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# Thrombolytic treatment of pulmonary embolism with APSAC

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*Thrombolytic treatment of pulmonary embolism with APSAC. J. Vander Sande, L. Bossaert, M. Brochier, B. Charbonnier, A. Serradigmini, A. Elias, H. Pintens, M.C. Lauwers.*

**ABSTRACT: BRL 26921 (Eminase registered trade mark in Belgium, Germany and The Netherlands) is the p-anisoyl derivative of the primary (human) lys plasminogen-streptokinase activator complex (APSAC). The acyl-enzyme has the theoretical advantage of causing fibrinolysis *in situ* in the presence of fibrin clotbound plasminogen. It was administered to 34 patients with severe pulmonary embolism (PE) in an open multicentre study. PE was suspected on clinical, blood gas, ECG, and radiographic data. Pulmonary angiograms performed pre- and post-treatment confirmed the diagnosis and were assessed using the Miller Index (MI). Fibrinogen, plasminogen, alpha-2-antiplasmin, fibrinogen degradation products (FDP), activated partial thromboplastin time (APTT), partial thromboplastin time (PTT) were closely monitored before and after each administration of APSAC. Median angiographic improvement was 50% (range 0–94%). The following adverse events were reported: bleeding at puncture sites (n=12), haematuria (n=1), epistaxis (n=3), fever (n=2). A blood transfusion was given in one patient with an inguinal haematoma. Systemic fibrinogenolysis occurred in 20/28 patients.**

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Severe pulmonary embolism (PE) is a frequently undiagnosed condition with a subsequent high mortality rate, ranging from 18–35% in untreated cases [1]. Early diagnosis and adequate treatment may reduce the mortality to 8% [2], whilst therapy is frequently associated with severe side effects. Before the 1970's heparin was the standard treatment, but MILLER *et al*. demonstrated that thrombolytic therapy was more effective [3]. A review of clinical trials, including the American embolism trial [4–7], confirmed this finding. A recent study demonstrated that fifteen months after thrombolytic treatment of acute massive PE, pulmonary arteriograms remained normal in 85% of the cases and the reserve capacity of the pulmonary vascular bed during heavy exercise was within normal limits [8].

Some problems associated with thrombolytic therapy remain: *e.g.* side-effects (systemic fibrinogenolysis, coagulation disturbances and life-threatening bleeding) [9–13], high cost, and the need for continuous infusion of unstable products with a short half-life.

The development of the acyl-enzymes was an attempt to improve the therapeutic ratio [14]. The acylation of the catalytic centre of the plasminogen-streptokinase complex leaves the lysine fibrin-binding sites free for binding to the fibrin in the thrombus [15]. After slow deacylation by hydrolysis, the active complex activates the fibrin-bound plasminogen *in situ* (fig. 1). Various acylated molecules were studied [16, 17], and as a result of these investigations BRL 26921, the p-anisoyl derivative of the primary (human) lys plasminogen-streptokinase activator complex (APSAC) was developed. This molecule with an *in vivo* deacylation half-life of 44 min was selected for clinical studies [18–22].

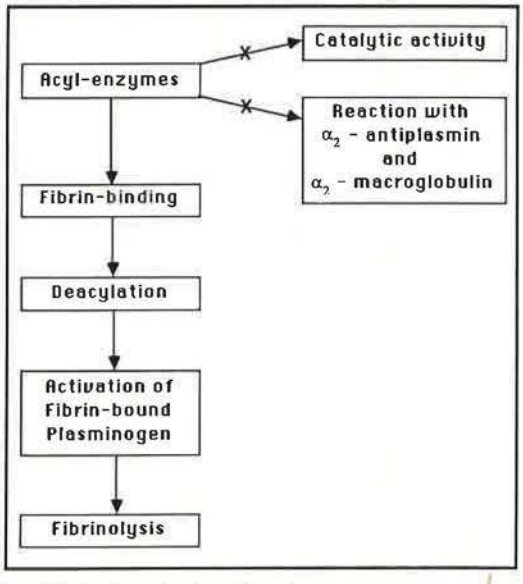


Fig. 1. – Mechanism of action of acyl-enzymes.

The aim of the present open multicentre study was to evaluate the efficacy and safety of BRL 26921 in patients with massive or submassive PE.

## Patients and methods

### *Patients*

Thirty four patients (19 M, 15 F) with a recent massive or submassive PE were studied. The study protocol was approved by the Hospital Ethical Committees. In table 1 patients, sex, age, dose regimens, angiographic Miller Index (before and after) are summarized. The mean age was 58 (range 25–78) yrs. In 31/34 cases diagnosis was based on initial selective pulmonary angiography.

