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Fibrinolysis *in vivo* Predicts a Favorable Outcome in Patients with Small Vessel Thrombi: Observations in Patients with Glomerular Thrombi during Treatment with Ancrod

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= Abstract =Fibrin deposits injure small vessels. To evaluate the effect of fibrinolysis, patients with glomerular diseases having glomerular thrombi received the snake venom enzyme, ancrod, for 14 days. Within 48 hours, the mean level of fibrin/fibrinogen degradation products(FDP) was very high, and bimodally distributed, defining low(n = 11) and high(n = 18) FDP responses.

In the low FDP group, the FDP rise and fibrinogen decrease were linearly related, suggesting that most FDP derived from fibrinogen degradation. Renal effects were minimal. In the high FDP group, the FDP level was not explained by fibrinogen degradation alone, indicating fibrin dissolution. Renal function improved, proteinuria increased, and glomerular fibrin deposition decreased.

Tissue type plasminogen activator, released by ancrod-frbirn from endothelial cells, converts fibrin-bound plasminogen to palsmin, which degrades fibirn. Alpha$_2$-antiplasmin, the most effective known inhibitor of fibrinolysis, was elevated in 9/11 in the low, and 5/18 in the high FDP group. Thus when fibrinolysis occurred, it was associated with rapid favorable effects on renal function and histology.

Key words: ***Fibrinolysis, Glomerulonephrits, Glomerular thrombi, Fibrinolytic drug***

INTRODUCTION

Hemostasis contributes significantly to glomerular damage and results in deposition of fibrinogen-related antigen(FRA) in several types of immune-complex glomerulonephritis including lupus nephrities, and in renal allograft rejection(Miller and Michael 1977). Altnough the exact pathogenetic significance of FRA deposition is unknown, fibrin deposition may be caused by a variety of mechanisms including specific immunologic glomerular injury(Koffler and Paronetto 1965; McClusky 1966; Hoyer *et al.* 1974).

Fibrin that is deposited does not dissolve spontaneously; rather, it is digested by plasmin, the main enzyme in fibrinolysis (Bernik and Kwaan 1967; Menon *et al.* 1968; Bernik *et al.* 1974), or phagocytosed by cells in glomeruli (Mauer *et al.* 1974). Fibrin degradation products(FDP), the dissolved products of fibrin, are biologically active (Saleen 1983), are injurious to endothelial (Dang *et al.* 1985) and mesangial cells(Tsumagari and Tanaka

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1984), and promote increased chemotaxis of monocytes (Richardson *et al.* 1976). These attributed enforce procoagulant activity at active inflammatory sites, and may thereby result in a multiplier effect that produces more coagulation damage in glomeruli(Cole *et al.* 1985).

There are many reports that anticoagulants may prevent FRA deposition and subsequent glomerular injury; however anticoagulants do not appear effective in treating ongoing injury. Few reports have been published on the effect of agents that promote and/or facilitate fibrinolysis (Miller and Michael 1977).

In previous studies, we showed that the intravenous injection of ancrod, the active principle of the venom of the Malayan pit viper (Agkistrodon rhodostoma), induced hypofibrinogenemia and was associated with consumption of plasminogen and increased levels of FDP. In most but not all pateints, ancrod treatment was associated with a significant decrease in glomerular fibrin deposition, and normalization of previously abnormal levels of tissue-type plasminogen activator(t-PA) and its inhibitor (Kant *et al.* 1985; Glass-Greenwalt 1985).

The time of onset and mechanism of fibrinolysis during ancrod treatment, and its effect on renal function were not fully evaluated previously. In this communication we report on the effect of ancrod on selected components of the fibrinolytic system, and on renal function in 26 patients with glomerular injury and glomerular thrombi. Enhancement of fibrinolysis was associated with rapid measurable effects on renal function.

MATERIALS AND METHODS

Patients

Selection of patients for treatment with ancrod was based on the initial renal biopsy findings. The major criteria were fibrin deposition in glomeruli and/or vessels($>$ grade $+$, on a scale 0-4 $+$ for either), and cellular or fibrocellular crescents with fibrin deposition. Patients with these findings were accepted irrespective of the nature of the glomerular disease and degree of systemic illness. Informed consent was obtained using the format approved by the committee on Human Research, University of Cincinnati Medical Center. As a part of the protocol, renal biopsies were performed after the course of ancrod treatment was completed to assess the effects of ancrod.

Between 1978 and 1986, 37 patients with glmerular disease and fibrin deposition were treated with ancrod. Excluded from the present analysis were: four patients in whom fibrinolysis data were not measured, and seven with severe glomerulosclerosis who were being treated by dialysis when acrod was first given. The data on the other 26 patients(19 females, 7 males) were analyzed.

