Rapid Haemodynamic Improvement Following Saruplase in Recent Massive Pulmonary Embolism

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Summary

In a single centre pilot study, saruplase (20 mg bolus plus 60 mg infusion over 1 h) was administered to twenty patients with an angiographically documented recent massive pulmonary embolism: Miller index of at least 20 and mean pulmonary artery pressure of at least 20 mmHg. The lytic ability of saruplase to cause normalization of haemodynamic parameters over the first 12 h and reperfusion of pulmonary arteries at 24 h was assessed. A decrease of 25 ± 10% in total pulmonary resistance was evident at 30 min. Haemodynamic parameters continued to improve with total pulmonary resistance decreasing by 29 ± 8% and 40 ± 11% at 1 and 12 h respectively. Relative improvement in Miller index 24 ± 6 h after saruplase treatment was 38 ± 9%. Two patients suffered recurrent pulmonary embolism, two severe bleeding events were observed. One patient died following a haemorrhagic stroke.

Introduction

The rapid improvement in haemodynamic parameters following recent massive pulmonary embolism is regarded to be of clinical significance for the subsequent prognosis of the patient (1). Thrombolytic agents such as streptokinase, urokinase and tissue-type plasminogen activator (t-PA) have been shown to induce a rapid lysis of massive pulmonary emboli and a subsequent decrease in pulmonary hypertension (2-4).

The efficacy of saruplase in acute myocardial infarction has been clearly established with a dosing schedule of 80 mg, administered as a 20 mg bolus followed by an infusion over 60 min (5). It was decided to employ the same regimen in this pilot trial of the treatment of patients with recent massive pulmonary embolism by saruplase following reports of trials with t-PA where the same dose as used in myocardial infarction was used successfully (3, 4). It was planned to include ten patients, but on the basis of good tolerability in the first patients and following data from Meneveau et al. (6), a protocol amendment was implemented to include a further ten patients and the upper age limit was removed.

Therefore in this pilot trial, saruplase was administered to 20 patients with angiographically demonstrated recent massive pulmonary embolism with the aim of investigating haemodynamic improvement and changes in embolic obstruction.

Materials and Methods

The trial was designed as a single centre pilot study. The study protocol was approved by the Ethics Committee of Tours and was carried out according to Good Clinical Practice from 13/02/93 to 23/01/94. Saruplase was supplied by Gruenenthal GmbH, Aachen, Germany.

Patient Enrollment

Patients were considered for inclusion if the first symptoms of pulmonary embolism occurred within one month and if the onset of symptoms suggesting a massive pulmonary embolism occurred within the 5 days preceding. The permitted age range for the first 10 patients was 18 to 75 years inclusive. The upper age limit was removed following ethics committee approval for the second 10 patients. After written informed consent was obtained, patients underwent a perfusion lung scan for documentation of percentage defect, followed by conventional pulmonary angiography to record the Miller index, which for inclusion was to be equal or greater than 20 (maximum possible score is 34). Mean pulmonary artery pressure (mPAP) on cardiac catheterisation of greater than or equal to 20 mmHg was required for patient enrollment.

The exclusion criteria were: usual contraindications to thrombolysis (1), severe hypoxemia requiring assisted ventilation, contraindication to pulmonary angiography (i.e. known allergy to X-ray dye, pulmonary artery systolic or mean pressure of greater than 70 mmHg or 50 mmHg respectively), contraindications for heparin administration, severe hypotension, cardiac arrest or allergic reaction during first angiography. Patients were followed until 3 months after thrombolysis.

Treatment Protocol

Saruplase (unglycosylated human type high molecular weight single-chain urokinase-type plasminogen activator) (7) was administered to all patients at a dose of 80 mg i.v., given as a 20 mg bolus over one min followed by a 60 mg infusion over 60 min. If not previously given a 5000 IU heparin bolus i.v. was administered prior to lysis, followed by 15 IU/kg/h i.v. infusion until at least the pulmonary angiography scheduled for 24 ± 6 h post-lysis. Heparin was titrated against the activated partial thromboplastin time such that it was prolonged by 2-3 times the control value. Subsequent anticoagulation was according to local routine.

Until haemodynamic monitoring was complete all interventions which could influence the response were prohibited unless clinically necessary. Therefore changes in oxygen delivery rate, inotropic and/or vasoactive drugs were avoided during this period.

