RECOVERY OF SERUM PROSTATE SPECIFIC ANTIGEN VALUE AFTER INTERRUPTION OF ANTIANDROGEN THERAPY WITH ALLYLESTRENOL FOR BENIGN PROSTATIC HYPERPLASIA

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Decrease in serum prostate specific antigen (PSA) concentration is inevitably associated with antiandrogen therapy for benign prostatic hyperplasia (BPH), and might mask the presence of prostate cancer or delay its diagnosis. To determine the appropriate timepoint for determination of correct PSA value, we sequentially measured serum PSA and testosterone levels after discontinuation of antiandrogen therapy for BPH. With informed consent, 12 patients (72.8±2.2* years old) with BPH were treated with allylestrenol 50 mg/day for 4 months. Serum testosterone and PSA concentrations were determined before and just after treatment, as well as every month after treatment up to 3 months. After treatment with allylestrenol for 4 months, mean serum testosterone and PSA levels were significantly decreased from 408±136* to 87.9±76.2* ng/dl, and from 2.81±0.87* to 2.04±0.82* ng/ml, respectively. The mean serum PSA level recovered to the pretreatment level within 2 months and mean serum testosterone concentration within one month after discontinuation of administration. In conclusion, during treatment of BPH with antiandrogen allylestrenol, a two-month washout is adequate for determination of correct PSA value (*: M±SD).

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Key words : BPH, Antiandrogen therapy, PSA

INTRODUCTION

Decrease in prostate specific antigen (PSA) concentration is unavoidable during treatment of benign prostatic hyperplasia (BPH) with antiandrogen[1,2]. To date, there is no evidence that the small amount of antiandrogen used in the treatment of BPH masks detection of prostate cancer or affects progression of prostate cancer. However, it is possible that the diagnosis of prostate cancer will be delayed if the PSA value is used in medical examination for prostate cancer in patients being treated with an antiandrogen. It is thus very important to determine correct PSA value during treatment of BPH with antiandrogen.

We have already reported that the PSA value decreased after treatment with antiandrogen allylestrenol but completely recovered to the pretreatment level within 4 months[3]. To determine the appropriate washout period for determination of correct PSA value, we sequentially measured serum PSA and testosterone levels after discontinuation of antiandrogen therapy for BPH.

PATIENTS AND METHODS

With informed consent, 12 patients (69–78 years old : 72.8±2.2 ; mean ± SD) with symptomatic BPH (24–53 ml : 36.7 ± 7.9 ; mean ± SD) were treated with allylestrenol (50 mg/day) for 4 months. Serum testosterone and PSA concentrations were measured before and just after treatment, as well as every month after treatment up to 3 months. Patients with a normal digital rectal examination and normal PSA value were selected for this study. Patients previously treated with antiandrogenic drugs, with impaired renal or liver function, with poor general condition, or with significant laboratory abnormalities were excluded from the study. Each blood sampling was done in the morning, and PSA values were expressed in Tandem-R.

RESULTS

After treatment with allylestrenol for 4 months, mean serum testosterone and PSA levels were significantly decreased from 408±136* to 87.9±76.2* ng/dl, and from 2.81±0.87* to 2.04±0.82* ng/ml, respectively. The mean serum PSA level recovered to the pretreatment level within 2 months and mean serum testosterone concentration within one month. Neither testosterone nor PSA value exceeded the pretreatment level at any time after discontinuation of allylestrenol (Fig. 1).

DISCUSSION

Allylestrenol is an effective and safe medical treatment for patients with symptomatic BPH because it decreases the size of adenoma[4]. The direct effects of allylestrenol on the prostate are inhibition of DHT-receptor complex formation, inhibition of serum testosterone uptake into

