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Invasive reperfusion study II. Multicentre European randomized trial of anistreplase vs streptokinase in acute myocardial infarction

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IRS II (Invasive reperfusion study II) was a multicentre randomized trial comparing the efficacy of a 2–5-min 30 U anistreplase intravenous injection with a 1 500 000 U 60-min streptokinase (SK) intravenous infusion in acute myocardial infarction. 116 patients were randomized within 6 h of onset of symptoms. Early coronary patency was assessable in 107 patients by coronary angiogram performed 102 min after thrombolytic treatment (range: 30–297 min) in the anistreplase group and 93 min (range: 22–330 min) in the SK group. The early coronary patency rate was significantly higher in the anistreplase group than in the SK group: respectively, 70% (38/54) and 51% (27/53), P<0·05. Fifty patients had assessable coronary angiograms at 90 min and 24 h. The 24-h patency rate was 92·3% (24/26) in the anistreplase group vs 87·5% (21/24) in the SK group. No early reocclusion occurred in the anistreplase group vs 15·4% (2/13) in the SK group (NS). Fibrinogen fell to 13·2 ± 19·8% on anistreplase vs 9·4 ± 10·3% on SK (NS). Bleeding complications occurred in 12% (7/58) of treated patients in the anistreplase group vs 20·7% (13/58) in the SK group (NS). Two cerebrovascular accidents occurred after thrombolytic treatment with anistreplase (3·4%) vs one after SK (1·7%) (NS). Thus, anistreplase is more effective than intravenous SK and easier to administer.

Introduction

Streptokinase (SK) intravenous (IV) infusion induces a 35–62% coronary artery reperfusion rate[1,2] and reduces short- and long-term mortality in acute myocardial infarction (AMI)[3–5]. Anistreplase, or Anisoylated Lys Plasminogen Streptokinase Activator Complex, is a third generation thrombolytic agent. Its catalytic centre is temporarily blocked by an anisoyl group. Progressive deacylation occurs in the bloodstream and in the thrombus after IV injection. Theoretically these characteristics give anistreplase an important specificity for fibrin and a long biological half-life (about 90 min after an IV injection, vs 15 min for SK). For these reasons, a high reperfusion rate and low reocclusion rate are expected with anistreplase.

A placebo-controlled randomized study[6] showed a 47·5% reduction in 30-day mortality and a 44·3% estimated reduction in 1 year mortality, for patients given antistreplase. The major aims of the Invasive Reperfusion Study II (IRS II), reported here, were to compare the early coronary artery patency rate, the safety and the biological effects between anistreplase and SK. In a subgroup of patients, the early reocclusion rate was also compared for the two drugs.

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Patients and methods

PATIENTS

To be eligible, patients had to fulfil the following criteria: age <70 years; chest pain suggestive of AMI lasting >30 min and <6 h and not relieved by sublingual nitrates; ST-segment elevation of ≥0·1 mV in one or more frontal leads and/or ≥0·2 mV in one or more precordial leads on the admission electrocardiogram (ECG). Informed consent was obtained from each patient. Patients were excluded if they met any of the following criteria; signs of cardiogenic shock (with systolic blood pressure <80 mmHg); oral anticoagulants; gastric or duodenal ulcer; previous cerebrovascular accident; prolonged or traumatic cardiac resuscitation; coronary artery surgery or percutaneous transluminal coronary angioplasty (PTCA) within the last 2 months; SK treatment within the last 6 months; previous cardiac valvular surgery; congestive cardiomyopathy with known intraventricular thrombus; known or suspected pregnancy; anticipated problems with heart catheterization.

Randomization was performed in an open label fashion and was stratified by site of infarct. Each patient was allocated the next available treatment from a preprepared list in each centre.

