

Oxymetholone Therapy in Patients with Familial Antithrombin III Deficiency

Akira Shibuya, Haruhiko Ninomiya, Masaki Nakazawa, Toshiro Nagasawa, Yasuhiro Yoda, and Tsukasa Abe

From the Division of Hematology, Institute of Clinical Medicine, University of Tsukuba, Ibaraki, Japan

Key words

Familial antithrombin III deficiency – Thromboembolism – Thrombolysis – Oxymetholone and warfarin

Summary

Three patients with familial antithrombin III (ATIII) deficiency, who also have histories of thromboembolism, were treated with oxymetholone in combination with warfarin. Thrombolysis was observed in one patient with acute thrombosis of inferior vena cava during the oxymetholone and warfarin therapy. No further thromboembolic episodes occurred in these patients after initiation of warfarin with or without oxymetholone. The levels of plasma ATIII, α_1 -antitrypsin, plasminogen and Cl-inactivator were significantly increased in all patients after the introduction of oxymetholone therapy. This suggests that oxymetholone augments anticoagulant and fibrinolytic activity. Hence we consider that oxymetholone in combination with warfarin may be possible thrombolytic therapy in patients with familial ATIII deficiency.

Introduction

Familial antithrombin III (ATIII) deficiency is a disease in which venous thrombosis occurs frequently (1). Heparin alone is not useful for the treatment of the thrombosis in this disease (2). Administration of heparin with ATIII concentrate may be beneficial to treat acute phase of venous thrombosis in this disease, but is inconvenient to maintain adequate ATIII level for long time. Therefore, an oral drug to normalize ATIII level is required.

Anabolic steroids have some effects on the concentration of several plasma proteins involved in the mechanism of blood coagulation and/or fibrinolytic system (3, 4, 5). However, their clinical usefulness to prevent thromboembolic diseases in patients with familial ATIII deficiency still remains controversial (6, 7, 8).

We conducted a clinical trial of oxymetholone (OML) in combination with warfarin for 3 patients with familial ATIII deficiency, including a case of acute thrombosis in inferior vena cava. We describe here the effects of OML in combination with warfarin on the clinical courses and laboratory data of plasma antiprotease inhibitors of coagulation factors and the fibrinolytic system.

Patients, Materials, and Methods

Patients' plasma was collected with trisodium citrate every week and concentration of ATIII was measured by the single radial immunodiffusion method using M-partigen (Behring Institute, Marburg, West Germany). Aliquots of the materials were kept frozen at -20°C until required. Subsequently, ATIII activity was determined by two different

methods using progressive antithrombin activity (PAT) (9) and heparin cofactor activity (HCF) (10) with chromogenic substrate S-2238 (Kabi AB, Stockholm, Sweden). Plasminogen (Pgn) level was assayed by the method of Friberger et al. (11) using chromogenic substrate S-2251 (Kabi AB).

α_1 -antitrypsin (α_1 -AT), α_2 -macroglobulin (α_2 -MG) and Cl-inactivator (Cl-I) were measured by using M-partigen (Behring Institute).

Case Reports

Case 1. An 18 year-old Japanese male was transferred to Tsukuba University hospital in June 1986, because of thrombosis of superior sagittal sinus and left leg vein extending to inferior vena cava, which had been insensitive to heparin therapy. On admission he had been on warfarin for the last 7 days. The plasma ATIII levels of the patient and his mother, aunt and cousins were significantly decreased. Thus a diagnosis of familial ATIII deficiency was made and $5\text{ mg kg}^{-1}\text{ day}^{-1}$ ticlopidine and $0.5\text{ mg kg}^{-1}\text{ day}^{-1}$ OML were started. The thrombus in the inferior vena cava had reached 5 cm below the left renal vein according to the findings of ultrasound and Doppler echography and computed tomography. OML was given for 17 weeks and then tapered off as shown in Fig. 1A. Follow-up study of ultrasound and Doppler echography showed that the thrombus had disappeared from the inferior vena cava by 2 weeks after the initiation of OML therapy and further from the left iliac vein by the 6th week.

Case 2 was a 49 year-old female, the mother of case 1. She has had multiple venous thrombi in the legs for the last 5 years. She was treated with $0.5\text{ mg kg}^{-1}\text{ day}^{-1}$ OML for 6 weeks in combination with warfarin. OML was then tapered off as shown in Fig. 1B.