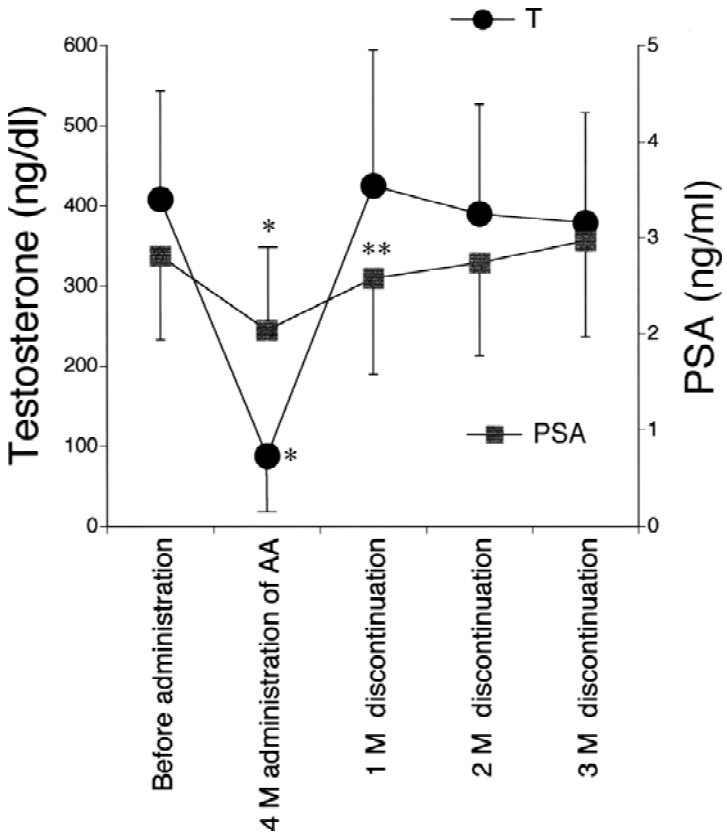

Fig. 1. After treatment with allylestrenol for 4 months, the mean serum testosterone was significantly decreased from 408 to 87.9 ng/dl and the mean PSA level was significantly decreased from 2.81 to 2.04 ng/ml. The mean serum PSA level recovered to the pretreatment level within 2 months and mean serum testosterone concentration within one month after discontinuation of allylestrenol. *: $p<0.001$, **: $p<0.05$ by ANOVA, AA : Allylestrenol 50 mg/day.

the prostate, and inhibition of testosterone-5α-reductase activity[5]. Allylestrenol also inhibits the hypothalamo-pituitary-testicular axis and decreases serum testosterone[3,5]. A significant decrease in serum PSA was demonstrated in our previous study[3]. However, serum PSA value decreased after treatment with antiandrogen allylestrenol but completely recovered to the pretreatment level within 4 months[3]. In the present study, we attempted to determine the appropriate washout period for correct determination of PSA value. The mean serum PSA level recovered to the pretreatment level within 2 months and mean serum testosterone concentration within one month without rebound phenomenon.

As hormonal therapy for BPH patients, the 5α-reductase inhibitor finasteride has demonstrated both efficacy and acceptable safety in randomized clinical trials[6,7]. Finasteride also lowers serum PSA during treatment, and the International Scientific Committee of the 5th International Consultation on BPH recommended that the PSA value could be corrected by simply multiplying the obtained value by two[8] Oesterling et al.[9] reported that doubling of PSA levels in finasteride-treated patients allows appropriate interpretation of PSA values and does not mask detection of prostate cancer. Brawer et al.[10] found that only 35% of men treated with finasteride exhibited 40–60% reduction in PSA level and concluded that the heterogeneity of PSA response to finasteride may be a problem when monitoring patients for the development of prostate cancer. In the present study, the serum testosterone level completely recovered within one month after discontinuation of allylestrenol, and mean PSA value returned to the pretreatment level within 2 months. These findings strongly suggested that the effects of allylestrenol on the hypothalamo-pituitary-testicular axis have completely disappeared after one month of discontinuation. Moreover, other direct effects of this agent on the prostate gland vanished within two months after the last treatment. Discontinuation of hormonal therapy appeared to be another option for determination of correct PSA value. We have already reported that IPSS and QOL scores of patients with BPH did not worsen up to 4 months after discontinuation of allylestrenol[3].

Percent free PSA is reported to be useful for detection of prostate cancer during treatment with finasteride for

BPH. Keetch et al.[11] and Pannnek et al.[12] found that total PSA serum levels decreased by an average of 50% during finasteride therapy but that percent free PSA did not change significantly, and suggested that the decrease in percent free PSA during treatment of BPH with finasteride could be an early sign of prostate cancer. In the present study, percent free PSA values were not stable during treatment with allylestrenol (data not shown).

Recently, chemoprevention of prostate cancer using a 5α-reductase inhibitor has been advocated. Thompson et al.[13] reported that finasteride prevented or delayed the appearance of prostate cancer in a randomized trial of seven-year administration of finasteride for participants with a normal rectal examination and with normal PSA value. They also demonstrated increased risk of high-grade prostate cancer in the finasteride group, and concluded that the greater absolute reduction in risk of prostate cancer must be weighed against the smaller absolute increase in risk of high-grade cancer. The present findings suggest an option of intermittent use of antiandrogen checking the correct PSA value by discontinuation of antiandrogen.

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和文抄録

アリルエストレノールによる前立腺肥大症の治療中断後，PSA 値の回復に必要な期間についての検討

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前立腺肥大症をアンチアンドロゲン剤にて治療するとテストステロンの低下にともない PSA が低下する．これにより前立腺癌の診断が遅れることが危惧されている．しかしながら，アンチアンドロゲン剤の中断後４カ月で，両者とも完全に前値に復することをすでに報告した．PSA 4.0 ng/ml 以下の前立腺肥大症の症例においてアンチアンドロゲン剤中断後のテストステロンと PSA の変化を経時的に観察し，治療前値に復するまでに要する期間につき検討した．症例は平均72.8±2.2歳の前立腺肥大症（前立腺体積：36.7±7.9 ml）患者でアンチアンドロゲン剤による治療およびテストステロン，PSA の経時的採血に文書同意を得た12症例である．アリルエストレノール 50 mg/day を４カ月間投与した．これを中断後１カ月ごとに採血してテストステロンと PSA を経時的に観察した．アリルエストレノールの投与４カ月でテストステロンは低下し，これに伴い PSA も有意に低下した．治療の中断後１カ月でテストステロンは前値に復し，PSA は中断後２カ月でほぼ前値に復した．以上より，前立腺肥大症のアリルエストレノールによる治療中に正確な PSA 値を知るために必要なアリルエストレノールの washout 期間は，ほぼ２カ月であることが示唆された．

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