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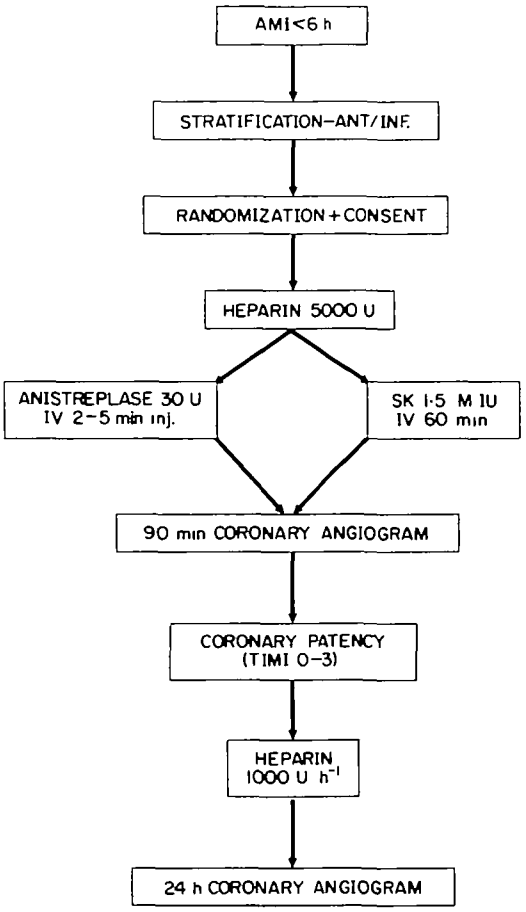

Figure 1 IRS II protocol. Stratification between anterior (ANT.) and inferior (INF.) acute myocardial infarction (AMI) was made before randomization.

METHODS

Treatment (Fig. 1)

After admission to the Intensive Care Unit, all patients received routine treatment of AMI, according to local practice plus a 5000 IU heparin IV injection and 100 mg hydrocortisone IV injection.

Patients randomized to the anistreplase group received a 2–5-min IV injection of 30 U of anistreplase. The patients allocated to SK received 1 500 000 U of SK administered by infusion pump over 60 min.

After thrombolytic treatment was started, the patient was transferred to the cardiac catheterization laboratory. Selective coronary arteriography was performed by the Judkins technique. In each group, a continuous intravenous infusion of heparin (1000 IU h^{-1}) was started 6 h after the beginning of thrombolytic treatment and lasted 5–10 days. Aspirin and other antiaggregant drugs were not allowed during the first 24 h.

Assessment of coronary arteriograms

The objective of the study was to compare the early patency of the infarct-related coronary artery between the two treatment groups at 90 min. Each angiogram was read locally by an experienced cardiologist and independently by a central assessor, blinded to the treatment group, who determined the relevant lesion and the coronary artery flow according to TIMI grades[2]. In cases of discrepancy, a third reading was taken by a second independent central assessor. Coronary artery reperfusion was considered a success if the flow grade was 2 or 3 and a failure if the flow grade was 0 or 1.

In a subgroup of 59 patients, a second coronary angiography was performed 24 h after treatment in order to assess early coronary reocclusion. The arteriograms of the 50 patients who had neither subsequent thrombolysis nor bypass surgery or PTCA were analysed by an independent central assessor blinded to the treatment group.

Clinical monitoring

During the first few days, heart rate, blood pressure and cardiac rhythm were monitored in the Intensive Care Unit. An electrocardiogram was recorded at the end of thrombolytic treatment, each day until discharge, and in cases of recurrent pain. Reinfarction was defined as a recurrent pain associated with electrocardiogram modifications and increase of cardiac enzymes.

Analysis of blood samples for coagulation and fibrinolytic assays

Blood samples were collected before thrombolytic treatment, 1 h after the start of infusion and then every 3 h for 24 h for assay of fibrinogen, α_2-antiplasmin, plasminogen, clot lysis time, activated partial thromboplastin time (APTT) and thrombin time. Fibrinogen level was determined by the Clauss method.

Statistical methods

The statistical tests used for assessing the significance between groups were either Fisher's Exact for 2×2 contingency tables or Student's *t*-test or ANOVA for assessing effects on continuous variables or likelihood chi-square for analysis of multi-way contingency tables. All analyses were performed using the commercial software packages SAS or RS/1.

Results

116 patients were randomized and treated in 17 months. Baseline characteristics on admission were similar in the two treatment groups, as shown in Table 1. Time from onset of symptoms to thrombolytic treatment was <4 h in 84% of the patients (97/116).