Case 3 was a 26 year-old Japanese male with a history of intestinal segmentary resection, because of thrombosis of the mesenteric vein occurring in November 1982. After the operation he had an episode of dyspnea and swelling with redness and tenderness of the left thigh which disappeared spontaneously. In February 1983, he was referred to our hospital because of swelling of the legs followed by palpitation and dyspnea on exertion. On admission pulmonary emboli in the middle of both lungs were demonstrated by perfusion lung scan. The ATIII levels of the patient and his father were significantly decreased. A diagnosis of familial ATIII deficiency was made. He was treated with $0.5\text{ mg kg}^{-1}\text{ day}^{-1}$ OML in combination with warfarin for 7 weeks and then OML was tapered off as shown in Fig. 1C. The symptoms disappeared soon after the initiation of the therapy.

No evidence of thromboembolic episode or side effects such as hemorrhage or liver injury were observed during warfarin therapy in combination with or without OML in those three patients. During this study all the patients received warfarin in combination with OML and their prothrombin time was maintained 1.5 to 2.0 times longer than the controls. Relevant laboratory data prior to OML therapy for each case are summarized in Table 1.

Results

Plasma ATIII levels in each patient as measured by the three different methods are shown in Fig. 1. ATIII levels rapidly reached normal or nearly normal ranges after the introduction of OML therapy and maximal levels were attained 2 to 3 weeks later. The levels of plasma ATIII decreased as OML was tapered down; and by 2 weeks after it was tapered off they had returned to almost pretreatment levels (Fig. 2).

Correspondence to: Yasuhiro Yoda, M.D., Institute of Clinical Medicine, University of Tsukuba, Tsukuba-Shi, Ibaraki 305, Japan

