

# Tissue plasminogen activator (alteplase) treatment for femoral artery thrombosis after cardiac catheterisation in infants and children

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## Abstract

**Objective**—To determine the efficacy of fibrinolytic therapy with tissue plasminogen activator (alteplase) in infants and children with arterial thrombosis after cardiac catheterisation.

**Design**—Use of alteplase (Actilyse) in a protocol with prospective data collection. Alteplase was administered to infants and children with arterial thrombosis after cardiac catheterisation. A dose of 0.5 mg/kg/h was given continuously via a peripheral vein for the first hour followed by 0.25 mg/kg/h till clot lysis occurred or treatment had to be stopped because of bleeding complications.

**Setting**—University hospital, intensive care unit.

**Patients**—17 consecutive infants and children with femoral artery thrombosis after cardiac catheterisation between 1 April 1988 and 31 October 1991.

**Main outcome measure**—Reopening of the vessel.

**Results**—Complete clot lysis was achieved in 16 of 17 patients within 4–11 hours after the start of treatment. In one patient only partial lysis occurred. After complete lysis rethrombosis developed in one patient 15 hours after the end of treatment. Bleeding complications were seen in nine patients. These were restricted to the arterial puncture site, except for one who showed mild epistaxis. Three patients had to be treated with packed erythrocytes.

**Conclusions**—Alteplase was an effective treatment of arterial thrombosis after cardiac catheterisation in infants and children. Further studies are needed to determine whether lower doses will reduce the frequently observed bleeding complications.

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Femoral artery thrombosis is a common complication of retrograde arterial cardiac catheterisation in infants and children.<sup>1–5</sup> Though severe tissue ischaemia causing amputation of the affected leg is rare, impairment of the growth and function of the leg can become severe, suggesting that treatment of femoral artery thrombosis is mandatory in this age group.<sup>6–8</sup>

Surgical thrombectomy has been performed with varying success in children.<sup>8–10</sup> Because the risk of extending vascular damage is high in neonates and infants, results may be poor in this age group.<sup>11,12</sup> Thrombolytic agents offer an alternative to surgical treatment, but there are only a few reports of the use of streptokinase or urokinase as a thrombolytic agent in infants and children.<sup>6,9,11,13,14</sup> Tissue plasminogen activator (alteplase) is a promising new fibrinolytic agent with several advantages over streptokinase and urokinase.<sup>15</sup> So far there is little experience with this substance in infants and children.<sup>16–21</sup> We describe the use of alteplase in 17 infants and children with femoral artery thrombosis after cardiac catheterisation.

## Clinical data

Patient	Age (mnh)*	Weight (kg)	Underlying disease	Duration alteplase (h)	Complications	Clot* lysis
1	24	10	PST, C-RV-F	8	Bleeding from puncture site	+
2	54	17	AST-Dil	8	Strong bleeding from puncture site	+
3	89	20	DORV, MA	6		+
4	23	8	TOF	7	Prolonged bleeding from puncture site	+
5	17	12	TA, PA	4	Oozing from puncture site	+
6	11	10	L-TGA	8		+
7	6	6	VSD, PST	4		+
8	4 days	3.6	TAPVR, PA	4		±
9	2 days	3	PA, UVH	9		±
10	13	10	CoA-Dil	7	Strong bleeding from puncture site	+
11	32	8.5	AVC, PAB	8	Epistaxis	+
12	9	8	PA, VSD	7.5		+
13	3	4	AVC	11		+
14	5	5	VSD, PAB, IAA	11	Strong bleeding from puncture site	+
15	15	10	TGA	7.5		+
16	27	15	AST	6	Bleeding from puncture site	+
17	47	15	AST-Dil	5	Oozing from puncture site	+

\*Unless stated otherwise. \*Clot lysis: + = complete clot dissolution; ± = partial clot dissolution; (r) = rethrombosis. AVC, complete atriocaval canal; AST, valvar aortic stenosis; COA, coarctation of the aorta; C-RV-F, coronary-right ventricular fistulas; DIL, balloon dilatation; DORV, double outlet right ventricle; IAA, interrupted aortic arch; L-TGA, corrected transposition of the great arteries; MA, mitral atresia; PA, pulmonary atresia; PAB, pulmonary artery banding; PST, valvar pulmonary stenosis; TA, tricuspid atresia; TOF, tetralogy of Fallot; TGA, transposition of the great arteries; TAPVR, total anomalous pulmonary venous return; UVH, univentricular heart; VSD, ventricular septal defect.