ANGIOGRAPHIC FINDINGS

Early coronary patency

Analysis of the 90-min coronary patency included 107 patients of the 116 treated patients. Two anistreplase group patients were excluded because AMI was not confirmed (pericarditis and unstable angina). One SK group patient was excluded because he did not fulfil the ECG inclusion criteria. One SK group patient was excluded because he had cardiogenic shock on admission. Another patient was excluded because SK infusion had been

Table 1 Baseline characteristics of patients

Variable	Group	
	Anistreplase (n = 58)	SK (n = 58)
Age (years)	55·2	54
Range	(28–69)	(29–69)
Males (%)	84	90
Anterior infarction (%)	50	48
Congestive heart failure (%)	7	5
Systolic/diastolic blood pressure	134/85	135/84
Heart rate (beats min^{-1})	77	75
Time to thrombolytic treatment (min)	162	168
Range	(30–360)	(30–336)

stopped after 5 min due to mental confusion followed by ventricular fibrillation. Four other patients were excluded for missing coronary angiograms (two anistreplase, one SK) or subsequent thrombolysis before evaluation (one SK). Mean time from thrombolytic treatment to angiography was similar in the two treatment groups: 102 min (range: 30–297 min) on anistreplase and 93 min (range: 22–330 min) on SK. Thirty-seven patients (68·5%) on anistreplase and 40 (75·5%) on SK had their first coronary angiogram within 75–105 min of the beginning of thrombolytic treatment (Fig. 2).

The early coronary patency rate was higher in the anistreplase group than in the SK group: 70% (38/54) vs 51% (27/53) ($P < 0·05$) (Table 2). Patients submitted to a first angiogram within 75–105 min showed a coronary patency rate of 70% (26/37) in the anistreplase group vs 50% (20/40) in the SK group ($P < 0·05$).

The early coronary patency rate was 73% (22/30) in the anistreplase group vs 47% (15/32) in the SK group ($P < 0·05$) for those randomized between hour 0 and hour 3, and 67% (16/24) and 57% (12/21) respectively for patients randomized between hour 3 and hour 6 (NS). The early patency rate was 74% (20/27) in the anistreplase group vs 54% (13/24) in the SK group for anterior AMI and 66% (18/27) vs 48% (14/29), respectively, for inferior AMI (Table 3).

Early coronary reocclusion and 24 h patency rate

Fifty-nine patients had a second coronary angiography 24 h after thrombolytic treatment (range: 15–50 h), nine patients were excluded because they had had PTCA (one anistreplase, two SK) or subsequent thrombolysis (two anistreplase, four SK) within the first 24 h. For the 50 patients with assessable coronary angiograms the early patency rate was 65% (17/26) in the anistreplase group and 54% (13/24) in the SK group. After anistreplase no reocclusion was observed at the second angiography and the 24-h patency rate was 92% (24/26). After SK, there were two reocclusions, one silent with no reinfarction and one associated with reinfarction; the 24-h patency rate was 87·5% (21/24) (Fig. 3). The early reocclusion rate was 15% (2/13) in the SK group (NS).

BIOLOGICAL RESULTS

The mean decrease of the haemoglobin value was identical in the two treatment groups: 1·6 g dl^{-1}. Anistreplase and SK both induced extensive systemic fibrinolytic activation. Fibrinogen fell to 13·2 ± 19·8% of the starting value in the anistreplase group vs 9·4 ± 10·3% in the SK group after 60 min (NS). The plasminogen level fell to 23·5 ± 23·5% at the third hour in the anistreplase group vs 24·5 ± 26·7% in the SK group. The α_2-antiplasmin level fell to 7·3 ± 12·9% after 60 min in the anistreplase group vs 3·10 ± 9·4% in the SK group. Fibrin degradation products value increased to 422·5 ± 297–3 ng ml^{-1} after 60 min in the anistreplase group vs 320 ± 196 ng ml^{-1} in the SK group (Fig. 4).

IN-HOSPITAL EVENTS (TABLE 4)

Major cardiac events

The recurrent AMI rate was similar in the two treatment groups: 8·6% (5/58) in the anistreplase group vs 6·7% (4/58) in the SK group (NS). In the anistreplase group, all reinfarctions occurred after the first 24 h, whereas in the SK group, one reinfarction occurred within the first 24 h and three between 24 h and discharge.