Seventeen had lupus nephritis, seven other types of glomerulonphritis and/or vasculitis, one hyperacute and one acute renal allograft failure. Most were severly ill. The serum creatinine level was $>$ 1.5 mg/dl (133 μ mol/l) in 20 and $>$ 3.5 mg/dl (309 μ mol/l) in four; the 24-hour urinary protein excretion was $>$3.5 g in 15. Diastolic blood pressure was $>$90 mmHg in 19, $>$110 mmHg in six; eight were being treated for hypertension with more than three drugs. Twenty-one were receiving prednisone, 16 in a dose exceeding 30 mg/day. With a single exception, the dose of prednisone was maintained or decreased during treatment with ancrod. Three patients with systemic lupus erythematosus had two episodes of active lupus nephritis and were treated on two separate occasions. The present observations are based on 29 courses of ancrod treatment in 26 patients. Details on many of the patients have been published previously(Pollak *et al.* 1982; Dosekun *et al.* 1982, 1984; Kant *et al.* 1985; Greenwalt *et al.* 1985).

Renal histology and method of analysis

The methods used to fix, stain, and to semiquantitatively analyze the renal histologic findings have been described fully, as have those to detect fibrin by light and immunofluorescence microscopy(Lendrum *et al.* 1962; Kant *et al.* 1981). All renal biopsy specimens were coded and anlyzed "blindly" by two observers. The findings were analyzed semiquantitatively, and graded on a scale from 0 to 4+ (Pirani *et al.* 1964). Particular attention was paid to glomerular capillary thrombosis, subendothelial deposits, and thrombosis in arterioles; the sum of the scores for these three abnormlities constituted the microvascular thrombosis index(Kant *et al.* 1985). The limited tissue, the focal distribution of deposited proteins, and the impossibility of making prolonged and repeated observations make it difficult to quantify changes by immunofluorescence microscopy. Nevertheless, the presence and degree of fibrin deposition was also estimated by imunofluorescence microscopy using an antiserum directed against fibrin(ogen) related antigen.

Ancrod administration

The initial dose, 1 U/kg body weight in 500 ml 5% dextrose in water, was infused over 8 hours to ensure gradual defibrinogenation (Kant *et al.* 1985; Glas-Greenwalt *et al.* 1985). Thereafter, the dose was that estimated to keep plasma clottable fibrinogen in the 0.2-0.5 g/l range. This was usually accomplished by an infusion over a 30-60 minute period once or twice daily for two weeks. Before, during, and after ancrod administration, components of fibrinolysis were measured repeatedly, and observations on renal function were made daily.

Laboratory methods

The fibrin degradation products(FDP) assay was carried out with the Thrombo-Wellcotest. Sera, collected with protease inhibitor, were diluted with 0.1 M glycin-buffered saline, pH 8.2. Semiquantitative estimations were performed and expressed as consecutive two-fold dilutions (Garvey and Black 1972; Arochia-Pinango 1972). The Thrombo-Wellcotest measures not only degradation products of fibrin but also reacts with degradation products of fibrinogen, as was shown when ancord was added to plasma in vitro (Arochia-Pinongo 1972). Clottable fibrinogen was measured by the Class method (Clauss 1957), and plasminogen was assayed using a fluorescent synthetic substrate (Pochron *et al.* 1978).

Serum creatinine was measured kinetically; the 24-hour urine protein excretion was measured using the biuret method.

Plasma fibrinolytic activity was measured by a standardized fibrin plate method (Haverkate and Brakman 1975). t-PA activity(previously referred to as vascular plasminogen activator [VPA]), was quantitated by addition of exogenous C1 inactivator to dextran-sulfate euglobulin fractions as described by Kluft (Kluft 1979). Activities were measured on plasminogen-rich fibrin plates(Glas-Greenwalt *et al.* 1984), and the specificity of the method corroborated by the quenching effect of recently available monoclonal antibodies against t-PA (Glas--Greenwalt *et al.*), as previously shown(Kluft 1978).

The assay for t-PA inhibitor (PA-I), previously referred to as IPA, has been described in detail (Glas-Greenwalt *et al.* 1984). Briefly, the degree of inhibition produced by untreated plasma on plasminogen activation was measured by mixing various plasma concentrations (100%, 75%, 50%, 37.5%, 25%) with an equal volume of urokinase (final concentration 5 CTA units) and by applying the mixtures to plasminogen-rich fibrin plates. Complete inhibition fo lysis by a plasma concentration fo 100% was defined as 932 inhibitor units, by 50% as 1864 inhibitor units, by 25% as 3728 inhibitor units, etc. If lysis was not blocked completely, the resulting lysis zones of the highest plasma concentration still outside the normal range was deduced from 932 and multiplied with the dilution factor. There was linear correlation between the inhibition of urokinase and that of t-PA(Glas-Greenwalt *et al.*).

