Vasculitis complicating treatment with intravenous anisoylated plasminogen streptokinase activator complex in acute myocardial infarction

CLIFFORD BUCKNALL, CHARLES DARLEY,* JOHN FLAX,†
RICHARD VINCENT, DOUGLAS CHAMBERLAIN

From the Departments of Cardiology and *Dermatology, Royal Sussex County Hospital, Brighton, and
†Beecham Pharmaceuticals, UK Division, Brentford, Middlesex

SUMMARY Vasculitis developed in six of 253 patients treated with intravenous anisoylated plasminogen streptokinase activator complex (APSAC) after acute myocardial infarction. All patients recovered spontaneously with no evidence of renal impairment and no long term sequelae.

Although leucocytoclastic vasculitis and serum sickness have been reported after streptokinase treatment, such allergic reactions have not been described as a complication of other thrombolytic agents.

Anisoylated plasminogen streptokinase activator complex (APSAC) is a thrombolytic agent offering potential advantages that include ease of administration by intravenous injection over a few minutes.

The common unwanted effects of a related thrombolytic compound, streptokinase, include haemorrhage, fever, and an immediate allergic reaction.¹ Serum sickness²⁻⁵ and crescentic glomerulonephritis⁶ have also been described after streptokinase treatment, and in each case the patient had a purpuric rash. A further two papers describe non-specific rashes caused by streptokinase.^{1,7}

We report the development of vasculitis in six of 253 patients treated with anisoylated plasminogen streptokinase activator complex after acute myocardial infarction.

Patients and results

In Brighton, up to June 1987, 253 patients presenting with suspected acute myocardial infarction had been treated with anisoylated plasminogen streptokinase activator complex (APSAC); all were treated within four hours of the onset of

major symptoms. Each patient was given 30 units of anisoylated plasminogen streptokinase activator complex intravenously over four minutes together with conventional treatment with opiate analgesia, an antiemetic, and intravenous heparin.

In six patients (five male, one female) a purpuric rash developed 7-15 days after the administration of anisoylated plasminogen streptokinase activator complex. In each case there was purpura, particularly of the extensor surfaces of the legs. In two patients the rash also affected the extensor surfaces of their arms. The lesions varied from areas of purpura (3-7 mm in diameter) to necrotic vesicles (figure). The rash began to resolve after 2-5 days and had completely disappeared after three weeks. The table gives further details of the patients.

Five of the six patients developed arthralgia with swelling around their ankles as well as the rash. Of these, three had abdominal distension with colicky abdominal pain and diarrhoea. One patient with abdominal symptoms had melaena; endoscopy showed that the gastric mucosa was purpuric. These abdominal symptoms had a similar time course to the rash. No patient had clinical evidence of progressive renal impairment, although urinalysis showed mild proteinuria and haematuria in two patients.

No fall in haemoglobin concentration was detected, even in the patient who had melaena. Similarly, the platelet counts in each patient remained

Requests for reprints to Dr Douglas Chamberlain, Cardiac Department, Royal Sussex County Hospital, Eastern Road, Brighton, East Sussex BN2 5BE.

Accepted for publication 17 September 1987

Figure Allergic vasculitis of the legs.

within the reference range. The plasma concentration of urea increased in the two patients with proteinuria and haematuria, from 6.7 to 10.1 mmol/l in one and from 5.2 to 23.5 mmol/l in the other (the patient with melaena), but the plasma concentration of creatinine did not exceed the upper limit of the reference range in either. During their hospital stay serum immunoelectrophoresis remained normal and antinuclear factors were negative in all six patients, but two patients had a positive rheumatoid factor. Skin biopsies were performed in two patients and showed lymphocytic vasculitis. Renal biopsies were not performed as all patients had a benign course.

Discussion

Drug induced vasculitis is a condition characterised clinically by a purpuric skin eruption that develops usually about 10 to 14 days after exposure to the

drug.⁸ Characteristically the rash affects the extensor surfaces of the arms or legs and resolves within three weeks of its onset.⁸ Associated symptoms can include abdominal pain, arthralgia, gastrointestinal bleeding, and haematuria, suggesting serum sickness disease.⁸ All six of our patients had a purpuric rash in the characteristic distribution, and five had associated symptoms. From a clinical point of view, therefore, the findings in these patients are suggestive of a vasculitis caused by the administration of anisoylated plasminogen streptokinase activator complex.

On skin biopsy, the features usually seen in patients with purpuric vasculitis are a neutrophil rich perivascular infiltrate, red cell extravasation, fibrinoid deposits in or around the blood vessel wall, and fragmentation of neutrophils (leucocytoclasia).⁹ The biopsy specimens from our patients showed minimal leucocytoclasia, predominantly mononuclear cell infiltration around dermal vessels, virtu-

Table Patient details

Patient	Age	Sex	Myocardial infarction			Rash			Associated symptoms		
			Site	AST max (0-41)* (U/l)	LDH max (120-360)* (U/l)	Site	Size (mm)	Onset (days)	Arthro- pathy	GI	Renal
1	57	M	Inf	457	733	Legs	3-5	9	+	+	-
2	64	M	Ant	431	553	Legs	5	10	-	-	-
3	60	M	LBBB	85	489	Legs/arms	3-7	8	+	+	+
4	61	M	Ant	314	1739	Legs/arms	3-5	15	+	+	+
5	62	M	Inf	100	643	Legs	5	7	+	-	-
6	73	F	Ant	121	471	Legs	5-7	11	+	-	-