Pulmonary Angiography

Pulmonary angiography, using a pigtail catheter was performed with brachial venous access. Contrast medium was injected into the main pulmonary trunk in an anteroposterior position. Angiography was performed both prior to lysis and again at 24 ± 6 h. Standard, large format cut film angiograms were produced. The severity of embolism was assessed by the method of Miller et al. (8). The angiograms were initially scored by the treating physician, but on completion of the trial a central analysis, with blinding of the sequence of angio-
grams, was performed by an experienced third-party (Prof. Claude Thery, University Hospital, Lille, France) external to the study centre.

**Haemodynamic Measurements**

Haemodynamic monitoring of mean pulmonary artery pressure (mPAP) was performed using a Swan-Ganz catheter. Cardiac index was measured by the thermodilution technique, with the mean of three determinations being taken. Total pulmonary resistance (TPR) was calculated as TPR (U/m²) = mPAP (mmHg)/cardiac index (l/min/m²). Zero reference was at the 5th intercostal space on the midaxillary line in the supine or 45° position, with all measurements for the same patient taken in the same position. In order to ensure stability, two pre-thrombolytic measurements were taken at a 15 min interval, with not more than a 10% variation in mPAP and cardiac index being accepted. Pre-lisis haemodynamic status was based on the second series of measurements. Thereafter, haemodynamic monitoring was performed post-lysis at 30 min, 1, 2, 4, 6 and 12 h.

**Perfusion Lung Scan**

Perfusion lung scans were performed on admission, at 48 ± 12 h post-lysis, at discharge and 3 month follow-up. Analysis was performed according to the method described by Brochier et al. (9).

**Haematologic and Haemostatic Measurements**

Blood samples were drawn on patient inclusion, prior to thrombolysis and then at 30 min, 1, 6, 12 and 24 h after thrombolysis for the analysis of haemoglobin, haematocrit, platelets, full blood count, fibrinogen, plasminogen and alpha-2-antiplasmin. Activated partial thromboplastin time was sampled as required for monitoring of heparin levels. All laboratory analyses were performed in the local centre, apart from plasminogen and alpha-2-antiplasmin which were assayed by Gruenenthal GmbH using the test kits Behrichrom Plasminogen and Behrichrom alpha-2-antiplasmin (Behringwerke AG, Marburg, Germany), respectively.

**Monitoring of Safety**

Blood pressure and heart rate were monitored closely before and during thrombolysis with measurements taken after the saruplase bolus and again at 5, 10, 30 min and 1, 2, 4, 6 and 12 h.

**Statistical Analysis**

Due to the open nature of the trial, statistical analyses were performed in a purely descriptive manner. An intent to treat population which included all patients entered in the trial with no substitution for missing data (n = 20) and an efficacy analysable population which included only those patients which neither deviated from inclusion criteria nor had major deviations from the study protocol were analyzed. All parameters are described by their mean and 95% confidence intervals (CI), unless otherwise stated.

An analysis of efficacy was performed on Miller index and on the haemodynamic parameters mPAP, cardiac index and TPR. For intra-individual comparison, a t-test for paired comparison, a sign test and Wilcoxon-Sign-Rank test were calculated to compare each measurement after treatment to baseline. Parameters of revascularisation, the improvement in the Miller index, the rate of reduction in mPAP and improvement of the cardiac index and TPR were analysed as above.

**Results**

Twenty consecutive patients with an angiographically documented recent massive pulmonary embolism and a mean age of 68 ± 12 years (range 41 to 85 years) were treated with saruplase 80 mg. Four patients had undergone recent surgery. Seven were male and 13 female. Seven patients had clinical signs of life threatening pulmonary embolism on admis-

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### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>30 min</th>
<th>1 h</th>
<th>12 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PAP (mmHg)</td>
<td>29 (26-32)</td>
<td>23 (20-26)</td>
<td>22 (19-24)</td>
<td>19 (14-19)</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.6 (2.2-3.0)</td>
<td>2.7 (2.4-3.0)</td>
<td>2.8 (2.5-3.1)</td>
<td>2.9 (2.5-3.3)</td>
</tr>
<tr>
<td>TPR (U/m²)</td>
<td>12 (10-15)</td>
<td>9 (7-11)</td>
<td>8 (7-9)</td>
<td>7 (5-8)</td>
</tr>
</tbody>
</table>

Any clinical event of a potentially adverse nature occurring during the study period was documented. A severe bleeding event was defined as one which required surgery to stop the bleeding or which required transfusion of 2 or more units of packed cells, or resulted in the early termination of the thrombolytic infusion or was intracranial.