Alpha$_2$-antiplasmin(alpha$_2$-AP) wa smeasured by a procedure similar to that described for PA-I, but with plasminogen-free fibrin plates and plasmin in place of urokinase. The specificity of this method has been corroborated by the use of quenching antibodies to alpha$_2$-AP (Glass-Greenwalt *et al.* 1984) correlation between the fibrin plate, lysis time, and chromogenic substrate S-2251 methods (Glas-Greenwalt *et al.* 1984).

The coefficient of variatin for the estimates of t-PA was 15%, of t-PA inhibitor was 4%, and or alpha$_2$-AP was 3%.

Statistical analysis of data

The data were tested for normality of distribution using the Wilk-Shapiro test; many were log normally disbributed. The test for goodness of fit was used to analyze whether observations were unimodally distributed. Where appropriate, data were log transformed, and values prior to and during ancord administration were analyzed by the paired and unpaired tests.

The significance of differences between means of values that were not normally distributed was analyzed by the Mann-Whitney U test. The significance of outliers was analyzed by Grubb's test for outliers (Grubbs 1969).

RESULTS

The early FDP response to ancrod defines two patient groups

In all, FDP level was meausred on 494 occasions. The geometric mean levels increased from 6.8 to 934 μg/ml within 24 hours, and decreased to 523 μg/ml on day 2. The distribution of the FDP level on the first day was plotted in Figure 1, as the distribution of the FDP values was skewed, the data were analyzed further.

In most pathologic states, the FDP level reflects the action of palsmin on fibrin. In the present study, where ancrod treatment was given, FDP was

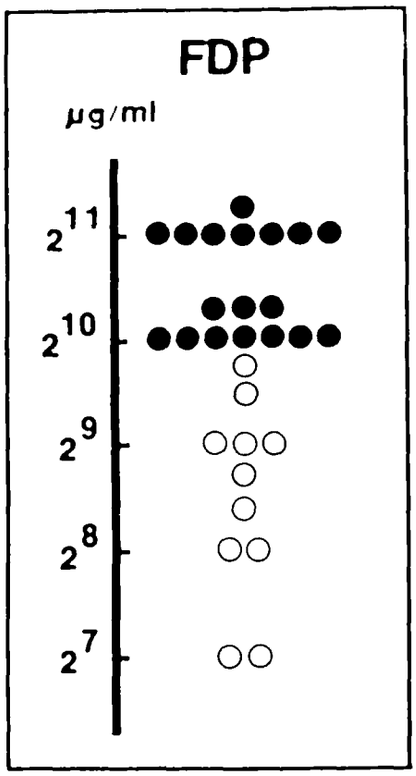

Fig. 1. FDP values on the first day after starting ancrod treatment. The distribution suggests two groups with low (○) and high (●) FDP resonses.

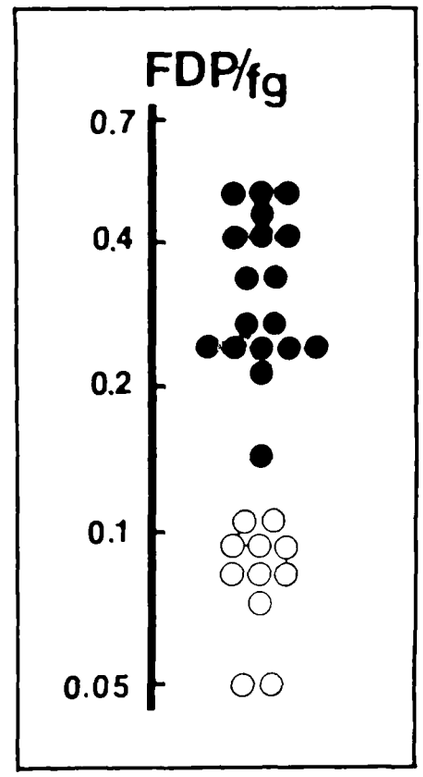

Fig. 2. Ratio (FDP/fg) of the geometric mean level of fibrin(ogen) degradation products(FDP) measured within 48 ours of starting treatment with ancrod to the geometric mean of the fibrinogen (fg) level measured on two occasions prior to the start of ancord treatment in low (○) and high (●) FDP groups.

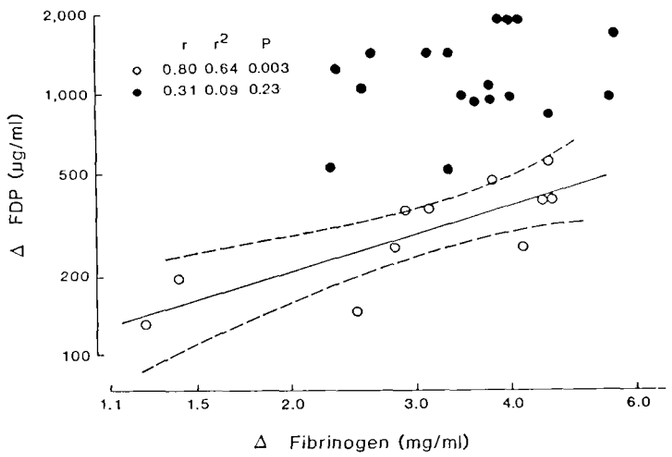

Fig. 3. The relation between the changes in FDP and fibrinogen. In the low FDP grop (○), the changes in FDP correlated significantly with the changes in fibrinogen; in the high FDP group (●), the points were all well above the 95% confidence limits of the relationship in the low FDP group.