Mechanical revascularization attempts tended to be more frequent after anistreplase than after SK: respectively, 29% (18/58) and 14% (8/58) (NS) (Table 4).

Early mortality

Two deaths occurred in the anistreplase group, both from cardiogenic shock, one on day 3 and the other on day 17. Three deaths occurred in the SK group: one on day 7 due to cerebral bleeding, one on day 5 from cardiogenic shock and one on day 15 from a catheterization accident during routine coronary angiography.

Treatment adverse effects (Table 5)

The confirmed haemorrhagic complication rate was, respectively, 12% (7/58) and 20·7% (12/58) on anistreplase and SK (NS). Details of haemorrhagic complications are shown in Table 5. A patient developed haemorrhagic shock 10 h after anistreplase injection, related to a retroperitoneal haematoma treated by laparotomy. This patient died 17 days later from cardiogenic shock. His coagulation parameters are unknown. Two cases of cerebral bleeding, confirmed by tomodensitometry occurred. A 63-year-old patient had hemiplegia and aphasia 21 h after anistreplase injection; APTT reached an abnormally high level, 12 h after thrombolytic treatment > 120 s) and was not controlled afterwards; he had a history of subarachnoid bleeding and therefore should have been excluded from the study. A 48-year-old patient had mental confusion after a 5-min SK infusion; he developed hemiplegia 9 h later and died after tomodensitometry had shown an extended temporoparietal haematoma; APTT was not abnormally increased at the time of the attack. A 51-year-old patient had hemianaesthesia 16 h after anistreplase injection; tomodensitometry did not show any sign of bleeding, but APTT was abnormally high at this time (182 s, 15 h after thrombolytic treatment).

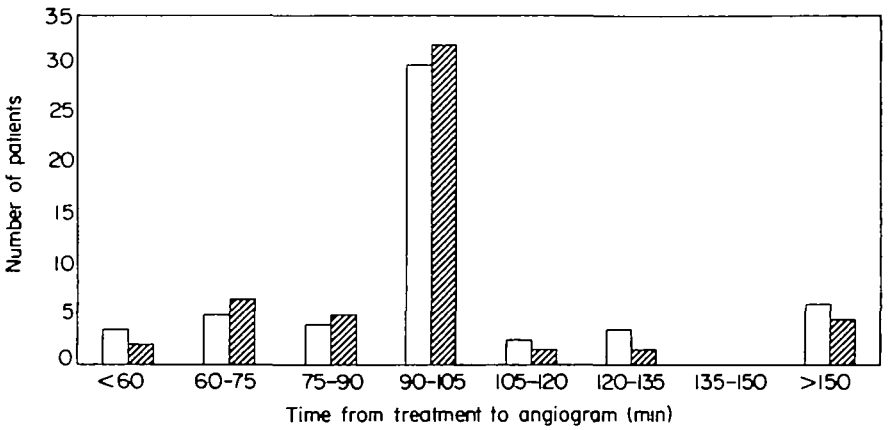

Figure 2 Number of patients according to the time between thrombolytic treatment and angiography. □ = anistreplase, ▨ = streptokinase.

Table 2 Early coronary patency rate

	Group	
	Anistreplase	SK
Assessable coronary angiograms (n)	54	53
Mean time from treatment to angiography (min)	102	93
Range	(30–297)	(22–330)
Coronary patency rate % (n)	70 (38)	51 (27)*

* = $P < 0.05$.

Table 3 Early coronary patency rate according to thrombolytic treatment delay and to infarct location

	Anistreplase	SK
Time to treatment:		
0–3 h	73	47*
(n)	(22/30)	(15/32)
3–6 h	67	57
(n)	(16/24)	(12/21)
Infarct location:		
Anterior infarction	74	54
(n)	(20/27)	(13/24)
Inferior infarction	66	48
(n)	(18/27)	(14/29)

* = $P < 0.05$.

A patient developed anaphylactic shock immediately after anistreplase injection; this shock was successfully treated with dopamine and hydrocortisone. No allergic reaction occurred in the SK group. Systolic blood pressure fell below 90 mmHg during or immediately after thrombolytic treatment in 5% (3/58) of the patients given anistreplase and 1·7% (1/58) of those given SK (NS).