### *Therapy protocol*

All patients received up to 3 *i.v.* bolus injections of APSAC at a dose of 5 or 10 mg according to the clinical condition (table 1). Heparin was administered subsequently at a dose of 800-1,000 $U \cdot h^{-1}$. The recommended dose regimen (5 or 10 mg at 8 hourly intervals) was administered to 29 of the 34 patients. Five patients received different dosages for various reasons: 10 mg (single dose) in four patients; 5 mg+5 mg in one. In two of the four patients receiving a single dose of 10 mg a considerable fall in fibrinogen was found. In one patient the pre-existing resuscitation measures should have precluded treatment. One patient presented an epistaxis. One patient received only 2x5 mg because of the risk of bleeding from previously documented sigmoid diverticuli.

Table 1. – Patients, dose regimens, Miller Index and clinical outcome

| | | | | APSAC dose mg | | | | Angiographic Miller Index | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient no. | Sex | Age | HR | Dose 1 | Dose 2 | Dose 3 | Total | MI Before | MI After | Diff. MI | % Change (R) | Clinical Outcome |
| 1 | M | 55 | 110 | 10 | 5 | 5 | 20 | 30 | 10 | 20 | 67 | Cured |
| 2 | F | 70 | 100 | 10 | 5 | 5 | 20 | 30 | 20 | 10 | 33 | Improved |
| 3 | M | 57 | 109 | 10 | 5 | 5 | 20 | 29 | 14 | 15 | 52 | Improved |
| 4 | M | 59 | 100 | 10 | 5 | 5 | 20 | 27 | 18 | 9 | 33 | Improved |
| 5 | M | 63 | 120 | 10 | 0 | 0 | 10 | 26 | 6 | 20 | 77 | Cured |
| 6 | F | 61 | 140 | 10 | 10 | 10 | 30 | 25 | 3 | 22 | 88 | Cured |
| 7 | F | 78 | • | 10 | 10 | 10 | 30 | 25 | 4 | 21 | 84 | Cured |
| 8 | M | 60 | 120 | 10 | 5 | 5 | 20 | 25 | 14 | 11 | 44 | Cured |
| 9 | M | 72 | • | 10 | 0 | 0 | 10 | 24 | 9 | 15 | 63 | Improved |
| 10 | F | 60 | 110 | 10 | 5 | 5 | 20 | 24 | 14 | 10 | 42 | Improved |
| 11 | M | 60 | 90 | 10 | 5 | 5 | 20 | 24 | 4 | 20 | 83 | Cured |
| 12 | M | 75 | 100 | 5 | 5 | 5 | 15 | 23 | 2 | 21 | 91 | Cured |
| 13 | F | 67 | 120 | 10 | 5 | 5 | 20 | 21 | 2 | 19 | 91 | Cured |
| 14 | M | 31 | 115 | 10 | 5 | 5 | 20 | 20 | 19 | 1 | 5 | No Change |
| 15 | M | 62 | 125 | 10 | 5 | 5 | 20 | 20 | 16 | 4 | 20 | Improved |
| 16 | M | 64 | • | 10 | 0 | 0 | 10 | 19 | 11 | 8 | 42 | No change |
| 17 | M | 68 | 110 | 5 | 5 | 5 | 15 | 19 | 13 | 6 | 32 | Deterioration |
| 18 | M | 60 | 120 | 10 | 5 | 5 | 20 | 19 | 16 | 3 | 16 | No Change |
| 19 | M | 60 | 136 | 10 | 5 | 5 | 20 | 19 | 10 | 9 | 47 | Cured |
| 20 | F | 65 | 70 | 10 | 5 | 5 | 20 | 19 | 15 | 4 | 21 | Improved |
| 21 | F | 70 | 140 | 5 | 5 | 0 | 10 | 18 | 5 | 13 | 72 | Cured |
| 22 | M | 25 | 128 | 10 | 5 | 5 | 20 | 18 | 9 | 9 | 50 | Cured |
| 23 | M | 25 | 88 | 10 | 5 | 5 | 20 | 17 | 5 | 12 | 71 | Improved |
| 24 | F | 77 | 80 | 5 | 5 | 5 | 15 | 16 | 1 | 15 | 94 | Cured |
| 25 | F | 57 | 120 | 10 | 5 | 5 | 20 | 16 | 16 | 0 | 0 | No Change |
| 26 | F | 59 | 60 | 10 | 5 | 5 | 20 | 14 | 11 | 3 | 21 | Improved |
| 27 | F | 55 | 80 | 10 | 5 | 5 | 20 | 14 | 6 | 8 | 57 | Improved |
| 28 | F | 41 | • | 5 | 5 | 5 | 15 | 13 | 2 | 11 | 85 | Cured |
| 29 | M | 72 | 45 | 10 | 10 | 10 | 30 | 12 | 3 | 9 | 75 | Improved |
| 30 | F | 60 | 150 | 5 | 5 | 5 | 15 | 10 | 9 | 1 | 10 | Improved |
| 31 | F | 55 | • | 10 | 5 | 5 | 20 | 10 | 5 | 5 | 50 | Improved |
| 32 | M | 30 | 135 | 10 | 10 | 10 | 30 | • | • | • | • | Improved |
| 33 | M | 53 | 78 | 10 | 10 | 10 | 30 | • | • | • | • | Improved |
| 34 | F | 56 | 128 | 10 | 0 | 0 | 10 | • | • | • | • | No Change |

• : missing values.