expected to derive from two sources, i.e. the degradation of fibrinogen and of fibrin, which cannot be differentiated by the Thrombo-Wellcotest we employed. To obtain an index of the contribution of fibrinogen to FDP level, the post-ancord FDP level was normalized against the pre-ancrod fibrinogen level, FDP/fg, and this is hown in Figure 2. This index seemed to have a bimodal distribution and was examined by a godness of fit test (Wilk-Shapiro), which showed that the sample could be best described as having derived from two populations, one with a higher mean FDP/fg ratio than the other. Subsequent analysis, therefore, was done by handling these two subgroups(high FDP="high FDP/fg"; low FDP="low FDP/fg") separately and their behavior was compared with each other.

Relationship of the change in FDP and those in fibrinogen levels in the first 48 hours

Relationship is plotted in Figure 3. For the groups as a whole the correlation was significant ($r=0.53$, $p<0.01$). When the two subgroups were analyzed separately this relationship was not significant in the high FDP group ($r=0.31$, $p>0.05$), but was highly significant in the low FDP group ($r=0.80$, $p<0.005$). This suggest that, in the low FDP

Table 1. Selected components of fibrinolysis prior to and in the first 48 hours starting treatment with ancrod

	Low FDP Group		High FDP Group	
	Pretreatment	48 hour	Pretreatment	48 hour
Fibrinogen (g/l)	3.4 (3.0, 3.9)	0.4*** (0.36, 0.47)	3.9 (3.7, 4.2)	0.3*** (0.23, 0.33)
t-PA (activator U/ml)	1.0 (0.46, 2.01)	4.4 (2.4, 8.2)	0.8 (0.41, 1.7)	4.0* (1.8, 8.8)
PA-I (inhibitor U/ml)	1,291 (1,175, 1,419)	950** (864, 1,045)	1,332 (1,260, 1,410)	706*** (618, 805)
Plasminogen (CTA U/ml)	2.90 (2.69, 3.11)	1.77*** (1.57, 2.00)	3.40 (3.23, 3.57)	1.52*** (1.40, 1.65)
α_2-antiplasmin (inhibitor U/ml)	1,243 (1,092, 1,415)	985 (930, 1,043)	983 (911, 1,061)	846* (784, 913)
FDP (μg/ml)	5 (2.9, 7.7)	260*** (220, 315)	9 (6.5, 14)	1,273*** (1,122, 1,443)

The levels are geometric means and, in parenthesis, ± 1 S.E. below and above the mean. In each of the low and high FDP groups, the difference between pretreatment and 48 hour values was tested using the paired t test: *$p<0.05$; **$p<0.01$; ***$p<0.001$.

group, most or all of the material reacting in the Thrombo-Wellcotest derived, not from fibrin, but from the breakdown of fibrinogen. In the high FDP group, all 18 points were well above the 95% confidence limits of the relationship in the low FDP group. This finding suggests that, in the latter group, major fractions of the FDP derived from sources other than fibrinogen, most probably the digestion of fibrin.

Levels of selected components of fibrinolysis in the first 48 hours

The geometric mean vlaues before treatment and in the first 48 hours after treatment was started are summarized for the low and high FDP groups in Table 1. Fibrinogen decreased significantly to very low levels in both groups, the absolute fall being significantly greater ($p<0.01$) in the high FDP group. t-PA levels increased in both groups, but the rise was statistically signifcant only in the high FDP group, The t-PA inhibitor (PA-I) levels fell significantly in both groups, the mean value to within the normal range only in the high FDP group. Both the fractional change ($p<0.05$) and absolute decrease ($p<0.001$) were greater in the high FDP group. Plasminogen fell very signifcantly in both groups. Both the fractional change and absolute decrease were greater in the high