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Fig. 1 Total pulmonary resistance expressed as percent of baseline value, over the first 12 h after the start of saruplase. Data represented as mean ± SEM
sion, i.e. shock and/or syncope or faintness. The mean delay between onset of symptoms of massive pulmonary embolism and saruplase was 64 ± 51 h. 8 patients were treated with heparin from 3 to 48 h prior to lysis. During the study period, 36 patients with acute massive pulmonary embolism were not enrolled for the following reasons: age (n = 16), contraindication to thrombolysis (n = 7), refusal to participate (n = 6) and pulmonary angiography missing for technical reasons (n = 7). Twenty-one of these patients were, however, treated with thrombolytic drugs (urokinase and alteplase).

**Haemodynamic Monitoring**

The haemodynamics of the patients were greatly compromised on study entry with mean values of mPAP of 29 mmHg (CI 26-32), cardiac index of 2.6 l/min/m² (CI 2.2-3.0) and TPR of 12 U/m² (CI 10-15). Haemodynamic improvement (intent to treat analysis) was evident 30 min after starting saruplase therapy and continued progressively over the period of monitoring (Table 1). The mean decrease of TPR was 25.3% at 30 min (CI 15.6-35.0), 28.8% at 1 h (CI 20.9-36.7) and 39.8% at 12 h (CI 28.5-51.1). For the efficacy analysable population 2 patients were excluded because the Miller index determined by the investigator locally at baseline was < 20 and/or pre-lysis mPAP was < 20, and 2 patients were excluded because the haemodynamic data was incomplete. Examination of the efficacy analysable population showed similar findings to the intent to treat population. The percentage reduction rate in TPR for the efficacy analysable population (n = 16) is given in Fig. 1. Haemodynamic results were similar whether or not patients had been treated with heparin prior to lysis.

**Pulmonary Revascularization**

18 patients were considered suitable for the evaluation of the Miller index (one with a missing follow-up angiogram and one with an angiogram not suitable for analysis). Examination of the films by an independent expert showed a marked decrease from 23 (CI 21-24) to 14 (CI 12-17) (p <0.0001) following thrombolysis (intent to treat analysis). The relative improvement in Miller index was 38.1% (CI 28.9-47.4).

A complete set of perfusion lung scan was available in 18 patients. Mean perfusion lung scan defect was 43% (CI 37-48) at baseline, 29% (CI 22-35) at 48 ± 12 h, 16% (CI 10-22) by patient discharge and 7% (CI 3-11) at 3 month follow-up.

**Haematologic and Haemostatic Results**

As would be anticipated following thrombolysis accompanied by invasive procedures, haemoglobin, haematocrit and erythrocyte levels fell during the first 72 h with full recovery by patient discharge.

Changes in the haemostatic parameters fibrinogen, plasminogen and alpha-2-antiplasmin confirmed plasminogen activation and consumption of alpha-2-antiplasmin by plasmin following saruplase therapy. Fibrinogen levels fell rapidly to around 23% of pre-lysis levels at 1 h with the lowest level of fibrinogen at 6 h (15% of pre-lysis levels). By 24 h fibrinogen levels had recovered to 41% of pre-lysis levels. Recovery to normal range was seen after 48 h for alpha-2-antiplasmin and after 48-72 h for plasminogen (Fig. 2).

