each ml of fluid prolongs catheter patency. Glucose shortens the line's life and makes it impossible to monitor blood glucose levels. The use of 0.45% rather than 0.9% sodium chloride reduces the risk of sodium overload. Clear the 1ml catheter 'dead space' carefully after sampling and consider using water rather than dextrose or saline for this in order to avoid sudden swings in blood glucose and the infusion of further unmeasured quantities of sodium chloride. It is not necessary to add further heparin to the fluid used to flush the dead space.

'Stopped off' lines and cannulas: 'Normal' saline containing 10 units/ml of heparin is commonly flushed through and left in 'stopped off' cannulas after use, but the addition of heparin does little to prolong patency. Central venous long lines are often left primed with a fluid containing 5,000 units/ml of heparin, but a solution containing 1 mg/ml of alteplase (q.v.) seems to be a better way of keeping the catheter patent.

Cardiac catheterisation: A 100 unit/kg IV bolus at the start of the procedure greatly reduces the risk of symptomatic thromboembolism.

Intravascular infusions: Neonatal trials have shown that adding heparin to the infusate prolongs the patency, not only of arterial catheters, but also of peripherally inserted central venous lines. The most recent trial in babies with a central venous line in place used a dose of 0.5 unit/kg per hour. Such use caused a five fold reduction in the number of catheters needing replacement because of blockage, but it did not reduce number needing replacement because of extravasation or suspected sepsis (an equally common reason for replacement), or the risk of a clot forming close to where the tip of the catheter was (or had been).

Continued

Full anticoagulation

The indications for this in the neonate remain unclear. There is no good evidence that anticoagulation reduces the risk of an existing clot enlarging, fragmenting and shedding emboli, or reforming after lysis. Neither is heparinisation called for in most cases of disseminated intravascular coagulation (DIC). If treatment is indicated start by giving a loading dose of 75 units/kg IV over ten minutes (a loading dose of 50 units/kg may be safer in babies with a postconceptional age of less than 35 weeks). Maintenance requirements vary – start with a continuous IV infusion of 25 units/kg per hour (1 ml/hour of a solution made up as described below) and assess the requirement by measuring the Activated Partial Thromboplastin Time (APTT) after 4 hours. Monitor the platelet level weekly.

Dose monitoring

The anticoagulant dose used during Extracorporeal Membrane Oxygenation (ECMO) and to lyse thrombi is one that raises the APTT to 1.8 – 2.0 times the normal level. Never take blood for this test from an intravascular line that has ever contained heparin: sufficient heparin will remain to invalidate the laboratory result even if the line is flushed through first. Normal neonatal APTT times are given in the monograph on fresh frozen plasma.

Antidote

Protamine sulphate is a basic protein which combines with heparin to produce a stable complex devoid of anticoagulant activity. The effect of heparin can, therefore, be neutralised by giving 1 mg of protamine sulphate IV over about 5 minutes for every 100 units of heparin given in the previous two hours. Excess protamine is dangerous because it binds platelets and proteins such as fibrinogen producing, in itself, a bleeding tendency.

Compatibility

It is known that adrenaline, atracurium, fentanyl, isoprenaline, midazolam, milrinone, morphine, noradrenaline, ranitidine, streptokinase, TPN (the standard formulation with or without lipid) and urokinase can be added (terminally) to a line containing heparin. So can plain amphotericin (but not the liposomal formulation because of concern that this may destabilise the colloid). So, too, can dopamine, but there are reports suggesting that although heparin is compatible with dobutamine when suspended in 0.9% sodium chloride, precipitation may occur (somewhat unpredictably) when the two drugs are mixed, even briefly, in a dextrose solution.

Supply and administration

Multidose vials: 5 ml multidose vials containing 1000 units/ml of standard, unfractionated heparin sodium cost 47p, while 5 ml 5000 unit/ml vials cost 92p. These vials can be stored for 18 months at room temperature (5–25°C), but are best not kept more than 28 days once they have been opened. Heparin is stable in solution so material in a syringe or IV line does not need to be replaced after some set time on these grounds.

Full anticoagulation: To give 25 units/kg of heparin per hour, take 1.25 ml (1250 units) from the multidose vial for each kilogram the baby weighs into a syringe, dilute this to 50 ml with 0.9% sodium chloride, and infuse at a rate of 1 ml/hour.

Flush solution: Accurate dilution is best achieved by making any syringe containing 1 unit/ml of heparin 'flush' solution up from a 500 ml bag of 0.9% (or 0.45%) IV sodium chloride freshly prepared by the prior addition of 0.5 ml (500 units) of heparin. Small 5 ml preservative-free (25p) ampoules of Hep-Lock[®] and Hepsal[®] flush solution contain 0.75 mmols of sodium and 50 units of unfractionated heparin.

Protamine sulphate: 5 ml ampoules containing 10 mg/ml cost 96p each.

References

See also the relevant Cochrane reviews ©

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