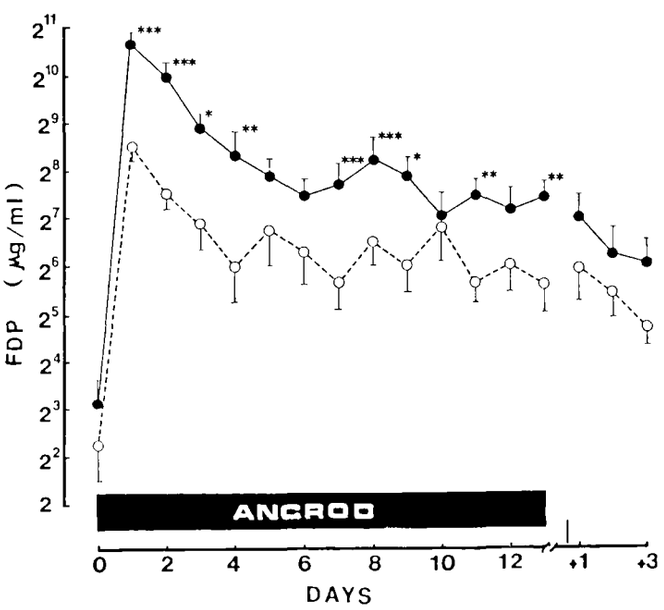

Fig. 4. Daily measurements of fibrin(ogen) degradation products in low (○) and high (●) FDP groups. Values are geometric means±1 S.E. (*$p<0.05$; **$p<0.01$; ***$p<0.005$).

FDP group ($p<0.001$). Alpha$_2$-AP levels decreased, but to a significant degree only in the high FDP group. Not suprisingly, both the fractional change and absolute increase in FDP levels were

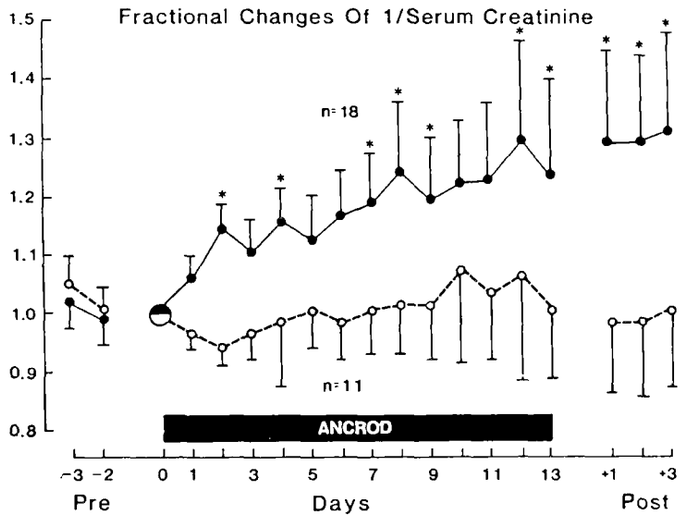

Fig. 5. Fractional change (mean±1 S.E.) in 1/serum creatinine from the baseline value, the means on the two days prior to ancrod treatment. The differences between the low (○) and the high(●) FDP groups were tested on each individual day by the Mann-Whitney U-test (*$p < 0.05$).

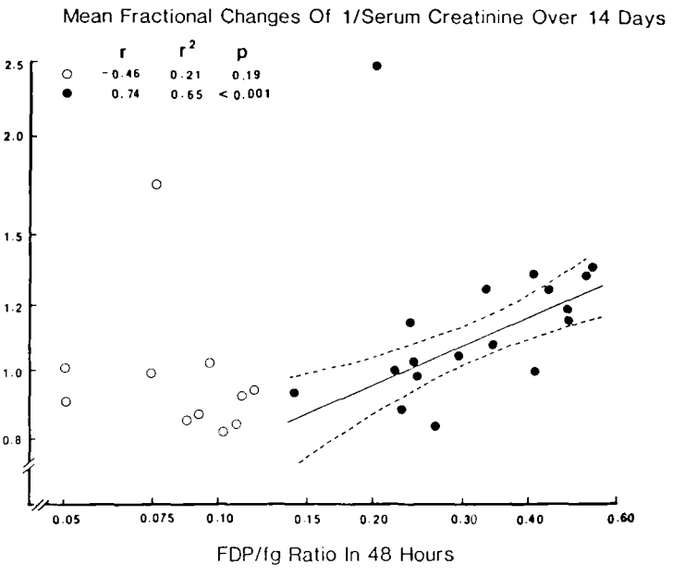

Fig. 6. The relationship of the 48 hour FDP/fg ratio to the mean changes in 1/serum creatinine during the 14 days of treatment with ancord. The correlation was significant in the high FDP group (●); in the low FDP group (○) the distribution was random. The correlation coefficients in each group were calculated after excluding two patients in whom changes in 1/serum creatinine were outliers ($p < 0.005$, by Grubb's test for outliers).