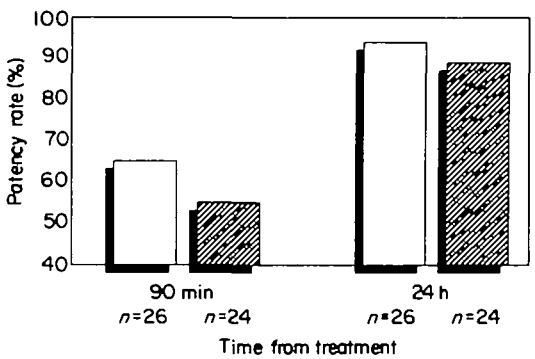

Figure 3. Early and 24-h coronary artery patency rate in the subgroup of 50 patients with assessable coronary angiograms at both times. □ = anistreplase, ▨ = streptokinase.

Ventricular arrhythmias

Ventricular tachycardia occurred in two of the anistreplase patients (3·4%) vs four of the SK patients (8·6%) (NS). Ventricular fibrillation occurred in four SK patients (6·9%) and none of the anistreplase patients (NS).

Discussion

IRS II confirms that a 30 U anistreplase IV injection, when administered within 6 h of the onset of AMI, gives a significantly higher early coronary patency rate than 1 500 000 IU of SK infused in 60 min; 70% and 51%, respectively ($P < 0.05$). The early coronary patency rate ranged from 84 to 88% in previous non-randomized trials[7–9]. Another similar but smaller trial[10] showed that efficacy was better with anistreplase than with SK, the 240-min coronary patency rate being 93 and 64%, respectively. Anistreplase, although it has never been compared with recombinant tissue type plasminogen activator (rt-PA) in a randomized trial, seems to provide a similar early coronary patency rate as rt-PA, the latter's 90-min coronary patency rate ranging from 61 to 70% in the two European cooperative multicentre randomized