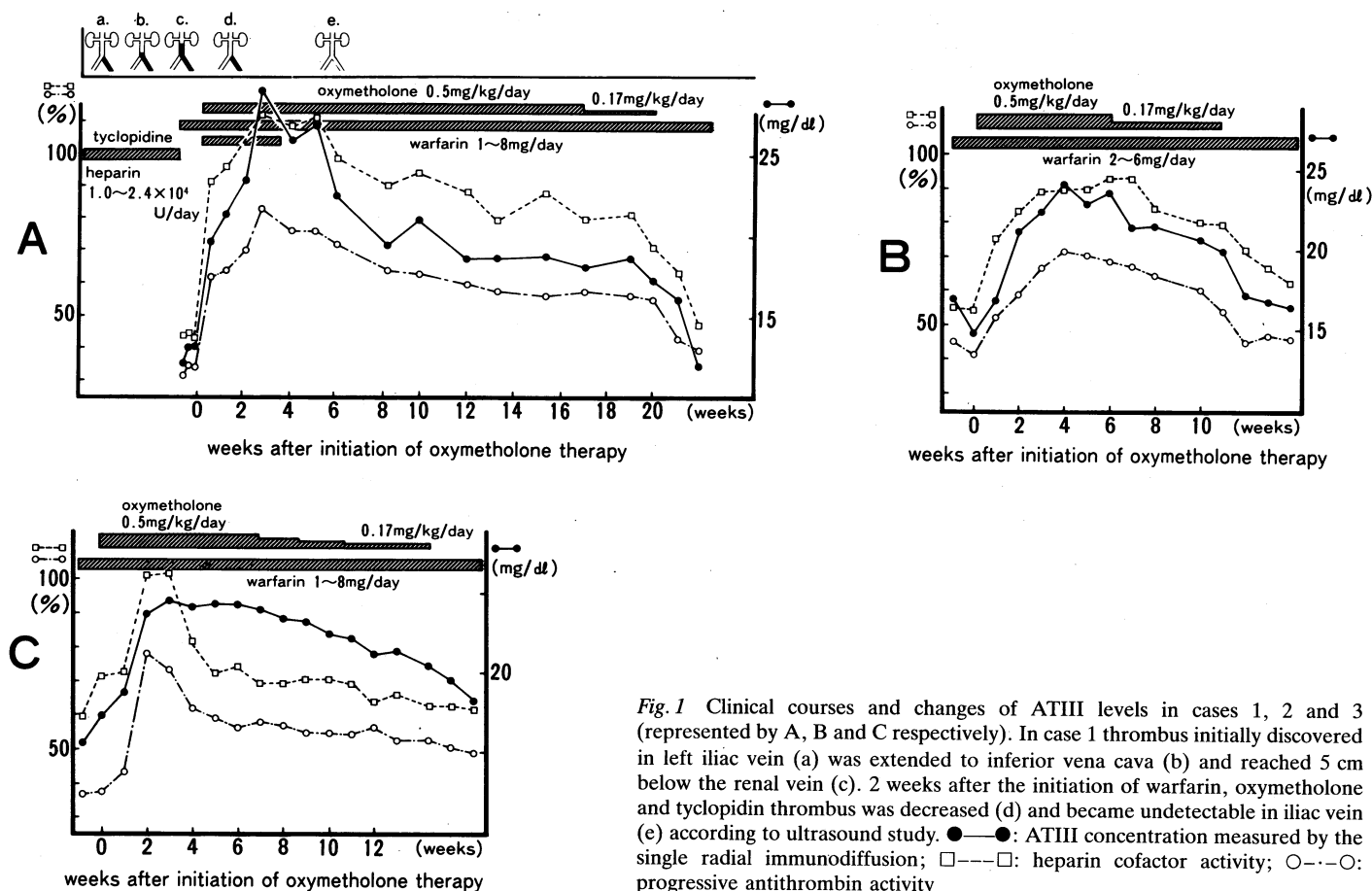


Fig. 1 Clinical courses and changes of ATIII levels in cases 1, 2 and 3 (represented by A, B and C respectively). In case 1 thrombus initially discovered in left iliac vein (a) was extended to inferior vena cava (b) and reached 5 cm below the renal vein (c). 2 weeks after the initiation of warfarin, oxymetholone and ticlopidin thrombus was decreased (d) and became undetectable in iliac vein (e) according to ultrasound study. ●—●: ATIII concentration measured by the single radial immunodiffusion; □---□: heparin cofactor activity; ○---○: progressive antithrombin activity

Table 1 Coagulation studies and episodes of thromboembolism

		Case 1	Case 2	Case 3
ATIII single radial immunoassay				
progressive antithrombin activity ¹	(mg/dl)	12.0	15.3	15.6
	(%)	35	52	37
heparin cofactor activity ¹	(%)	45	55	61
PT ²	(sec)	21.9	11.6	11.1
APTT ²	(sec)	100	28.9	28.9
Fibrinogen	(mg/dl)	113	200	246
FDP	(μg/ml)	40	10	<10
Plasminogen ¹	(%)	66	76	129
α ₁ -antitrypsin	(mg/dl)	212	170	194
α ₂ -macroglobulin	(mg/dl)	426	210	171
C ₁ -inactivator	(mg/dl)	41	37	56
Episodes of thromboembolism		SSS IVC LV	LV	MV PA LV

¹ Activity relative to that of pooled plasma from 10 healthy individuals.

² Ci-Trol Coagulation Control (American Dade, AHS del Caribe, Inc., Aguada Puerto Rico) was used as a control. PT of the control was 10.9 to 11.7 sec; APTT, 27.3 to 28.9 sec; PT: prothrombin time; APTT: activated partial thromboplastin time; FDP: fibrin degradative product; SSS: superior sagittal sinus; IVC: inferior vena cava; LV: leg veins; MV: mesenteric veins; PA: pulmonary artery.

Fig. 3 shows obvious increases in plasma levels of α₁-AT, Pgn and CI-I: maximal percent changes relative to the pretreatment levels were observed between 3 and 4 weeks after the initiation of OML therapy. In contrast, as shown in Fig. 3, the plasma level of α₂-MG decreased after the introduction of the therapy. Those

plasma proteins returned to almost pretreatment levels by 2 weeks after discontinuing OML.

The values of ATIII, Pgn and α₁-AT on day 14 were significantly increased (p < 0.05), and value of α₂-MG decreased (p < 0.05) as compared to the initial values on day 0.

Discussion

In this study of OML and warfarin for patients with familial ATIII deficiency, significant increases in anti-thrombotic and/or anticoagulative factors such as ATIII, Pgn, α₁-AT and CI-I were observed. Concentrations of those factors remained at a constant level during the periods of OML therapy for 6 to 17 weeks and gradually decreased as it was tapered off. This suggests that the increase of the factors' concentration is closely related to the administration of OML. It is also possible that anticoagulation by warfarin decreased the consumption of these proteins and that their concentrations increased accordingly. However, this effect may be negligible since the normalized levels of those proteins could not be maintained by warfarin alone. In contrast, a significant decrease of α₂-MG was observed following the introduction of OML therapy. The plasma level of this protein gradually increased and returned to pretreatment level with the tapering off of OML. This indicates that the decrease of α₂-MG was also caused by the effect of OML, probably as a result of decreased biosynthesis.