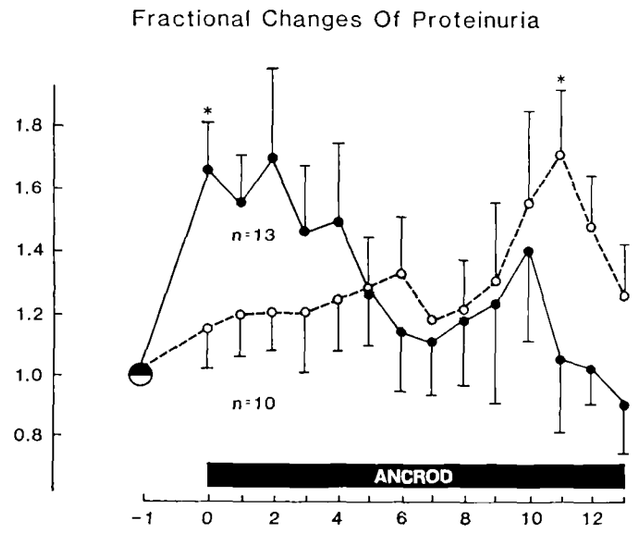

Fig. 7. Fractional change (mean±1 S.E.) in 24 hour protein excretion from the baseline value, means on the one day prior to ancrod treatment. The differences between the low (○) and high (●) FDP groups were tested on each individual day by the Mann-Whitney U-test (*$p<0.05$). The 24 hour urine on day 0 spanned periods immediately prior to, during, and after the initial infusion of ancrod.

greater ($p<0.001$) in the high FDP group.

FDP values during the 14 days of ancrod treatment

These are summarized for the two groups in Figure 4. At 24 hours the geometric mean values were 1621 and 376 μg/ml respectively in the high and low FDP groups; at 48 hours the values were respectively 1000 and 179 μg/ml. Thereafter, and throughout the 14 daya of ancrod administration, the FDP values were higher in the high FDP group.

The FDP response and renal function

Serum creatinine(Cr) was measured on 563 occasions in the 29 treatment courses. The percentage change of its reciprocal (1/s Cr) is plotted in Figure 5. In the high FDP group, the fractional change in 1/s Cr increased by day 1 and continued to increase thereafter; there was very little change in the low FDP group. The difference between the two groups was significant.

The relationship of the 48 hour FDP/fg ratio to the mean change in 1/s Cr is shown in Figure 6. One patient in each group behaved differently from the other 27. In both patients, renal function was improving prior to the start of ancrod and continued to improve rapidly during ancrod treatment, the percentage change in 1/s Cr of these 2 patients were > 3 SD above the means. Excluding the 2 outliers, the correlation was highly significant in the high FDP but not in the low FDP group. This is

Table 2. Microvascular thrombosis index in renal biopsies taken before and after treatment with ancrod*

FDP response	Pretreatment α_2-AP	n	Time between biopsies (weeks)	microvascular thrombosis index Pre	Post
Low	Normal	2	3.3	8.0	3.5
Low	High	9	3.4	3.3 ± 0.87	2.7 ±0.71
	Subtotal	11		4.2 + 0.99	2.9 ±0.59
High	Normal	12	3.7	2.2 ± 0.46	1.1 ±0.36*
High	High	5	3.9	3.9 ± 1.37	2.3 ±1.39
	Subtotal	17		2.7 ± 0.52	1.4 ±0.46**

All values are mean scores on a scale 0-12; *p <0.02, p<0.01 by paired t test.

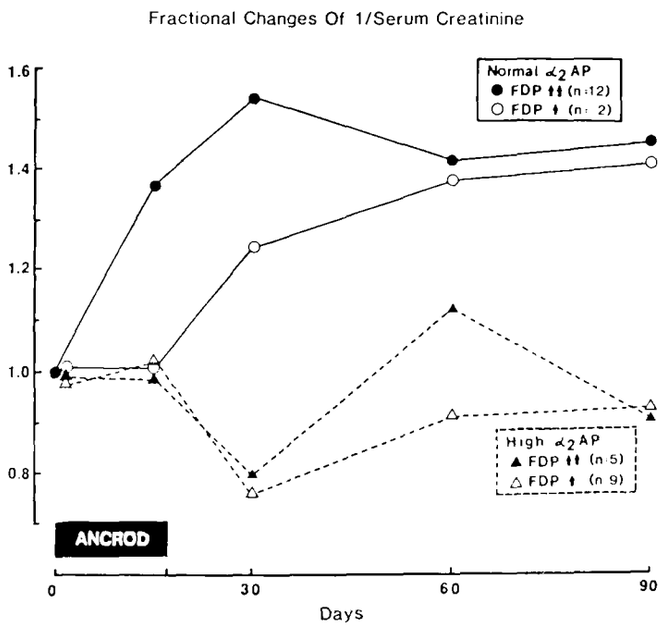

Fig. 8. The influence on renal function of pretreatment α_2-AP levels and the FDP response to ancrod treatment. With normal α_2-AP levels and a high FDP response group (●), the renal function improvement was early and maintained; with normal α_2-AP levels and a low FDP response (○), the renal function improved slowly, but by 60 days was equal to that in the high FDP group. In those who had an elevated level of α_2-AP, renal function changed little whether the FDP response was high (▲) or low (△).

compatible with the view that enhanced fibrinolysis was associated with improvement in renal function.

