First Vienna Shock Forum

Part A: Pathophysiological Role of Mediators and Mediator Inhibitors in Shock

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FEASIBILITY STUDY OF VERY HIGH APROTININ DOSAGE IN POLYTRAUMA PATIENTS

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INTRODUCTION

Polytrauma patients at risk to develop adult respiratory distress syndrome (ARDS) and/or multiple organ failure present a great therapeutic challenge. Newly developed concepts on the role of proteolysis, proteases (e.g. plasma kallikrein, plasmin) and proteolytic breakdown products (e.g. fibrin degradation products) in the pathogenesis of these diseases stimulated us to reconsider the role of proteinase inhibitors as therapeutic agents in polytrauma and shock (Manwaring and Curreri, 1982; Schapira et al., 1983, 1985). The inhibitor that has most widely been used in this indication is the proteinase inhibitor from bovine lung, aprotinin or Trasylol® (Verstraete, 1985; Fritz and Wunderer, 1983). Aprotinin inhibits proteinases such as kallikrein, plasmin and trypsin with high affinity. Theoretical considerations based on enzyme kinetics and substrate availability suggested that an aprotinin concentration of about 200 KIU (kallikrein inactivator units) per ml plasma (corresponding to 4 µmol/l) would suffice to effectively control and inhibit plasma kallikrein as well as systemic fibrinolysis executed by plasmin (Philipp, 1978; Fritz and Wunderer, 1983). Only recently it has become possible to relate empirical dosage with actual aprotinin plasma levels in patients. Specific, fast and reliable test procedures have been established, i.e. an enzymatic kallikrein inhibition test (Jochum et al., 1984) and an enzyme-linked immunosorbent assay specific for aprotinin (Mueller-Esterl et al., 1984).

The question was then, whether it would be possible in a clinical situation to obtain plasma concentrations of the exogenous inhibitor which are high enough to provide the predicted inhibition of plasma kallikrein. Here we report on a clinical feasibility study in polytrauma patients with the aim of obtaining more data about aprotinin plasma levels and especially of examining the tolerability of aprotinin given in elevated dosage. In the first part of this study a moderately increased aprotinin dose per patient was applied, in the second part the dosage was very high as compared to previously reported clinical work.

PATIENTS AND METHODS

The following admission criteria were observed: Patients selected for the study had been brought to the accident department immediately after having suffered severe injury with polytrauma, defined as external blood loss greater than 500 ml, multiple bone fractures, extensive soft tissue trauma and involvement of intra-thoracic or intra-abdominal lesions. Excluded were patients with severe head injuries requiring neurosurgery and patients where first medical aid had been delayed (more than 30 minutes after the accident) or where the start of the aprotinin infusion was not possible within the first hour after the time of accident.

Preclinical therapy consisted of immediate intubation followed by ventilation with PEEP, initial volume replacement in the ambulance with colloids (gelatine) and electrolytes, sedation (flunitrazepam), and analgetic support (fentanyl). Clinical management included continuous ventilation, further infusion of crystalloid solutions until circulatory stabilization and adequate excretion was reached, continued analgesia and sedation, dopamine 4 µg/kg/min, nitroglycerine 2 mg/h, heparin for thrombosis prophylaxis and ranitidine together with antacids for the prophylaxis of stress ulcers. Surgical management followed the principles of Wolff et al. (1978) which are aimed at the prevention of post-traumatic complications by an optimal coordination of surgery and intensive care.

Patients fulfilling the admission criteria were given additional infusions of aprotinin. Two dosage regimens were applied: Group I received a total dose of 6 million KIU (kallikrein inactivator units) by discontinuous application

within 36 hours (2 million KIU initially over 30 min; 1 million KIU at 6, 12, and 18 hours; 0.5 million KIU at 24 and 36 hours). Group II received within 24 hours a total dose of 17.5 million KIU (2.5 million KIU initially; continuous i.v. infusion of 1 million KIU/h for 12 hours, followed by 0.25 million KIU/h for another 12 hours). Aprotinin was supplied as Trasylol^{R} infusion 500,000 KIU in 50 ml flasks from Bayer AG, Leverkusen (Germany).

Blood samples were taken before the infusion was started and 0.5, 1, 2, 4, 6, 9, 12, 15, 18, 24, 36, and 48 hours later. Out of these plasma was prepared and deep frozen immediately. Plasma concentrations of aprotinin were determined by ELISA according to the method described by Mueller-Esterl (1984). Plasmin inhibiting capacity in plasma was determined by chromogenic substrate assay with S-2251 (Deutsche KabiVitrum GmbH, München). For the immunological assay of α_2-antiplasmin rocket immuno-electrophoresis according to Laurell (1972) using specific antibodies (Behring Werke AG, Marburg) was applied.

Data were biometrically evaluated in a descriptive manner. Aprotinin plasma levels are given as median values with ranges between the 25 % and 75 % quartils. Graphs represent mean values and standard deviation, if not otherwise indicated.

RESULTS

At total of 23 severely injured patients were admitted according to the criteria described above. Table 1 summarizes the main characteristics of the patients investigated.

