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The Effects of Orchiectomy, Oestrogens and Cyproterone-Acetate on the Antithrombin-III Concentration in Carcinoma of the Prostate

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Summary. The incidence of thromboembolic complications is increased in patients with oestrogen-treated prostatic carcinoma. Because reduced antithrombin-III (AT-III) levels are associated with increased risk of thromboembolism we have determined AT-III concentrations during oestrogen therapy and other treatments. Forty-six patients with carcinoma of the prostate were allocated to either treatment with subcapsular orchiectomy, oestrogen administration, or cyproterone acetate. AT-III was determined before treatment, at 2 weeks and 2 months later. During oestrogen therapy there was a significant reduction in AT-III to 77% of the base-line value. No significant changes were found after orchiectomy. During cyproterone-acetate treatment there was a slight but significant increase in AT-III at 2 months. The reduction in AT-III could indicate an increased risk of thromboembolism during oestrogen treatment of patients with carcinoma of the prostate. On the other hand, the unchanged AT-III levels after orchiectomy and the increased levels during cyproterone acetate therapy could mean that the risk of thromboembolism is less with these two forms of treatment.

Key words: Antithrombin-III, Oestrogen, Orchiectomy, Cyproterone-acetate, Malignancy, Prostate.

Treatment of patients with carcinoma of the prostate is based mainly on the hypothesis that the tumour is androgen dependent (12). Accordingly, orchiectomy, oestrogens, and cyproterone-acetate have all been reported to give good tumour regression (7, 8, 23). Oestrogen therapy has proved to be associated with increased cardiovascular mortality (3). Patients treated by orchiectomy showed no increased mortality from cardiovascular disease but higher mortality from the cancer (23). The risks associated with cyproterone-acetate treatment have been debated. Some workers believe the risk of cardiovascular complications to be less than with oestrogen therapy whereas others report similar complication rates with the two regimens (16, 17, 18).

Several studies have shown that the intake of oestrogens in the form of oral contraceptives is associated with an increased risk of thromboembolism (13, 19). The mechanism for the thrombogenic effect of oestrogens is unclear. Recent studies have indicated that the reduction of the AT-III concentration in women on combined oral contraceptives may contribute to the increased incidence of thrombosis (6, 15).

We have studied the AT-III level during oestrogen treatment of carcinoma of the prostate, as these patients are known to show increased morbidity from thromboembolism (3, 23). The effect of oestrogen treatment on the AT-III concentrations was compared with the effects of orchiectomy and of cyproterone-acetate therapy.

MATERIALS AND METHODS

46 patients (average age 71 years, range 51 to 86) with cytologically confirmed prostatic carcinoma were included in this study. Using the Union International Contre le Cancer classification (22) 3 patients had T 2, 21 patients T 3, and 22 patients T 4 tumours, (grade of malignancy: 5 G 1, 22 G 2, 19 G 3). Nineteen patients had distant metastases.

The 46 patients were allocated to one of 3 treatment groups regardless of the classification of the carcinoma. The three groups were comparable with regard to tumour stage and to other complicating diseases.

Group 1. 15 patients (mean age 73 years, range 60-84) were treated by bilateral subcapsular orchiectomy under local anaesthesia.

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Group 2. 16 patients (mean age 69 years, range 51-81) received oestrogens. Treatment was started with 160 mg polyoestradiol phosphate[1] (PEP) intramuscularly once monthly, and 1.0 mg ethinyl oestradiol[2] (EE) orally daily for 1 month. After 1 month they were given 80 mg PEP intramuscularly once monthly and 0.5 mg EE orally per day.

Group 3. 15 patients (mean age 71 years, range 58-86) received continuous treatment with cyproterone-acetate[3] 200 mg daily by mouth.

No patient had previously received anti-androgenic or hormonal treatment. Any existing drug regimen was kept unchanged throughout the observation period, and analgetics were given as required. One patient was given diuretics and digitalis when heart failure occurred during oestrogen treatment.