The fractional changes in 24-hour urine protein excretion differed in the two groups(Fig. 7). In the high FDP group, there was an immediate striking increase in fractional protein excretion, but in the low FDP group there was only a slight increase in fractional protein excretion at the beginning of Greatment. In the high FDP group, the fractional change decreased from about the fourth day onward, reaching a level of 1; in the low FDP group there was further increase in the fractional protein excretion toward the end of treatment.

The FDP response and alpha$_2$-antiplasmin

The circulating alpha$_2$-antiplasmin level prior to the treatment was compared with the fibrinolysis response, measured by the ratio FDP/fg within the first 48 hours of ancrod treatment. In 18 courses of treatment, a fibrinolysis response was judged to have occurred by the FDP/fg ratio; the alpha$_2$-AP level was elevated above normal in only five instances. In 11 courses, the fibrinolysis response was low or minimal; the alpha$_2$-AP level was elevated above normal in nine. The levels were significantly different in the two groups ($X^2[1]=5.39$, $p<0.02$)

Changes in renal function over a 90 day period were compared with both pretreatment alpha$_2$-AP levels and the FDP response to ancrod treatment-(Fig. 8). When the alpha$_2$-AP level was elevated prior to treatment, there was little evidence of improved renal function in both high and low FDP grops. When the alpha$_2$-AP levels were not high prior to treatment, there was a striking early improvement in renal function in the high FDP group; this was maintained for 90 days. In the two patients in the low FDP group, there was a slow improvement of renal function, first clearly evident at 30 days; by 60 days the response was as marked as in the high FDP group. In one subject, the levels of two nonspecific inhibitors of plasmin, alpha$_2$-macroglobulin and antithrombin III were both elevated prior to treatment. In the other, the level of the plasmin precursor, plasminogen, was

signifcantly below the nromal range prior to treatment.

Microvascular thrombosis

The microvascular thrombosis index in biopsies done before and after ancrod treatment is summarized Table 2. In the lowe FDP group there was a decreases from a mean score of 8 to 3.5 in the two patients with a normal $alpha_2$-AP level; there was little change in the nine with an elevated $alph_2$-AP level. In nine pairs of biopsies from the low FDP group the mean fibrin score, measured by immunoflureoscence microscopy, decreased from 1.45 to 1.05.

There was a significant decrease in the microvascular thrombosis index in the high FDP group as a whole and in the subset of patients with a normal $alpha_2$-AP level. In nine pairs of biopsies from the high FDP group the mean fibrin score, measured by imunofluorescence microscopy, decreased from 1.67 to 0.34.

DISCUSSION

In a previous study, evidence was presented that the fibrinolytic systemm was activated during ancrod infusion(Kant *et al.* 1985; Glas-Greenwalt *et al.* 1985). The present study confirms and extends these observations.

One of the biologic actions of plasmin is the digestion of fibirn, when this occurs the FDP level in serum increases. The Thrombo-Wellco test was used to measure FDP's. With this and al other clinically employed tests for FDP, there is cross reaction between fibrinogen degradation products (Garvey and Black 1972; Wilner 1978). The measured FDP levevl not only on the amount of fibrin digested by plasmin, but also on the amount of fibrinogen digested during ancrod treatment. The ratio of the FDP to the initial fibrinogen level was clearly bimodal (Fig. 2). In the lowe FDP group, the inverse linear relationship between the changes in FDP and in fibrinogen levels (Fig. 3) is strong evidence that most FDP in this group derived from fibrinogen breakdown. In the high FDP group, both the FDP level and the very different behavior of the relationship strongly suggests that a significant portion of the measured FDP derived from the plasmin digestion of fibrin.

There is other evidence that there was more activation of fibrinolysis in the high FDP than the low FDP group(Table 1 and Fig. 2): 1) The initial FDP response was much higher in the high FDP group; the difference in the FDP level between the two groups was maintained throughout the period of ancrod administration (Fig. 4); 2) In general, the decrease of other selective fibrinolysis components was greater in the high FDP group; 3) In a previous study(Kant *et al.* 1985; Glas-Greenwalt *et al.* 1985), fibrinolytic responders were characterized by the normalization of the PA-I level. There was concordance of the high FDP group with the responder group as defined previously ($X^2[3]=10.65$, $p<0.02$). 4) The changes in the microvascular index following treatment was significantly greater in the high FDP group, indicating more effective removal of fibrin from the glomerulus. There were similar differences in the change in fibrin deposition in the two groups.

