

STREPTOKINASE (Commentary)

Managing pleural effusions

While most pleural effusions can be left to resolve spontaneously, large and infection effusions require drainage, and untreated fibrotic change can seriously restrict lung function. Urokinase (q.v.) is the fibrinolytic drug that has been most widely studied in children, and there is one trial in adults (Bouros *et al.* 1997) suggesting that it may be more effective than streptokinase. Streptokinase has, however, been the drug most commonly used in adults, and a Cochrane review of four small trials (Cameron and Davies, 2004) concluded that fibrinolytics reduce hospital stay, shorten the period of fever, produce clearer radiological improvements, and reduce the incidence of treatment failure. However a further larger, multi-centre double blind trial (Maskell *et al.*, 2005) which recruited a very heterogeneous range of patients, concluded that fibrinolytic treatment was of little benefit and should be stopped. The implication is that treatment should only be used selectively, is best used early in the disease process, and should be used with caution where there is an infected pleural empyema. Medical thoracoscopy, or video-assisted thoracoscopic surgery (Patrakis *et al.*, 2004), should be considered if fibrinolytic therapy is not successful within 3–5 days.

Bouros D, Schiza S, Patsourakis G, *et al.* Intrapleural streptokinase versus urokinase in the treatment of complicated parapneumonic effusions. A prospective double-blind trial. *Am J Respir Crit Care Med* 1997;**155**:291–5. [RCT]
 Cameron R, Davies HR. Intrapleural fibrinolytic therapy versus conservative management in the treatment of parapneumonic effusions and empyema. *Cochrane Database of Systematic Reviews* 2004, Issue 2. Art. no: CD002312. [SR]
 Patrakis IE, Kogerakis NE, Drositis IE, *et al.* Video-assisted thoracoscopic surgery for thoracic empyema: primarily or after fibrinolytic failure. *Am J Surg* 2004;**187**:471–4.
 Maskell NA, Davies CW, Nunn AJ, *et al.* UK controlled trial of intrapleural streptokinase for pleural infection. First Multicenter Intrapleural Sepsis Trial (MIST 1). *N Engl J Med* 2005;**352**:865–74. [RCT]

Managing neonatal clots and emboli

Clots (or thrombi) can form in any large vessel, and loose clots (or emboli) can lodge anywhere. Thromboembolism is diagnosed during about one in every 500 neonatal unit admissions, but the true incidence is almost certainly higher than this, since the condition is not always considered in the differential diagnosis of seizures (neonatal stroke can go undiagnosed), respiratory distress (pulmonary emboli are seldom looked for), or later renal hypertension.

Who is at risk? Thrombi form, after a while, on most intravascular lines (as x-ray angiography clearly reveals), and nobody knows what happens to these clots when the catheters are taken out! While most never cause any recognisable trouble, the presence of a “long line” greatly increases the risk of symptomatic thromboembolism. Renal vein thrombosis (where trouble first starts in the intra-renal venules) is the only condition where this is not true. Other predisposing factors include infection, and disturbances of blood flow due to dehydration, asphyxia and polycythaemia. Emboli from the placenta can cross into the baby around the time of birth and, since the foramen ovale and arterial duct are still open at this time, lodge in a limb or in a cerebral artery. In other circumstances the lung acts as a silent filter for small venous emboli. Hereditary thrombophilia (other than homozygous protein C deficiency, which is lethal but very rare) only precipitates trouble if other risk factors are present, but is certainly worthy of retrospective consideration.

How to make the diagnosis: Symptoms and signs of thrombosis vary, depending on the site and extent of the obstruction. A baby with renal vein thrombosis will present with haematuria and an enlarged kidney; a baby with a thrombosed iliac or femoral artery with a cool, pale, pulseless leg. When thrombosis is suspected clinically the diagnosis should be confirmed before any potentially harmful treatment is started. Doppler flow ultrasonography is the commonest imaging technique used, but its accuracy has been doubted: in a study that involved contrast angiography to validate each ultrasound examination, a significant number of false-positive and false-negative ultrasound diagnoses were encountered.

How to prevent thrombosis: Avoidance of known risk factors is the best possible prevention. The indication for inserting any intravascular catheter needs to be weighed against the risk incurred. Catheters need to be withdrawn as soon as they are no longer needed, or become infected. A low dose of heparin prolongs the patency of central and peripheral line, but it is still far from clear whether it can be used to reduce the risk of catheter-related vessel thrombosis and risk of embolisation without increasing the risk of iatrogenic haemorrhage.

When to start treatment: There is no consensus on this issue, and the neonatal literature is too anecdotal to be of help. Extrapolation from the sound evidence that does exist on the management of thromboembolism in adults may not be appropriate, since all three components of “Virchow's triad” (blood flow, blood coagulability and the vessel wall) are all very different. Because both the efficacy and the safety of neonatal treatment remain uncertain, a conservative approach is often the wisest option. Clots in the atria or in the superior or inferior vena cava clearly merit treatment since they can shed emboli. Other thrombosed veins seldom cause symptomatic emboli, but subclavian thrombi can cause thoracic duct

obstruction and chylothorax. An anticoagulant *may* stop the clot getting bigger. A fibrinolytic agent is probably only appropriate where arterial occlusion is threatening to cause ischaemic damage. Surgery has rarely been of value. There is no evidence that treatment alters the long term outcome in patients with renal vein thrombosis. Uncertainty will persist until randomised trials are done.

What drugs to use: Unfractionated heparin is the most commonly used anticoagulant, although a few centres have begun to introduce low-molecular weight heparin (which is given subcutaneously and easier to monitor than standard, unfractionated, heparin). Oral warfarin is best avoided in the first month of life: titrating the dose is extremely difficult, both with and without vitamin K prophylaxis at birth, and serious bleeding is a potential hazard. Streptokinase, urokinase and tissue plasminogen activator have all been used to lyse thrombi, but urokinase is not readily available in some countries at present. Dose regimens have varied greatly. Until comparative studies are done, choice will remain best influenced by familiarity and cost.

What is the outcome? Most lesions are not life threatening, although thrombi in the heart and great vessels can be fatal. All renal lesions require follow up. Hypertension of early onset usually resolves without surgical intervention, but tubular function and concentrating capacity remain abnormal in some children with renal vein thrombosis, and a quarter develop persistent late renal hypertension.

Last updated March 2008