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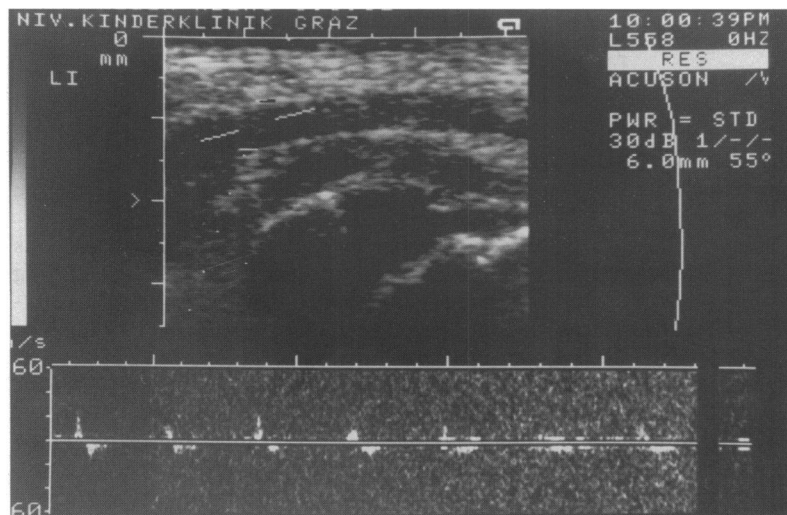


Figure 1 Cross sectional and M mode echocardiograms of the left femoral iliac artery (5 MHz, linear transducer) of patient 16 (table) 18 hours after cardiac catheterisation showing hazy intraluminal echoes in the vessel. The Doppler gate ( $\alpha = 55^\circ$ ) was correctly positioned but no proper signals could be obtained. This indicated thrombosis.

## Patients and methods

### PATIENTS

Between 1 April 1988 and 31 October 1991 we treated 17 consecutive patients (13 males, four females; aged 2 days to 7 years 5 months (mean 22 months) with congenital heart disease who had developed arterial thrombosis after retrograde cardiac catheterisation. Their weights ranged from 3 kg to 20 kg (mean 9.7 kg). Arterial thrombosis had developed after selective retrograde catheterisation of the left ventricle in 14 and after balloon dilatation of valvar aortic stenosis or aortic coarctation in three patients (table).

### HEPARIN THERAPY AND ALTEPLASE REGIMEN

All patients were given an intravenous bolus of 100 U/kg heparin after arterial puncture. A continuous infusion of heparin (300 U/kg/day) was given if arterial pulsation became reduced or disappeared, if blood

pressure fell, or if pallor or reduced skin temperature developed in the cannulated leg. Femoral arterial thrombosis was diagnosed, if after 24 hours of heparin therapy the leg was still pulseless, blood pressure was low or unrecordable, and if there was poor skin perfusion and pallor compared with the other leg. Absence of pulses was confirmed by Doppler ultrasonography. In most patients arterial thrombosis was confirmed by colour coded Doppler sonography (Acuson 128 XP 10, 3–7 MHz transducer) (fig 1).

After 24 hours heparin was stopped and alteplase (Actilyse) was infused at a rate of 0.5 mg/kg/h for the first hour followed by 0.25 mg/kg/h until pulses were palpable and blood pressure in both legs was similar or bleeding complications occurred. Except for those cases with severe bleeding complications, the heparin infusion (300 U/kg/day) was continued to 24 hours after alteplase treatment was stopped.

### LABORATORY TESTING

Before treatment with alteplase was started a complete blood cell count was obtained and prothrombin time (PT) activated partial thromboplastin time (aPTT), thrombin time, fibrinogen, antithrombin III, liver enzymes (aspartate and alanine aminotransferases), urea, and creatinine were measured. Fibrinogen, thrombin time, PT, and aPTT were measured before, 2, 4, 8, and 24 h after starting treatment with alteplase.