The renal functional response differed in the two groups, and improved only in the high FDP group; this occurred despite marked heterogeneity of diseases, clinical severity, and therapeutic modalities other than ancrod. Thus, there appeared to be a striking relationship between evidence for the plasmin digestion of fibrin, increase in proteinuria, and improvement of renal function, an improvement often clearly detectivle within 48 hours. The reasons for the decrease in serum creatinine and increase in proteinuria might be: 1) dislodgment of fibrin thrombi during fibrinolysis, so that more capillaries are perfused; 2) the biologic action of FDP, resulting in increased permeability of capillaries and a vasodialtory efect on the microvascular tree (Saleen 1983); and 3) the action of FDP on enodthelial and measangial cells, with a consequent change in glomerular filtration (Tsumagari and Tanaka 1984; Dang *et al.* 1985; Brenner *et al.* 1986).

In the comparison of the seventeen clinical items inlcuding age, sex, duration of illness, the physical and laboratory findings between the low and high FDP group, we found the only difference was the age in those patients with high FDP was signifcantly older than the low FDP group.

We have previously proposed that, following ancrod treatment, ancord-fibrin activates the fibrinolytic system through enhanced t-PA release from endothelium (Kant *et al.* 1985; Glas-Greenwal *et al.* 1985). As a consequence of its high affinity for fibrin, t-PA interacts with palsminogen bound to both circulating soluble ancrod-fibrin and fibrin precipitated pathologically in thrombi in the microcirculation, where it converts palsminogen to plas-

min. In turn, the plasmin degrades fibrin. The data in the present study are consistent with this hypothesis, and suggest that the reaction occurs relatively rapidly.

This reaction is likely to be modified by $alpha_2$-AP. In plasma, $alpha_2$-AP binds very rapidly and specifically to palsmin (Moroi and Aoki 1976). In fibrin clot, $alpha_2$-AP interferes with binding of plasminogen to fibrin (Moroi and Aoki 1976, 1977). In the presence of a high $alpha_2$-AP level, less plasminogen is available as substrated for the action of t-PA, and less plasmin is formed. Furthermore, $alpha_2$-AP crosslinked to fibrin slowly inhibits plasmin generated on the surface of fibrin-(Moroi and Aoki 1976, 1977). Thus, clots occurring in the presence of a high level of $alpha_2$-AP are likely to be less susceptibel to fibrinolysis(Aoki *et al.* 1978; Sakata and Aoki 1980). In patients with a pretreatment $alpha_2$-AP level in the normal range, the FDP/fg ratio in the first 48 hous was 0.30; in those with a high $alpha_2$-AP level, it was 0.17. The diference was signifiant (Mann-Whitney U-test; $p < 0.025$).

A prolonged favorable effect on renal function was noted in those with a normal but not in those with an elevated $alpha_2$-AP level.

We could postulate that the action of ancord, 1) vasodilation and decreased platelet agregation mediated by icreased prostacyclin production in the endothelial cells, 2) activation of fibrinolysis, decreased coagulation and inactivation of C_3 by protein S and C system, 3) immunosuppression by FDP which was formed by plasminogen activator. Further study along with other parameters such as prostaglandin and protein S and C should be performed.

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= 국문초록 =

신사구체소혈관내 혈전증에서 섬유소용해의 효과

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섬유소의 혈관내 침착은 소혈관의 손상을 초래한다. 저자들은 신조직생검 소견에서 사구체내에 혈전이 있었던 사구체신염환자 26명에서 29회에 걸쳐 섬유소용해제인 ancrod를 14일간 투여하고 섬유소용해가 사구체신염에 미치는 효과를 관찰하였다.

48시간 내에 섬유소와 섬유소원분해산물의 비가 증가하였고, 이를 기준으로 낮았던 군(11건)과, 높았던 군(18건)을 비교하였다. 섬유소원 분해산물의 증가가 낮았던 군에서는 섬유소원분해산물의 증가와 비례하여 섬유소원의 감소가 있어 섬유소원분해산물의 증가는 섬유소원의 분해에 의한 것으로 확인되었으며, 신기능이나 조직소견의 개선도 없었다.

반면 섬유소원분해산물의 증가가 높았던 군에서는 섬유소원분해산물의 증가가 섬유소원 감소에 비하여 월등하여, 이는 섬유소원의 분해와 아울러 혈관내 침착된 섬유소의 분해에 기인하였고, 신기능의 호전, 단백뇨의 증가와 신조직생검에서 사구체내의 섬유소의 침착도 감소하였다.

내피세포로부터 ancrod-섬유소에 의하여 유리된 조직성 plasminogen 활성인자는 섬유소에 붙어있는 plasminogen을 plasmin으로 활성화시킴으로써 섬유소를 분해한다.

한편 섬유소성 용해의 가장 강력한 억제제로 알려진 alpha$_2$-antiplasmin은 섬유소원해산물이 낮았던 11건 중 9건에서 증가되었고, 높았던 18건 중 5건에서 증가되었다. 따라서 혈중에서 섬유소용해가 있으면 신기능과 신조직소견이 급속히 호전됨을 알 수 있었다.