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## A New Medication in Succession to Heparin for Disseminated Intravascular Coagulation Caused by Aortic Dissection — A Case Report —

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**Abstract** A forty-nine-year-old female was admitted with a right hypochondralgia and a bleeding tendency. Blood examinations revealed coagulation disorders. We diagnosed the patient as suffering from disseminated intravascular coagulation (DIC). Computed tomography and aortic angiogram revealed aortic dissection (DeBakey IIIb) accompanied with DIC. The right hypochondralgia was considered to be due to ischemia of the gall bladder. This development was caused by the celiac trunk being branched out from the pseudo-lumen. The orifice of the celiac trunk was severely stenotic. Initially, heparin and Gabexate mesilate (FOY®) were used intravenously for treating the DIC. Then only heparin was used subcutaneously. Finally, we were able to change the drugs to Danazol and Camostat mesilate per os. Those drugs seemed to be effective in succession to the heparin therapy for treating DIC in the subacute phase.

*Key Words* : Aortic dissection, Disseminated intravascular coagulation, Medication

### Introduction

Disseminated intravascular coagulopathy (DIC) occurs as a result of several causes (1). Aortic dissection is a relatively rare cause of DIC (2,3). As medications have no effect to some patients with DIC, we ought to operate those patients. It is known, however, that the operative result of aortic dissection complicated by DIC is poor because of bleeding tendency. Heparin (4,5) and/or protease inhibitor (6,7) therapy is useful in suppressing DIC, however, there are some cases that DIC will recur immediately after withdrawal of these drugs. So, we have to continue to give those drugs for a long time.

we present here a case, which was success-

fully treated with Danazol (BONZOL®)(8) and Camostat mesilate (FOIRAN®) per os in subacute phase in succession to the heparin therapy.

### Case Report

The patient was a forty-nine-year-old female complaining of right hypochondralgia and a bleeding tendency. Physical examination revealed a large area of ecchymosis on the both thighs and a large subcutaneous hematoma on the right hip. The laboratory data were as follows: bleeding time 5 min. (control, <3 min.), hemoglobin 10.8 g/dl, white blood cell count 6000/mm<sup>3</sup>, platelets  $5.7 \times 10^4$ /mm<sup>3</sup>, prothrombin time 14.9 sec

(reference range, 11-13 sec.) and activated partial thrombin time 34.9 sec. (reference range, 25-35 sec.). Plasma fibrinogen level was 105 mg/dl (reference range, 200-400 mg/dl) and fibrin degradation product (FDP) 40  $\mu$ g/dl (control, <10 Mg/dl). Antithrombin III (AT-III) was 44% (reference range, 79-121%). The erythrocyte sedimentation rate was 4 mm per one hour. GOT was 131 IU/L (reference range, 8-40 IU/L), GPT 57 IU/L (reference range, 5-35 IU/L), LDH 568 IU/L (reference range, 100-400 IU/L), ALP 10.7 IU/L (reference range, 2.0-11.0 IU/L), LAP 233 IU/L (reference range, 70-200 IU/L) and g-GTP 88 IU/L (reference range, 0-40 IU/L). DIC score from these laboratory data was 7 points, which defined DIC (9). We concluded

from this data that the patient was suffering from DIC.

Continuous intravenous infusion of heparin ( $10 \times 10^4$  U/day) and Gabexate mesilate (FOY<sup>®</sup>) (1200 mg/day) were initially administered for 9 days. The computed tomography (CT) (Figure 1-A, B) revealed aortic dissection which was classified as DeBakey IIIb type based on the findings of aortic angiography (Figure 2-A, B) and the gall bladder wall thickening. The angiograms showed that the dissection arose in the proximal descending aorta, just distal to the origin of the left subclavian artery, and extended to the iliac arteries. A celiac trunk was branched from the pseudo-lumen, while the other arteries such the superior mesenteric artery and bilateral renal arteries from the true lumen. Magnetic resonance imaging (MRI) showed a severe stenosis of origin of the celiac artery (Figure 3). It was diagnosed that thickening of the gall bladder wall and the right hypochondralgia were due to ischemia of the gall bladder. It was difficult to decide that which part of aortic dissection mainly contributed to DIC from CT, aortic angiogram and MRI. It was doubtful that the ischemic damage of gall bladder was concerned to DIC. However, the wall thickening of gall bladder was disappeared about 1 week after admission.

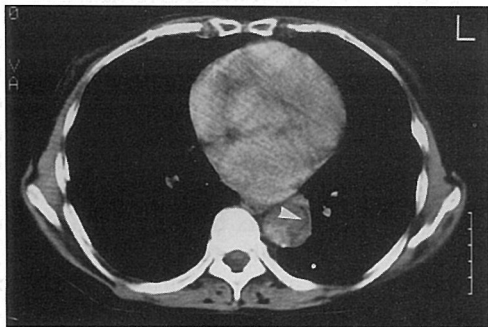


Fig. 1-A CT image of the chest after intravenous administration of contrast material showing the aortic dissection (arrow).