Coagulation parameters (fibrinogen, plasmin, thrombin time, APTT, alpha-2-macroglobulin, FDP, plasminogen and alpha-2-antiplasmin) were measured every 6 h during and after treatment [23–24]. Alpha-2-macroglobulin was measured using a single radial immunodiffusion assay (Behringwerke) and FDP using the Thrombo Wellcotest (Burroughs Wellcome). In some individual patients blood samples were not obtained at this exact timing to avoid interference with diagnostic or therapeutic procedures.

*Angiographic assessment*

Protocol of the pulmonary angiograms was performed independently by the investigators and the radiologist, using the Miller Index. This scoring system attributes points up to a maximum of 34 for involvement by thrombi and for the reduction of flow in the lung segments [3]. An overall score of 0/34 means a normal status, an overall score of 34 means total obstruction and no flow.

MI was measured in 31 patients before treatment. In 27 of the assessable patients the score was MI≥ 14 (mean 21.5), indicative of a massive (MI>18; n=22) or submassive (MI=14–18; n=5) pulmonary embolism (table 1). Four patients had a MI between 10 and 13.

In some cases angiography was performed eight hours after each administration of APSAC to guide therapy. In all of the assessable patients final evaluation by angiography was performed between 8 and 12 h after the last administration of the drug. The percentage improvement in pulmonary circulation (R) was calculated using the following formula:

$$R\% = \frac{\text{MI before treatment - MI after treatment}}{\text{MI before treatment}} \times 100$$

## Results

Table 1 shows the pre- and post-treatment Miller Index scores (MI). Median MI before treatment was 20 (range 10–30) and after treatment 10 (range 1–20).

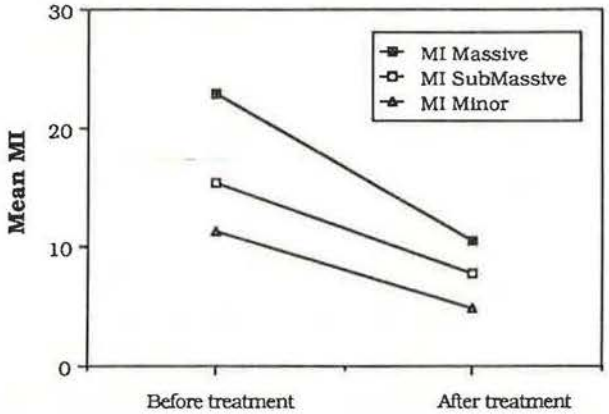


Fig. 2. – Evolution of the means of MI, before and after treatment, for the three severity classes of MI defined before treatment (massive, submassive and minor). MI: miller index

Median improvement of pulmonary circulation expressed by R was 50% (range=0–94%). Figure 2 shows the evolution of the means of the Miller Index, before and after treatment, for the three severity classes of MI defined before treatment, being: minor <14, submassive 14–18 and massive >18 PE.

Coagulation parameters showed major disturbances. The most obvious of these changes were the drops in fibrinogen and plasminogen respectively, depicted in figures 3 and 4.

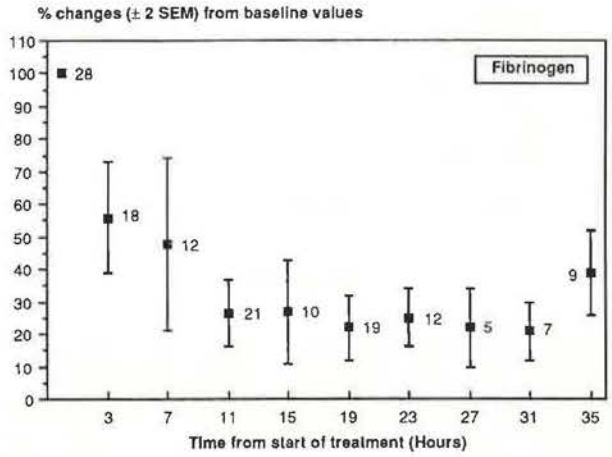


Fig. 3. – Mean change in fibrinogen (±2 SEM); values in percent of baseline values. The number of samples is indicated at each sampling time.