### Results

Clot dissolution (fig 2) was complete in 16 patients. In one patient poor skin perfusion and pallor disappeared, posterior tibial pulses became palpable, and blood pressure in both legs was similar after six hours of alteplase treatment but the tibial pulses disappeared again 15 hours after alteplase was stopped. At thrombectomy a 10 cm long clot was recovered from the femoral artery of this patient. In one patient pulses reappeared and alteplase was stopped four hours after treatment started despite reduced blood pressure in the catheterised leg (table). This did not accord with the study protocol. This patient was discharged with partial clot dissolution and reduced blood pressure in the affected leg. Nine months later his pulses were normal and there was no blood pressure difference between the legs.

The mean duration of lysis was 7.1 (range 4–11 h). Eight patients bled from the arterial puncture site. In three bleeding was severe and they had to be treated with packed erythrocytes because of acute hypotension or a decrease of haematocrit of >15% or both. In one of these three patients compression of the puncture site had been stopped too soon after the ultrasonographic examination. One patient showed mild epistaxis. No patient had a severe systemic bleeding diathesis or other side effects of alteplase treatment (table). The duration of treatment with alteplase was similar in patients with bleeding and in those

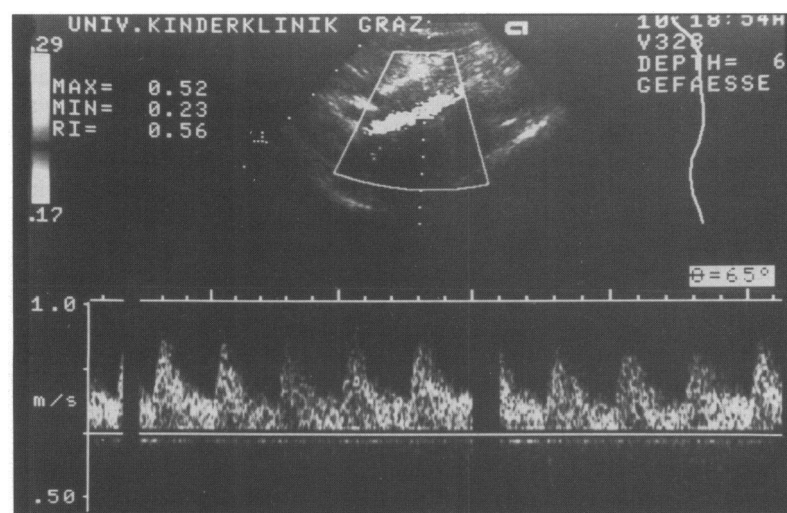


Figure 2 Black and white version of colour-coded Doppler echocardiogram of the left femoral iliac artery (3 MHz, sector transducer) in patient 16 (table) 10 hours after treatment with alteplase was started. The vessel was well perfused and a Doppler gated image ( $\alpha = 65^\circ$ ) showed flow that indicated recanalisation.

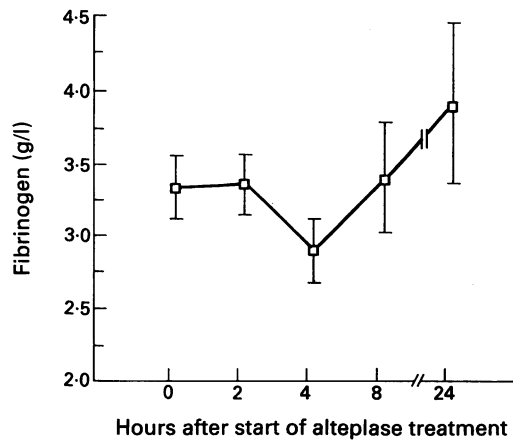


Figure 3 Mean (1 SD) fibrinogen and time after the start of alteplase treatment in 17 consecutive children with femoral artery thrombosis after cardiac catheterisation.

without, but bleeding was more common in older patients. The mean age of patients with bleeding was 26.9 months, whereas in patients without bleeding it was 16.7 months.

#### LABORATORY DATA

Fibrinogen concentrations remained constant during the first two hours of treatment and fell by a mean of 0.45 g/l from the second to the fourth hour of treatment. By 24 hours after starting alteplase, fibrinogen concentrations had increased by a mean of 0.55 g/l (fig 3). PT, aPTT, and thrombin times showed no clear trend.