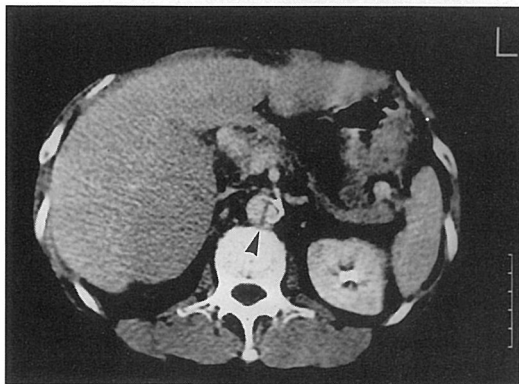


Fig. 1-B CT image of the abdomen with intravenous administration of contrast material showing the abdominal aortic dissection (arrow).

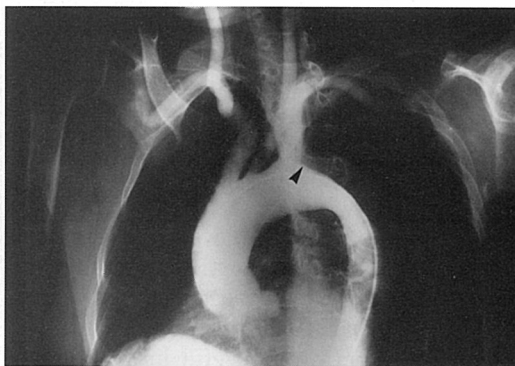


Fig. 2-A An aortic angiogram showing the aortic dissection (DeBakey IIIb). The dissection arised in the proximal descending aorta, just distal to the origin of the left subclavian artery (arrow).

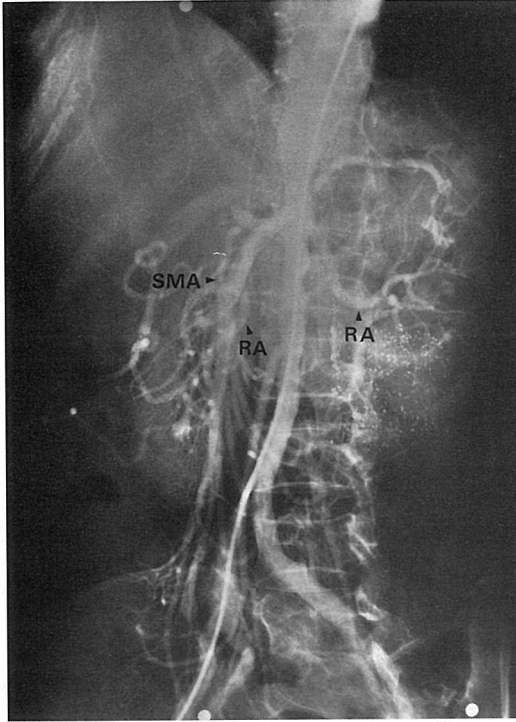


Fig. 2-B An aortic angiogram showing the aortic dissection (DeBakey IIIb). The celiac trunk was branched from the pseudo-lumen and the other major vessels were branched from the true-lumen. SMA; superior mesenteric artery, RA; renal artery.



Fig. 3 Sagittal magnetic resonance imaging (MRI) demonstrating the severe stenosis of the celiac trunk orifice (indicated by an arrow).

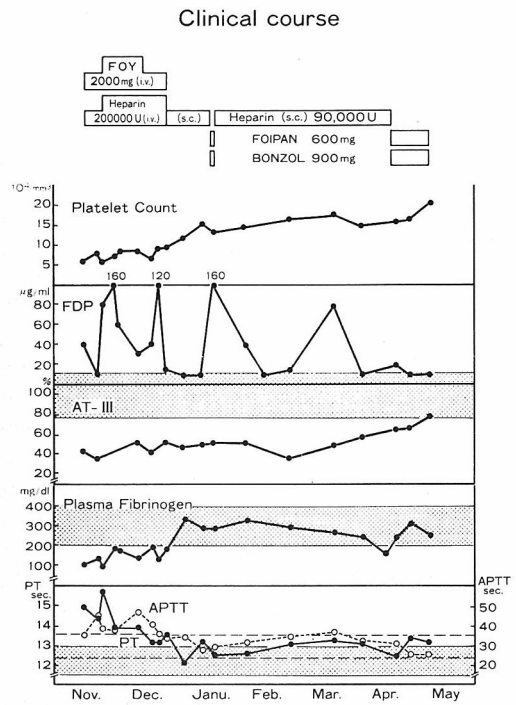


Fig. 4 Dosage regimens and the laboratory data are depicted. FDP; fibrin degradation product, AT-III; antithrombin III, PT; prothrombin time, APTT; activated partial thromboplastin time. Shaded areas indicate reference ranges. Reference range of APTT is indicated by border lines.