Sex Distribution	13 male, 10 female
Mean Age	men: 29.5 years
	women: 43.6 years
Mortality	n = 4 (17 %)
Sepsis	n = 10 (42 %)
Respiratory Failure (ARDS)	n = 5 (21 %)
Artificial Respiration	$\bar{x}$ = 9.7 days
Stay in ICU	$\bar{x}$ = 13.9 days
Transfusion Requirement	$\bar{x}$ = 15.5 units of blood

Table 1. Main characteristics and outcome of 23 polytrauma patients.

In the first series of 10 patients receiving intermittent bolus application of aprotinin, plasma samples were taken at 6, 12, 18, 24, and 36 hours just before the next infusion was started. Therefore, the aprotinin levels obtained from group I represent trough values. The discontinuous dosage schedule of group I (6 million KIU aprotinin within 36 hours) resulted in transitory plasma levels of aprotinin ranging from 100 to 200 KIU/ml (2 - 4 µmol/l), which then declined within 6 hours to 15 - 20 KIU/ml (about 0.3 µmol/l). This trough value concentration of aprotinin could be maintained by repeated re-infusions of 1 million KIU every 6 hours. 12 hours after the last infusion plasma levels were below 5 KIU/ml (0.1 µmol/l) (Fig. 1).

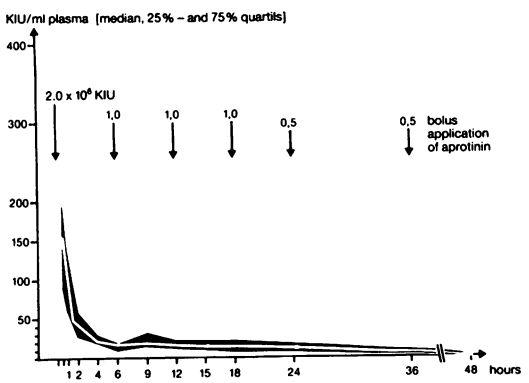


Figure 1. Aprotinin concentration in patient plasma (Group I, n = 10)

The continuous dosage schedule of group II (17.5 million KIU aprotinin within 24 hours) resulted in initial peak plasma levels of about 400 KIU/ml (8 µmol/l) which returned to 100 - 150 KIU/ml during subsequent continuous infusion of 1 million KIU/h over 12 hours. Under the infusion of the reduced dose of 0.25 million KIU/h the plasma level fell further to about 50 KIU/ml plasma. 24 hours after the aprotinin infusion was finished, plasma levels were below 15 KIU/ml (0.3 µmol/l) in all cases, with a median value of only 2.5 KIU/ml (Fig. 2).

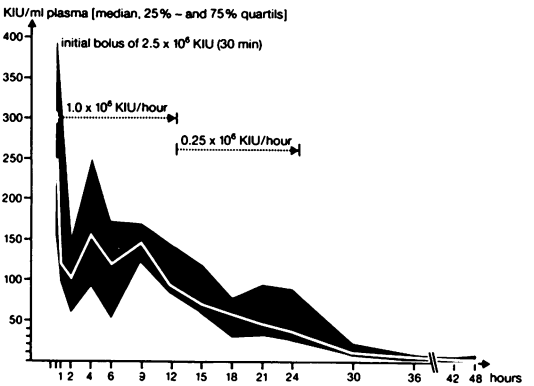
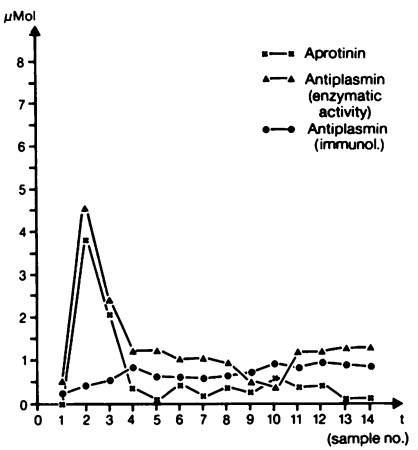


Figure 2. Aprotinin concentration in patient plasma (Group II, n = 13)

Plasmin inhibiting capacity was measured in plasma samples of patients from both dosage groups. Fig. 3a and 3b are representative examples of one patient each, demonstrating sufficient correlation between aprotinin antigen levels and antiplasmin activity assayed enzymatically. The natural



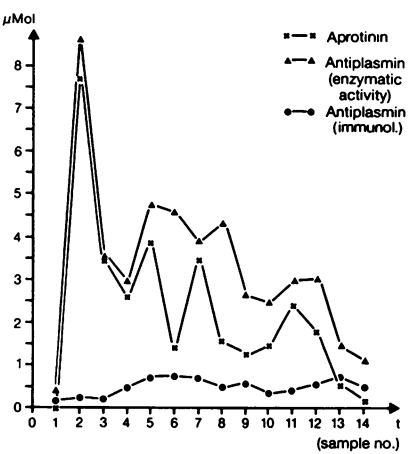


Figure 3a. (Group I) Figure 3b. (Group II)
Plasmin inhibiting capacity in plasma from 1 patient

plasmin inhibitor in plasma, α_2-antiplasmin, as determined immunologically was rather low in the beginning (< 1 µmol/l) and there was only a slight increase during the early phase of treatment. Among the routine coagulation tests no major changes during the period of high aprotinin plasma levels have been observed (data not shown). As an example Fig. 4 demonstrates prothrombin time for both dosage groups at 6 hours and 24 hours after start of treatment without any particular differences.