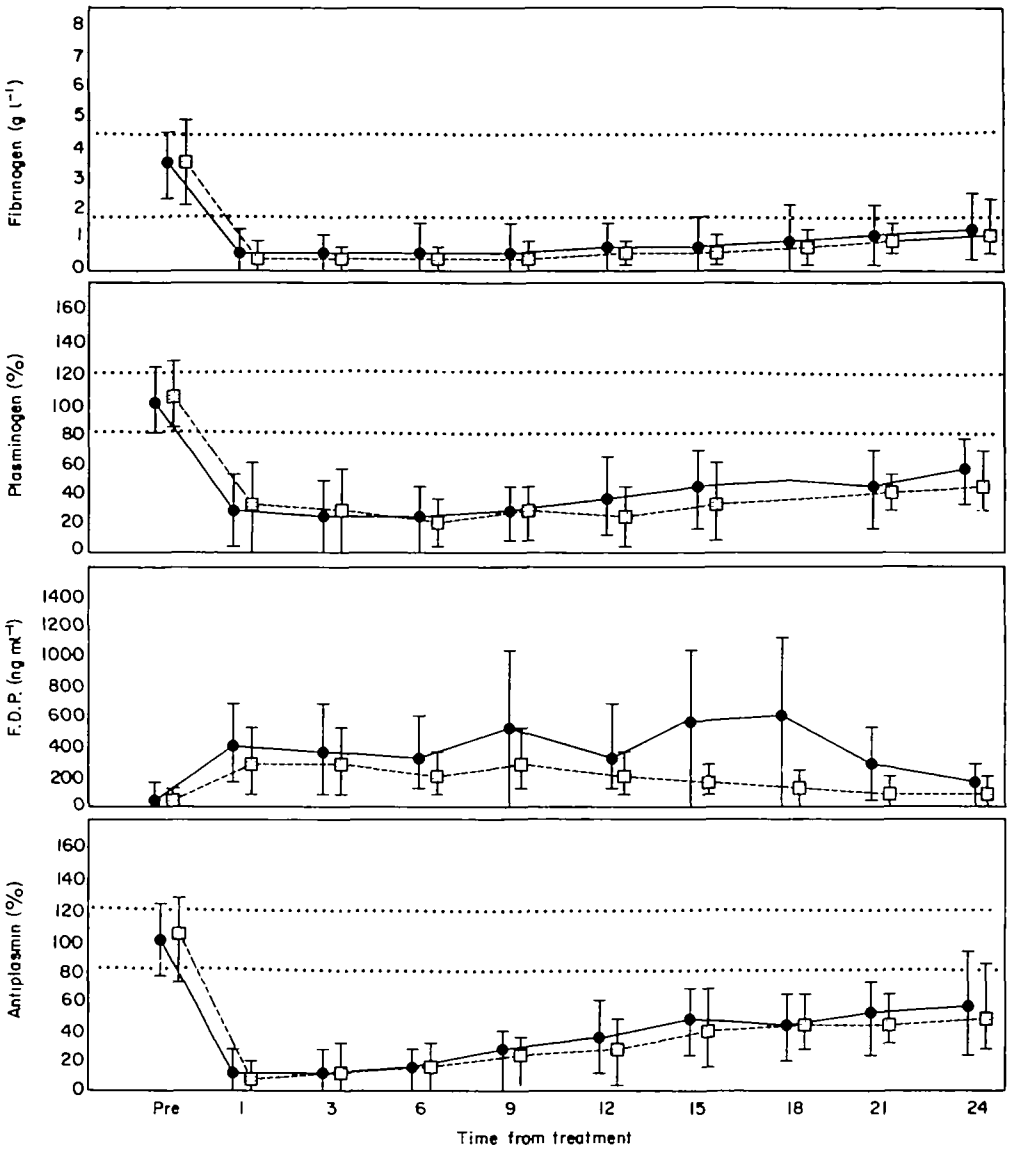

Figure 4 Evolution of fibrinolytic system parameters after thrombolytic treatment —●— = anistreplase, – – ⊡ – – = streptokinase.

Table 4 In-hospital events

	Group	
	Anistreplase n = 58 n(%)	SK n = 58 n(%)
Ventricular arrhythmias		
ventricular tachycardia	2 (3·4)	4 (6·9)
ventricular fibrillation	—	4 (6·9)
Coronary surgery	4 (6·9)	—
PTCA	14 (24·1)	8 (13·8)
Reinfarction	5 (8·6)	4 (6·7)
Death	2 (3·4)	3 (5·2)

PTCA = percutaneous transluminal coronary angioplasty.

Table 5 Adverse effects

	Group	
	Anistreplase n = 58 n(%)	SK n = 58 n(%)
Anaphylactic reaction	1 (1·7)	—
Hypotension	3 (5·0)	1 (1·7)
Bleedings		
—Puncture site	4 (6·9)	8 (13·8)
—Retropéritonéal	1 (1·7)	—
—Gastrointestinal	1 (1·7)	2 (3·4)
—Haematuria	1 (1·7)	2 (3·4)
Cerebrovascular accidents	2 (3·4)	1 (1·7)

studies using a 0·75 mg kg^{-1} rt-PA IV infusion[11,12], and 75% in TIMI IIb using a 100 mg rt-PA IV infusion[13].

Two randomized trials comparing the efficacy of a 30 U anistreplase IV injection with intracoronary SK showed a similar or slightly inferior reperfusion rate with the former: respectively, 53 vs 67% in the first study[14] and 64 vs 68% in the second[15]. The reperfusion rate obtained with anistreplase is equivalent to the 60% rate obtained with rt-PA in the TIMI study[2]. Reperfusion delay seems to be shorter with anistreplase than with rt-PA, as it was 35 min for patients with total coronary occlusion in one anistreplase study[16] vs 60 min with rt-PA in the TIMI study[2].

In IRS II, anistreplase was more effective than SK only in patients randomized within 3 h after the onset of symptoms. Anderson *et al.* found similar results in a randomized study comparing anistreplase with intracoronary SK[14]; the reperfusion rate being respectively 56 vs 40% in patients treated within 4 h and 25 vs 78% in patients treated between 4 and 6 h after the onset of symptoms.