U/day of heparin and of 1200 mg/day of Gabexate mesilate (6) were ineffective in suppressing the DIC. Therefore the doses of both heparin ( $20 \times 10^4$  U/day) and Gabexate mesilate (2000 mg/day) were increased for a period of 20 days. At the end of that period the various parameters of coagulation disorders improved partially. Thereafter only heparin was administered subcutaneously at an intermittent doses of  $9 \times 10^4$  U/day. After 20 days with heparin therapy, the platelet count, plasma fibrinogen, FDP and the activated partial thromboplastin time recovered to normal, while the prothrombin time and AT-III level remained abnormal. Since ecchymosis and petechiae were no longer visible on her body, Danazol (900 mg/day) and Camostat mesilate (600 mg/day) were

administered per os after cessation of heparin administration. Subsequently, the FDP level increased and the bleeding tendency recurred, and it was necessary to return to subcutaneous heparin therapy ( $9 \times 10^4$  U/day). After three months, the FDP and the AT-III levels were not fully recovered to normal, but were near the upper limit of the normal range. The platelet count, plasma fibrinogen level, prothrombin time and activated partial thromboplastin time stayed normal. Although DIC score (9) was 6 points indicating suspected DIC, no clinical symptoms indicating DIC were observed and laboratory data had been showing consistent improvement. It was therefore decided to return to administration of Danazol (900 mg) and Camostat mesilate (600 mg) per os. The laboratory data were stable and no symptoms of a coagulation disorder recurred. Two weeks later, at the time of discharge, the results of coagulation studies were normal. Two months after discharge, the aortic angiography showed no change in aortic dissection; the false lumen was still open. The course during the following six months has been uneventful and uncomplicated.

## Discussion

Aortic dissection has been a relatively rare cause of DIC since the first report by Fine et al. in 1967 (10). In the medical treatment of DIC, heparin is widely used regardless of the cause including case of an aortic dissection (4, 5). Currently protease inhibitors (ex. Gabexate mesilate (FOY<sup>®</sup>), Nafamostat mesilate (FUTHAN<sup>®</sup>) (7) are used instead of heparin or combined with heparin. However, it is quite difficult to suppress DIC caused by aortic dissection in some cases, because coagulation and fibrinolysis are continuously activated in the aortic lumen. To save those patients we ought to operate under DIC status in some cases. Since the operative prognosis in patients with DIC is poor because of the bleeding tendency, medical treatment for DIC is undoubtedly the preferred option in patients excluding Stanford A type aortic dissection and with concomitant impending rupture and organ ischemia.

The efficacy of the medical treatment for

DIC is varied. In some cases heparin and/or protease inhibitor treatment improves DIC for a short period. On the other hand, even though heparin and/or protease inhibitor therapy were initially successful, the blood examination revealed a coagulation disorder which became progressively worse after withdrawal of heparin in some cases. Our case was one of the latter cases. In patients whose DIC can not be controlled without heparin, we have to give intravenously or subcutaneously over a long period. It is also difficult to decide the timing of withdrawing those drugs. In the present case we used Danazol and Camostat mesilate in succession to the heparin therapy, which successfully controlled DIC. Some papers have mentioned that Danazol has the effect of elevating antithrombin III and suppressing the coagulation (8,11). Our first attempt to change the mode of treatment from heparin to oral anti-coagulants was a failure. It might be that the intraaortic coagulation was too active to be suppressed by oral anti-coagulants. The second attempt was successful without recurrence of the symptoms and coagulation disorder. At the time of the second attempt, the coagulation disorder was improving but was still border line to DIC. It might be that no recurrence of coagulation disorder would occur without these oral agents, even though FDP and AT-III did not recover to normal at the time of second attempt. It was dangerous to stop the heparin subcutaneous therapy at that time due to the fear of recurring coagulation disorder. Therefore, the above oral anti-coagulants were used in succession to the heparin therapy. we recommend the use of Danazol and Camostat mesilate, especially in cases such as this case in which laboratory data of coagulation show improvement, but there are concerns over the withdrawal of heparin. Danazol and Camostat mesilate administration in succession to heparin therapy seemed to be effective to control DIC in this Case.

## Conclusion

We reported that the patient was suffering from aortic dissection accompanied with DIC. In the active stage, heparin and Gabex-

ate mesilate (FOY®) are useful for treating DIC. Heparin also has a strong effect on DIC itself. In the subacute phase, Danazol (BONZOL®) and Camostat mesilate (FOIPAN®) seemed to be useful for treating DIC. Danazol and Camostat mesilate might be ineffective in treating active DIC but effective in cases where intraaortic coagulation is slightly decreased and for the prevention of the development of DIC.

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