Ant, anterior myocardial infarction; AST, aspartate transaminase; GI, gastrointestinal; Inf, inferior myocardial infarction; LBBB, left bundle branch block; LDH, lactate dehydrogenase.
*Normal range.

ally no red cell extravasation, and no fibrinoid deposits. The biopsy specimens were taken just before the rash began to resolve in both cases. This may explain the absence of characteristic histological features.⁹

A large number of drugs have been reported to precipitate vasculitis. Sulphonamides, penicillins, and aspirin are prime offenders, but many high molecular weight drugs may act as antigenic sources.⁸ Two patients had been prescribed thiazide diuretics before the onset of their reaction, but the four other patients had not received any medication before admission. An alternative cause for the rash may be heparin treatment, which had been given to all six patients. Heparin has been associated with hypersensitivity reactions after intravenous administration, but these have been of the immediate type.⁸ Heparin is used routinely on our unit and we have never seen this type of rash before, although localised purpura at the injection sites has been seen after subcutaneous heparin.

The treatment of allergic vasculitis, usually a benign disorder, is largely empirical. The main factor determining prognosis is the degree to which the kidneys are affected, although gastrointestinal infarction and pulmonary involvement may occasionally lead to death.⁸ Patients with multisystem involvement are often treated with corticosteroids, but evidence is lacking to show that such treatment alters the course of the illness.⁸

Awareness of this late complication of treatment with anisoylated plasminogen streptokinase activator complex is important for those treating acute myocardial infarction with this agent. The distinction must be drawn, however, between the long

term benefit of myocardial salvage and the small risk of a transient allergic reaction that seems on present evidence to be benign.

References

- 1 Valentine RP, Pitts DE, Brooks-Brunn JA, Williams JG, Van Hove E, Schmidt PE. Intravenous versus intracoronary streptokinase in acute myocardial infarction. *Am J Cardiol* 1985;55:309-12.
- 2 Alexopoulos D, Raine AEG, Cobbe SM. Serum sickness complicating intravenous streptokinase therapy in acute myocardial infarction. *Eur Heart J* 1984;5:1010-2.
- 3 Totty WG, Romano T, Benian GM, Gilula LA, Sherman LA. Serum sickness following streptokinase therapy. *Am J Radiol* 1982;138:143-4.
- 4 Weatherbee C. Serum sickness following selective intracoronary streptokinase. *Curr Ther Res* 1984;35:433-8.
- 5 Noel J, Rosenbaum LH, Gangadharan V, Stewart J, Galens G. Serum sickness-like illness and leukocytoclastic vasculitis following intracoronary arterial streptokinase. *Am Heart J* 1987;113:395-7.
- 6 Murray N, Lyons J, Chappell M. Crescentic glomerulonephritis: a possible complication of streptokinase treatment for myocardial infarction. *Br Heart J* 1986;56:483-5.
- 7 Ganz W, Geft I, Shah PK, et al. Intravenous streptokinase in evolving acute myocardial infarction. *Am J Cardiol* 1984;53:1209-16.
- 8 Olsen T. Peripheral vascular diseases, necrotising vasculitis, and vascular-related diseases. In: Moschella SL, Hurley HJ, eds. *Dermatology* Vol. 1. 2nd ed. Philadelphia: WB Saunders, 1985:1000-86.
- 9 Sams WM, Thorne EG, Small P, Mass MF, McIntosh RM, Stanford RE. Leukocytoclastic vasculitis. *Arch Dermatol* 1976;112:219-26.

Vasculitis complicating treatment with APSAC

term benefit of myocardial salvage and the small risk of a transient allergic reaction that seems on present evidence to be benign.

References

- 1 Valentine RP, Pitts DE, Brooks-Brunn JA, Williams JG, Van Hove E, Schmidt PE. Intravenous versus intracoronary streptokinase in acute myocardial infarction. *Am J Cardiol* 1985;55:309-12.
- 2 Alexopoulos D, Raine AEG, Cobbe SM. Serum sickness complicating intravenous streptokinase therapy in acute myocardial infarction. *Eur Heart J* 1984;5:1010-2.
- 3 Totty WG, Romano T, Benian GM, Gilula LA, Sherman LA. Serum sickness following streptokinase therapy. *Am J Radiol* 1982;138:143-4.
- 4 Weatherbee C. Serum sickness following selective intracoronary streptokinase. *Curr Ther Res* 1984;35:433-8.
- 5 Noel J, Rosenbaum LH, Gangadharan V, Stewart J, Galens G. Serum sickness-like illness and leukocytoclastic vasculitis following intracoronary arterial streptokinase. *Am Heart J* 1987;113:395-7.
- 6 Murray N, Lyons J, Chappell M. Crescentic glomerulonephritis: a possible complication of streptokinase treatment for myocardial infarction. *Br Heart J* 1986;56:483-5.
- 7 Ganz W, Geft I, Shah PK, et al. Intravenous streptokinase in evolving acute myocardial infarction. *Am J Cardiol* 1984;53:1209-16.
- 8 Olsen T. Peripheral vascular diseases, necrotising vasculitis, and vascular-related diseases. In: Moschella SL, Hurley HJ, eds. *Dermatology* Vol. 1. 2nd ed. Philadelphia: WB Saunders, 1985:1000-86.
- 9 Sams WM, Thorne EG, Small P, Mass MF, McIntosh RM, Stanford RE. Leukocytoclastic vasculitis. *Arch Dermatol* 1976;112:219-26.