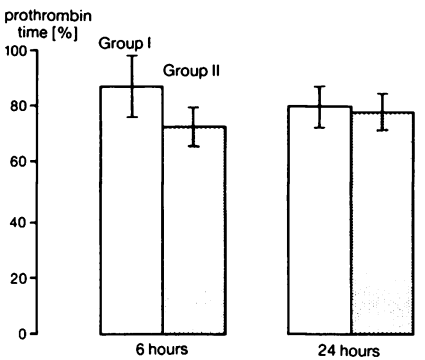


Figure 4. Prothrombin time at 6 and 24 hours

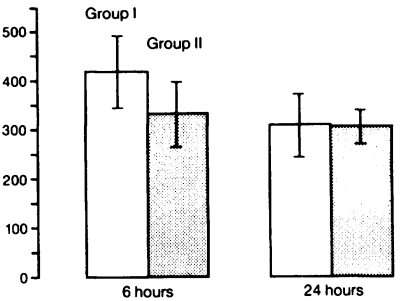


Figure 5. p_aO_2/FIO_2 ratio at 6 and 24 hours

Lung function was assessed by monitoring the p_aO_2/FIO_2 ratio (Fig. 5). Although group II with the higher aprotinin dosage tended to exhibit a more stable situation as compared to group I, there were no obvious differences in this parameter between both groups after 24 hours.

Urine output was measured continuously and volumes were calculated in ml/h. Fig. 6 shows the course of average urine production per hour over the initial 48 h-period for both dosage groups. There was an increase of urine output from 288 ml/h to 392 ml/h in the high dosage group II during the second half of the first 12 h-period when 1 million KIU aprotinin per hour was given by continuous infusion. This increase in urine output was suspended following the reduction of aprotinin dosage after 12 hours (from 1 million KIU to 0.25 million KIU/h), but the average ml/h in group II remained higher than in group I.

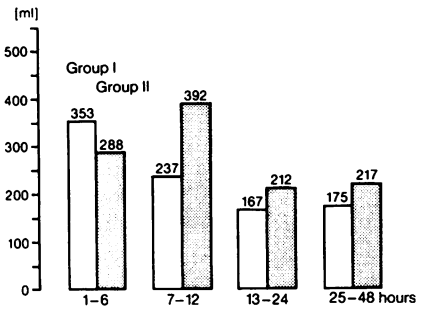


Figure 6.
Average urine output per hour (mean values)

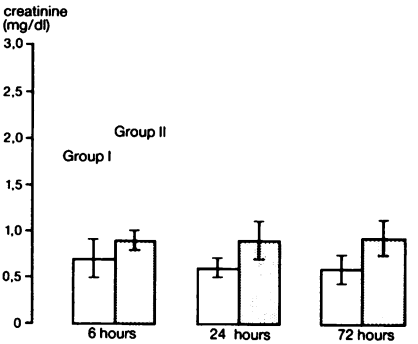


Figure 7.
Serum creatinine at 6, 24, and 72 hours after start of aprotinin

Serum creatinine concentrations had been determined at 6, 24, and 72 hours after start of treatment. They remained in the normal range throughout the observation period, with no apparent differences between both dosage groups (Fig. 7).

DISCUSSION

Plasma levels of aprotinin as determined in this study followed in general the predicted course calculated from the pharmacokinetic constants of this inhibitor (Kaller et al., 1978). To secure a continuously elevated plasmatic concentration the dosage scheme with intermittent administration is clearly not suitable (group I). By contrast, the alternative application scheme applying continuous infusion (group II) ensured aprotinin plasma concentration within the desired range of 100 - 200 KIU/ml over a period of 12 hours. However, a considerable interindividual variation from patient to patient was observed, probably because patient-related differences in metabolism and excretion could not be excluded; yet this needs further investigation. Our results are in line with those of Dittmer (1985), who found also in polytrauma patients aprotinin plasma levels between 40 and 50 KIU/ml during continuous infusion of 250,000 KIU/h.

Tolerability of very high doses of aprotinin was apparently good. Neither coagulatory nor microcirculatory disturbances due to the trial drug have been observed. The incidence of pulmonary complications in our study was comparable to that reported for polytrauma in the recent literature (Johnson et al., 1985). Special attention was given to renal function during high aprotinin dosage. Whether the observed temporary increase in urine output in Group II was an effect of aprotinin or a chance finding cannot be decided at the moment. In fact, there have been similar observations made recently with high continuous administration of aprotinin (F. Schumann, personal communication). Impairment of renal function due to aprotinin application has not been observed in our patients.

In summary, our study has shown that a dosage schedule of aprotinin resulting - at least temporarily - in plasma levels of 200 KIU/ml is clinically feasible. It must be emphasized, however, that due to the design of this study and the limited number of patients investigated as yet no conclusion concerning effectiveness is allowed.

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