Determination of Antithrombin III

The AT-III activity was measured by a technique using the chromogenic substrate S-2238 (20) (Kabi Diagnostica, Mölndal, Sweden). The normal range for adults is 0.26 - 0.38 g/l, or 80 - 120% (1). Venous blood samples were obtained from an antecubital vein with the patient recumbent between 07.00 and 08.00 a m after an overnight fast. Blood was collected in evacuated tubes containing K_3-EDTA 1,2 mg/ml (Vacutainer®). The plasma was separated and stored at -70°C until assayed. The samples were taken 1 day before and 2 weeks and 2 months after starting treatment.

RESULTS

The results are given in Table 1. The base-line values were identical in all groups.

In the oestrogen group there was a significant fall in AT III levels after 2 weeks and 2 months of treatment. In all oestrogen-treated patients the AT-III level dropped below the base-line value (Fig. 1). The decrease in AT III concentrations was significantly correlated to the AT-III ($r = 0.64$, $p < 0.01$) before starting oestrogen therapy (Fig. 2); in other words, the higher the base line value the greater the reduction of AT-III during oestrogen treatment.

No significant change of AT-III was found after orchiectomy. During cyproterone-acetate treatment the mean value of AT-III was slight but significantly increased at 2 months.

[1]Estradurin®, Leo AB, Helsingborg
[2]Etivex®, Leo AB, Helsingborg
[3]Androcur®, Schering AG, Berlin

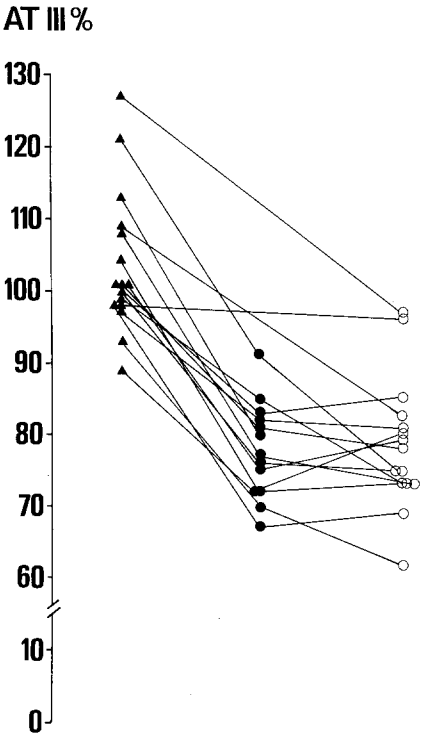

Fig. 1. Individual antithrombin-III concentrations before treatment and 2 weeks and 2 months after starting oestrogen treatment. Antithrombin-III concentrations are given % of 0.3 g/l. ▲ = before treatment; ● = 2 weeks after starting oestrogen treatment; o = 2 months after starting oestrogen treatment

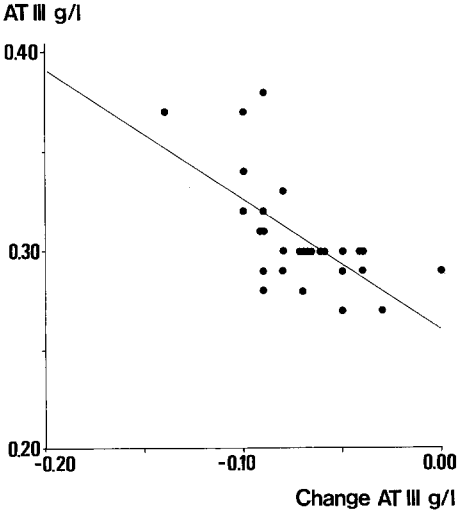

Fig. 2. Correlation between the antithrombin-III concentrations before oestrogen therapy, and the change in antithrombin-III concentrations 2 weeks and 2 months after starting oestrogen treatment. R = 0.64 p = <0.01