Barbosa et al. (3) noted that 17-α alkylated anabolic steroids induced elevation of Pgn. Walker et al. (12) reported that OML increases ATIII level and α₁-AT and decreases α₂-MG in patients with ischemic heart disease. These reports are consistent with the results of our current study. Laurell and Rannevik (13) and Preston et al. (5) propounded the hypothesis that hepatocytes

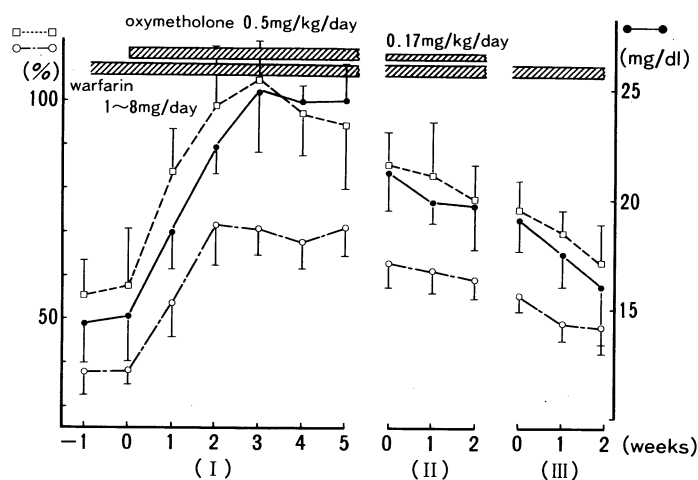


Fig. 2 Mean \pm SD of ATIII levels of 3 cases during the periods of oxymetholone therapy (I), on tapering dose (II) and after tapering off the drug (III). Vertical lines indicate 1 SD. ●—●: ATIII concentration measured by the single radial immunodiffusion; □—□: heparin cofactor activity; ○—○: progressive antithrombin activity

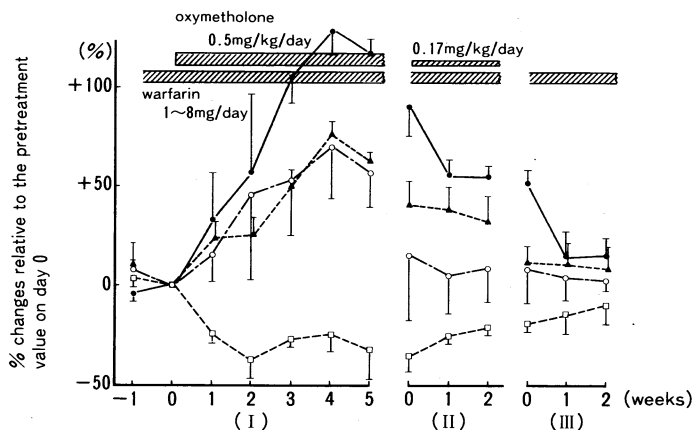


Fig. 3 Mean \pm SD of % changes relative to the pretreatment value on day 0 of each plasma protein of 3 cases during the periods of oxymetholone therapy (I), on tapering dose (II) and after tapering off the drug (III). Vertical lines indicate 1 SD. ●—●: plasminogen; □—□: α_1 -antitrypsin; ▲—▲: Cl-inactivator

have steroid receptors capable of reacting with danazol or stanozolol which alter the hepatic synthesis of a large number of plasma proteins by competitive receptor binding at hepatocytes. It is considered that the concentration of such plasma proteins could vary depending on the specificity of receptor binding of each steroid. In view of the similarity of chemical structure of those anabolic agents, it is likely that OML exerts its effects by a similar mechanism.

The increase of heparin cofactor activity was always higher than that of progressive antithrombin activity as shown in Fig. 1. This may be because the former activity is determined in the presence of excess of heparin (10) and the latter represents a natural antithrombin activity without exogenous heparin (9).

It is noteworthy that the huge thrombus was lysed rapidly in 2 weeks after administration of OML and warfarin in case 1. This may be explained in part by the augmented fibrinolytic capability including the increase of Pgn level as shown in Fig. 3. Decreased fibrinolytic activity in thromboembolic diseases can be recovered by anticoagulation because the consumption of fibrinolytic factors such as Pgn is compromised. In addition, anabolic steroids could further enhance the fibrinolytic activity by increasing the biosynthesis of fibrinolytic factors. Investigation of tissue Pgn activator and Pgn activator inhibitor may be necessary to confirm this explanation. We suppose that the thrombolysis in case 1 was facilitated in part by the additive effects of OML and warfarin. Accumulation of more cases may be necessary to substantiate this hypothesis. It may also be worthwhile to attempt this therapy for other patients with thromboembolism, not only for those with familial ATIII deficiency. Side effects of OML such as liver injury or musculization in female are reversible and may not interfere with the treatment of thromboembolism in a limited period.

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