**Safety Data**

In order to ensure that blood pressure is not unduly modified following thrombolysis of patients with massive pulmonary embolism, both blood pressure and heart rate were monitored intensively over the first 12 h after saruplase. Transient hypotension with dizziness resulted in temporary suspension of the saruplase infusion in one patient with full recovery. The heart rate remained stable throughout. 7 h after the start of the saruplase administration, one patient had severe melaena and haematemesis, requiring two packs of plasma as well as standard treatment. On oesophago-gastro-duodenoscopy, an oesophageal ulcer was found. Intra-cerebral bleeding, occurring 14 h after initiation of saruplase administration and confirmed by CT-scan, resulted in the death on day 3 of one 82 year old patient with a history of atrial paroxysmal tachycardia and hypertension. Two patients suffered symptomatic recurrent pulmonary embolism which was confirmed by perfusion lung scan. In one patient the embolism occurred three days post-lysis and no specific treatment was necessary. Thrombolysis with t-PA was needed in the other patient following a life threatening recurrent pulmonary...
embolism six days after saruplase. A single episode of mild pericardial effusion occurred one day after thrombolysis and did not require any specific therapy. No episode of cardiac tamponade was observed. Two cases of mild pulmonary infarction were reported with full recovery.

**Patient Follow-Up**

The mean duration of the hospital stay was 9 days (range 7 to 14). Patients were reviewed after three months at which time time 15/19 reported having no limitation in functional state and no patient had symptoms at rest. During the follow-up phase no patient suffered from a recurrent pulmonary embolism. Three patients were diagnosed as having chronic post-embolic pulmonary hypertension.

**Discussion**

Thrombolysis has been recognised in the past few years as a valuable alternative to surgical embolectomy in patients with massive pulmonary embolism and severe pulmonary hypertension. In these patients, the primary goal of therapy should be to lower pulmonary hypertension as quickly as possible. Several studies have provided in the past decade convincing results in achieving this goal with various thrombolytic regimens. Petitpretz et al. reported in 1984 a 23% decrease of TPR 1 h after lysis in a short series of 7 patients treated with low dose i.v. bolus of urokinase (2). More recently Meyer et al. have demonstrated in a larger randomized study that a 100 mg t-PA i.v. infusion over 2 h was more efficient than urokinase administered at a dose of 4400 U/kg/h over 12 h, the decrease in TPR being respectively 36% and 18% 2 h after the initiation of treatment (3). Lately Sors et al. (4) have shown in a similarly designed trial that the bolus administration of t-PA at low dose (0.6 mg/kg) did not improve the haemodynamic efficacy of this drug in comparison to the conventional regimen; 30 min post-lysis the TPR decrease was 26% in the bolus group versus 20% in the conventional regimen group (n.s.). Saruplase is a pro-urokinase produced by recombinant DNA technology. This thrombolytic agent has been used successfully in the treatment of acute myocardial infarction. The PRIMI study published in 1989 has demonstrated that this drug was more efficient than streptokinase in terms of early coronary patency rate (5). Safety data analyzed by Veerme et al. from a cohort of 1698 patients suffering from a myocardial infarction and treated with saruplase were found to be comparable to what had been previously reported with streptokinase and t-PA (10). This pilot study is the first one to investigate the effects of saruplase in pulmonary embolism. Twenty patients suffering from a recent massive pulmonary embolism with significant pulmonary hypertension were treated with the same regimen as that used in myocardial infarction (both in respect of the thrombolytic regimen and heparin adjunctive treatment). The haemodynamic results indicate a very early effect of saruplase with a 25% decrease in TPR 30 min after onset of treatment, a result which is comparable to that obtained by Sors et al. with the two t-PA regimens (4). Beyond this time point, TPR continued to decrease progressively to reach 40% of baseline value at 12 h. The overall tendency seems also comparable to data from t-PA trials (3, 4). Both angiographic and perfusion lung scan follow-up data are in accordance with results obtained in previous thrombolytic trials with a 38% angiographic relative improvement at 18 to 30 h (1, 2) and a 14% absolute improvement in perfusion lung scan detect 36 to 60 h post-lysis (4, 11, 12). Haemostatic results revealed that the saruplase regimen used in the present trial induces systemic plasminogen activation. Severe bleeding was seen in 10% of the patients, a figure which is consistent with the rates observed with other thrombolytic drugs. Nevertheless, considering the small size of the study population, no conclusion can be drawn from this figure. Unfortunately one 82 year old patient died from intracranial bleeding; the past medical history of this patient included paroxysmal atrial fibrillation and systemic hypertension which may have contributed to this adverse outcome. In conclusion the overall clinical results observed in this series of 20 patients suffering from a recent massive pulmonary embolism, 7 of which were considered as life threatening on admission, appear satisfactory with a low mortality rate and 15 patients free from symptoms at the 3 month follow-up.

**Acknowledgements**

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**References**


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