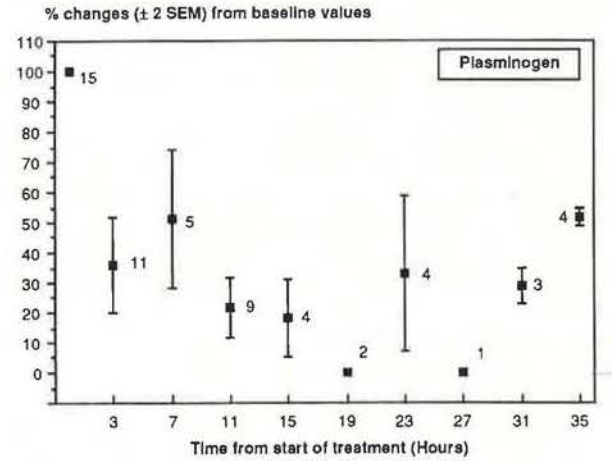


Fig. 4. - Mean change in plasminogen (±2 SEM); values in percent of baseline values. The number of samples is indicated at each sampling time.

One or more adverse events, listed in table 2 were experienced by eighteen patients. The most frequent event was bleeding at puncture sites which occurred in twelve patients; only one of these required transfusion.

One patient (no. 17) died in cardiogenic shock, caused by right ventricular myocardial infarction on day two post-treatment. A second patient (no. 19) died of septic shock on day fifteen from start of treatment; this patient

had a previous lobectomy for carcinoma and fractured ribs due to cardiopulmonary resuscitation prior to treatment, which should have excluded him from the protocol.

Table 2. – Adverse events experienced by eighteen patients

| Adverse events | No. patients |
|---|---|
| Bleeding at puncture site | 12* |
| Fever | 2 |
| Vomiting | 2 |
| Haematuria | 1 |
| Nausea, somnolence, disorientation | 1 |
| Epistaxis | 3 |
| Flush | 2 |
| Shivering | 3 |

*: blood transfusion required in one patient.

## Discussion

In 34 patients in the present study, 22 with massive and 5 with submassive PE treated with APSAC, a mean improvement of 50% of the MI score was demonstrated within 24–28 h of the start of treatment. This is in line with the results of the study by RUCKLEY *et al.*, where an improvement of 48% was demonstrated [25]. In nine patients with massive PE treated with APSAC, HEINRICH *et al.* reported a mean improvement of 57% after 24 h [26]. In comparison, the results obtained with urokinase and streptokinase in the UPET-study (27%) [6] and the US PAT-study (33%) [7] proved to be less satisfactory from the angiographic point of view.

The results of coagulation tests are different from the observations of PROWSE *et al.* [20] in healthy volunteers who showed no drop in fibrinogen, plasminogen or alpha-2-antiplasmin using 5 or 7 mg of APSAC. A marked drop in fibrinogen and plasminogen levels was observed in twenty patients indicating a systemic lytic state (figs 3 and 4). Although most of these patients received an initial dose of 10 mg, some presented a major drop after a starting dose of not more than 5 mg.

No apparent correlation was found between disturbances in coagulation parameters and the occurrence of major spontaneous bleeding. In spite of the marked drop in fibrinogen, only one patient required a blood transfusion because of bleeding and recovered without any ultimate adverse effects.

A further advantage of APSAC is the fact that intermittent bolus injections proved to be as satisfactory as continuous infusion of other - more unstable - products, saving much work and use of infusion pumps.

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RÉSUMÉ: BRL 26921 est le dérivé p-anisoyl du complexe activateur primaire (humain) lys plasminogène-streptokinase (APSAC). Cet enzyme acylé a l'avantage théorique de provoquer la fibrinolyse in situ en présence du plasminogène du caillot fibrineux. Il a été administré à 34 patients atteints d'embolie pulmonaire sévère dans le cadre d'une étude multicentrique ouverte. L'embolie pulmonaire a été suspectée sur la base de données cliniques, gazométriques, électrocardiographiques, et radiographiques. Les angiographies pulmonaires, réalisées avant et après le traitement, ont confirmé le diagnostic et ont été appréciées au moyen de l'Index de Miller. Le fibrinogène, le plasminogène, l'alpha-2-antiplasmine, les produits de dégradation du fibrinogène, le temps partiel de thromboplastine activée, et le temps partiel de thromboplastine, ont été suivis de près, avant et après chaque administration d'APSAC. L'amélioration angiographique médiane fut de 50% (extrêmes 0–94). Les complications suivantes ont été observées: saignement aux sites de ponction (n=12), hématurie (n=1), épistaxis (n=3), fièvre (n=2). Une transfusion sanguine a été administrée à un patient avec hématome inguinal. Une fibrinogénolyse systémique a été observée chez 20 des 28 patients.