Table 1. Mean antithrombin-III concentration (g/l ± SEM) during treatment with orchiectomy (Group 1), polyoestradiol phosphate and ethinyl oestradiol (Group 2), or cyproterone-acetate (Group 3)

Treatment	n	Before	2 weeks	2 months
Group 1	15	0.30 ± 0.02	0.32 ± 0.01	0.31 ± 0.01
Group 2	16	0.31 ± 0.01	0.23 ± 0.01[a]	0.24 ± 0.01[a]
Group 3	15	0.30 ± 0.01	0.33 ± 0.01	0.34 ± 0.01[b]

[a] $p < 0.001$, [b] $p < 0.05$

DISCUSSION

The incidence of cardiovascular complications is increased after oestrogen treatment for carcinoma of the prostate (3, 23). With regard to the mechanism of this, interest has been focused on the coagulation and fibrinolytic systems. Eisen (11) found increased aggregability of platelets in patients receiving oestrogen therapy for prostatic carcinoma. Blombäck et al (4) found reduced concentrations of AT-III in patients on oestrogen therapy, and a further reduction of AT-III when estramustine-17-phosphate[1] was given. They also found that fibrin-fibrinogen degradation products were increased in patients with progressive disease. Carlsson and Åstedt (9) found a significant reduction of the fibrinolytic activity in vein walls in patients with carcinoma of the prostate treated with oestrogens.

AT-III is the clinically most important naturally-occurring antithrombin, and it affects the coagulation system at different stages. Its importance is further underlined by the high incidence of venous thromboembolism in patients with hereditary or acquired deficiency of AT-III (10, 15). Hereditary AT-III deficiency is one of several states in which a rare disposition for thrombosis has been clearly correlated to abnormalities of the coagulation system.

AT-III can be determined by immunological methods (14) or with chromogenic substrate (1, 20, 21). The assay of AT-III using chromogenic substrate has proved simple and reliable, and is used routinely in many laboratories (5). Patients with malignant disease often show abnormalities of the coagulation and fibrinolytic systems. In the present study the base-line values of AT-III were in the normal range. The unchanged AT-III concentrations during treatment indicated that the reduction seen in the oestrogen treatment group was due to the treatment and not to the development of tumour disease.

A fall in AT-III concentrations during oestrogen therapy, as found in the present study, is in accordance with Blombäck's results (4); in this study, however, the author did not measure the AT-III levels before treatment, and was therefore unable to give base-line values or the degree of AT-III reduction. Changes in AT-III after orchiectomy and during cyproterone-acetate treatment have not previously been evaluated.

Our results show that the base-line AT-III values can not be used to predict which individuals run the greatest risk of thromboembolism during oestrogen therapy, as the AT-III fell in all subjects, and those with the highest base-line values showed the greatest reduction in AT-III during oestrogen therapy.

Reduced AT-III levels are associated with an increased tendency to thrombosis. The reduction in AT-III in the oestrogen-treated group indicates as increased risk of thromboembolism. The unchanged AT-III after orchiectomy and the increased AT-III during cyproterone-acetate treatment may indicate that the risk of thrombosis is less with these two forms of therapy. As a gestagenic drug cyproterone-acetate is capable of increasing the AT-III level. This tallies with previous reports that the AT-III levels were increased in women using progesteron for contraception (2).

This short-term study does not allow evaluation of the incidence of thrombosis, as no patient developed clinical thrombosis during the observation period of 2 months. Long-term studies are called for to assess the clinical importance of AT-III concentrations before and during different kinds of endocrine treatment.