The early reocclusion rate ($\leqslant$24 h) is important to consider, as it can compromise the early results of thrombolytic treatment before PTCA can be performed on a severe residual stenosis. With rt-PA, the reocclusion rate seems to be closely related to the dose and to the duration of infusion; Gold *et al.*[17] found a 45% (5/11) reocclusion rate within 1 h after the end of a 0·4–0·75 mg kg^{-1} infusion administered for 1–2 h vs no reocclusion (0/13) when a 10 mg h^{-1} complementary infusion was administered for 4 h. Serruys *et al.*[18] and Verstraete *et al.*[19], in a similar trial, did not find the same results, but mean diameter residual stenosis was 53% in their study vs 87% in Gold's study[17]. Collen *et al.*[20] found a 15·3% (2/13) reocclusion rate within 30 min of the end of a 0·75 mg kg^{-1} rt-PA infusion and, in a German trial[21], the reocclusion rate within 24 h was 10·5% (6/57) after a 70 mg rt-PA infusion administered over 90 min. In IRS II, anistreplase tended to be more effective than SK, as there was no early reocclusion in the anistreplase group (0/17) vs a 15·4% reocclusion rate (2/13) in the SK group (NS). Bonnier *et al.*[15] found a 5% reocclusion rate (1/22) within 24 h with anistreplase vs 13% (3/23) with intracoronary SK. Anderson *et al.*[14] found a 9% reocclusion rate (6/67) within the 90-min laboratory observation with anistreplase vs 15% (11/73) with intracoronary SK.

Anistreplase fibrin specificity is only seen with less than 10 U IV injections[22–25] but this dose does not provide a high reperfusion rate, as shown by Marder *et al.*[16]. In IRS II, major systemic fibrinolysis occurred in all SK patients, and all but one anistreplase patient. It was similar in the two groups, with an 87% reduction of fibrinogen in the anistreplase group vs 90·5% in the SK group (NS). The same results have been shown by other studies using the same regimen[14,16,26,27]. Systemic fibrinolysis is less pronounced with rt-PA, with a 39% drop in the fibrinogen level in the European cooperative multicentre randomized study of rt-PA vs SK[12].

The haemorrhagic complication rate in the anistreplase group was slightly less than that of the SK group (respectively 12 and 20·7%, NS); however the spontaneous bleeding rate was similar in the two groups (6·9 vs 8·6%). The cerebrovascular accident rate was 3·4% (2/58) in the anistreplase group vs 1·7% in the SK group. Four severe complications were related to thrombolytic treatment (three cerebrovascular accidents and one retroperitoneal haematoma). However, in two cases, APTT reached an abnormally high level with heparin at the time of the attack and in one of these cases, there was also a formal contra-indication of thrombolytic treatment (previous subarachnoid bleeding). These facts underline the absolute necessity of paying attention to contra-indications of thrombolytic treatment and of close surveillance of the associated heparin treatment. Johnson[28], in 1987, pooled the clinical results of various studies concerning 590 patients treated with anistreplase and found a 9% bleeding complication rate, 1% being gastrointestinal 1% bronchopulmonary and 1% cerebrovascular accidents. Preliminary results of the AIMS study[6] showed a 0·4% cerebrovascular accident rate with anistreplase (30 U IV injection) vs a 1% rate in the placebo group. The cerebrovascular complication rate with anistreplase and IV SK are quite similar if we refer to the widest study using IV SK[16] which showed a 0·7% cerebrovascular accident rate. As for rt-PA, the bleeding complication rate seems to be largely dose-dependent, as shown in the TIMI IIb study, in which cerebral bleeding occurred in 0·6% of patients given 100 mg IV (which provides an early coronary patency rate similar to that of anistreplase) and 1·6% in those given 150 mg IV[13].

Conclusion

A 30 U anistreplase IV injection, when administered within 6 h of the onset of AMI, offers a better early coronary patency rate than a 60 min IV SK infusion of 1 500 000 IU. The greater efficacy of anistreplase is most obvious within 3 h of the onset of symptoms. The early reocclusion rate seems to be very low with this drug. The safety of these two drugs is similar.

For these reasons, anistreplase appears to be well adapted for the treatment of AMI during the first few hours, especially in mobile care units and community hospitals.

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