Fibrinogen concentrations at the end of fibrinolytic treatment were known in seven patients without bleeding complications and in five patients with bleeding from the arterial puncture site. The mean fibrinogen concentration was 3.44 g/l in the group without bleeding and 2.15 g/l in the group with bleeding. Fibrinogen concentrations at the end of fibrinolytic treatment had increased by 0.18 g/l in the group without bleeding complications and decreased by 0.67 g/l in the group with bleeding from the arterial puncture site.

#### Discussion

There are few reports on fibrinolytic therapy in childhood and most are of urokinase and streptokinase therapy.<sup>6 9 11 13 20</sup> Alteplase has several advantages over these drugs—most importantly specific and strong binding to fibrin leading to preferential, efficient activation of fibrin-bound plasminogen.<sup>15</sup> Though alteplase is a poor activator of circulating plasminogen, when it is bound to a fibrin surface it becomes several hundred times more effective.<sup>22</sup> Fibrin-bound plasmin is stereochemically protected from the most potent plasmin inhibitor  $\alpha_2$ -antiplasmin.<sup>15</sup> Thus alteplase induces clot-selective fibrinolysis rather than the widespread proteolysis associated with activation of circulating plasminogen induced by streptokinase and urokinase.<sup>23</sup>

The plasma half life of alteplase is five minutes and is shorter than that of streptokinase and urokinase, allowing better dosage management.<sup>24</sup> Because tissue plasminogen acti-

vator is produced by human tissues as a therapeutic agent, alteplase, it is generally regarded as non-immunogenic.<sup>25</sup>

Experience with the use of alteplase in childhood, however, is limited and there are no prospective studies of its effects in thrombotic diseases in children and no clear dosage recommendations for this age group.<sup>16-21</sup>

In 16 of our 17 patients clot lysis was achieved with alteplase. In the remaining patient, who showed only partial clot dissolution, alteplase was stopped too soon. The duration of treatment (4 h) was short compared with a mean lysis time of 7.1 hours for the whole group.

The frequency of rethrombosis was low and similar to other reports on streptokinase or urokinase in children with femoral artery thrombosis after cardiac catheterisation.<sup>6 13 14</sup>

Bleeding complications were seen in nine patients (53%), with bleeding and oozing from the arterial entry site, and all were controlled by groin compression. Bleeding always occurred when clinical signs of reperfusion of the leg appeared. Levy *et al* reported a similar high rate of bleeding complications in children when the dose of alteplase was 0.46–0.5 mg/kg/h.<sup>16</sup>

Low concentrations of fibrinogen at the end of fibrinolytic treatment seemed to correlate with bleeding complications: mean fibrinogen was lower in patients with bleeding than in patients without. In patients with bleeding complications mean fibrinogen was lower at the end of lysis than before the start of alteplase treatment. In patients without bleeding complications the fibrinogen concentration remained constant. Close monitoring of fibrinogen during alteplase treatment may aid recognition of patients at an increased risk of bleeding complications. Bleeding and a decrease in fibrinogen did not seem to be correlated with duration of treatment, but bleeding was more common in older children. Bleeding complications may have been caused because the dose was adjusted for body weight in neonates, infants, and older children—hence a pharmacologically higher dose in older children.

The results of giving continuous heparin infusions during treatment with alteplase were better than when alteplase only was given.<sup>26 27</sup> This suggests that treatment with a combination of alteplase and continuous heparin may achieve the same therapeutic effects with lower doses of alteplase, which might reduce the risk of bleeding complications.

But a trial of very low doses of alteplase in adults with venous thromboses did not yield good results.<sup>28</sup> Children, however, usually do not show the same vascular risk factors for bleeding as adults and thus may tolerate relatively higher doses without bleeding.<sup>28</sup> Much lower doses of alteplase have been used as local infusions but this approach is not to be practical in patients with arterial thrombosis at the puncture site after cardiac catheterisation.<sup>29</sup>

We conclude that alteplase was effective in inducing clot lysis in children with arterial thrombosis after cardiac catheterisation.

Because bleeding complications were common, however, further studies with lower doses of alteplase in combination with heparin and doses adjusted for age will be required.

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