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REFERENCES

1. Abildgaard, U., Ödegård, O. R.: A simple method for determination of functionally active antithrombin III. Scandinavian Journal of Clinical and Laboratory Investigation 36, 109 (1976)
2. Bergsjö, P., Fagerholm, M. K., Albildgaard, U.: Antithrombin III concentration in women using low-dose progesteron for contraception. American Journal of Obstetrics and Gynecology 112, 983 (1972)

3. Blackard, C. F., Mellinger, G. T., Byar, D. P. : Incidence of cardiovascular disease and death in patients receiving diethylstilbestrol for carcinoma of the prostate. Cancer 26, 249 (1970)
4. Blombäck, M., Edsmyr, F., Kockum, C., Paul, C. : Blood coagulation studies in papatients with advanced carcinoma of the prostate treated with 2, 6-cisdiphenylhexamethylocyclotetrasiloxane or estramustine-17-phosphate. Urological Research 6, 95 (1978)
5. Blombäck, M. : Koagulationsdiagnostik med kromogena substrat. Ronden 12, 209 (1979)
6. Bounameaux, H., Cuckert, F., Walter, M., Bounameaux, F. : The determination of antithrombin III. Comparison of six methods. Effect of oral contraceptive therapy. Thrombosis Haemostas 39, 607 (1978)
7. Bracci, U. : Antiandrogens in the treatment of prostatic cancer. European Urology 5, 303 (1979)
8. Byar, D. P. : The Veterans Administration Cooperative Urological Research Group's Studies of cancer of the prostate. Cancer 32, 1126 (1973)
9. Carlsson, S., Åstedt, B. : Oestrogenic treatment of prostatic cancer lowers the fibrinolytic activity in vein walls. Scandinavian Journal of Urology and Nephrology 8, 169 (1974)
10. Egeberg, O. : Inherited antithrombin deficiency causing thrombophilia. Thrombosis et Diathesis Haemorrhagica 13, 516 (1965)
11. Eisen, M., Napp, H. E., Vock, R. : Inhibition of platelet aggregation caused by estrogen treatment in patients with carcinoma of the prostate. Journal of Urology 114, 93 (1975)
12. Huggins, C., Hodges, C. V. : Studies on prostatic cancer. The effects of castration, of estrogen and androgen injection on serum phosphateses in metastatic carcinoma of the prostate. Cancer Research 1, 293 (1941)
13. Inman, W. H. W., Vessey, M. P., Westerholm, B., Engelund, A. : Thrombembolic disease and steroidal content of oral contraceptives. A report to the Commitee on safety of drugs. British Medical Journal 2, 203 (1970)
14. Mancini, G., Canbonara, A. D., Hermans, S. F. : Immunochemical quantitation of antigens bei singly radial immunodiffusion. Immunochemistry 2, 235 (1965)
15. Sagar, S., Stamatakis, J. D., Thomas, P. D. Kakkar, V. V. : Oral contraceptives, antitrombin III activity and postoperative deep-vein trombosis. Lancet 6, 509 (1976)
16. Scott, W. W., Schirmer, H. K. A. : A new oral progestational steroid effective in treating prostatic cancer. Transactions of the American Association of Genito-Urinary Surgeons 58, 54 (1966)
17. Tveter, K. J., Otnes, B., Hannestad, R. : Treatment of prostatic carcinoma with cyproterone acetate. Scandinavian Journal of Urology and Nephrology 12, 115 (1978)
18. Wein, A. J., Murphy, J. J. : Experience in the treatment of prostatic carcinoma with cyproterone acetate. Journal of Urology 109, 68, (1973)
19. Vessey, M. P., Doll, R. : Investigation of relation between use of oral contraceptives and trombembolic disease. British Medical Journal 2, 651 (1969)
20. Ödegård, O. R. : Evaluation of an amidolytic heparin cofactor method. Thrombosis Research 7, 351 (1975)
21. Ödegård, O. R., Lie, N., Abildgaard, U. : Heparin cofactor activity measured with an amidolytic method. Thrombosis Research 6, 287 (1975)
22. Union Internationale Contre Le Cancer, TNM classification of malignant tumours, Geneva 1978
23. Veterans Administration Cooperative Urological Research Group: Treatment and survival of patients with cancer of the prostate. Surgery, Gynecology and Obstetrics 124, 1011 (1967)

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