

SERUM CONCENTRATIONS OF FLUTAMIDE AND GOSERELIN IN A PROSTATE CANCER PATIENT WITH OBSTRUCTIVE NEPHROPATHY: A CASE REPORT

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A 72-year-old man presented with pollakiuria and dysuria. His prostate was the size of an apple and hard on digital rectal examination and the serum prostate specific antigen (PSA) level was 73 ng/ml (RIA). Ultrasonography revealed bilateral hydronephrosis and the serum creatinine level was 13.2 mg/dl. CT scanning of the abdomen demonstrated swelling of paraaortic lymph nodes.

Transrectal needle biopsy of the prostate gave a diagnosis of moderately differentiated adenocarcinoma. Accordingly, the final diagnosis was prostate cancer (cT3N4M1, stage D2). Immediately after bilateral percutaneous nephrostomy, treatment with an LH-RH agonist (goserelin) and flutamide was commenced. Serum creatinine was 6.6 mg/dl at the start of antiandrogen therapy and decreased to 1.8 mg/dl after 27 days.

A 125 mg flutamide capsule was administered at 7 a.m., and blood samples were collected 4 hours later on days 1, 2, 3, 5, 6, 8, 12, 14, 17, 18 and 27. The OH-flutamide concentration was measured. There was no significant correlation between serum creatinine and the OH-flutamide concentration.

After implantation of goserelin (3.6 mg depot), blood samples were obtained at 11 a.m. on days 8, 12, 14, 15 and 25. The serum goserelin level was measured. The serum goserelin level increased to a peak on day 14, as described previously, but the peak value of 9.63 ng/ml was higher than that reported before (mean $\pm$ SD 2.848 $\pm$ 0.199).

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Key words: Prostate cancer, Obstructive nephropathy, Flutamide, Goserelin

INTRODUCTION

In general, prostate cancer with obstructive nephropathy caused by lymph node metastasis is treated by percutaneous nephrostomy and subsequent hormonal therapy. The longer the duration of ureteral obstruction, the slower is the recovery of renal function. During this time, it is difficult to decide the appropriate doses of antiandrogen agents. However, there have been few reports on antiandrogen drug levels in patients with impaired renal function, since most of these agents are mainly metabolized in the liver. Here we report on the serum concentrations of flutamide and goserelin in a patient with obstructive nephropathy.

CASE REPORT

A 72-year-old man presented with pollakiuria, dysuria, and fatigue. His prostate was the size of an apple and hard on digital rectal examination and the serum prostate specific antigen (PSA) level was 73 ng/ml (radioimmunoassay, RIA). Ultrasonography revealed bilateral hydronephrosis and the serum creatinine level was 13.2 mg/dl. CT scanning of the pelvis revealed an enlarged prostate and swelling of the regional lymph nodes, while CT scanning of the abdomen demonstrated swelling of paraaortic lymph

nodes. A bone scan showed multiple hot areas.

Transrectal needle biopsy of the prostate gave a diagnosis of moderately differentiated adenocarcinoma. Accordingly, the final diagnosis was prostate cancer (cT3N4M1, stage D2). Immediately after bilateral percutaneous nephrostomy, treatment with an LH-RH agonist (goserelin) and flutamide was commenced.

At 23 days after the start of hormonal therapy, urinary flow from the bilateral nephrostomy tubes started to decrease and the voided volume increased gradually. Serum creatinine was 6.6 mg/dl at the start of antiandrogen therapy and decreased to 1.8 mg/dl after 27 days. After 43 days of hormonal therapy, although the paraaortic lymph node metastases were still observed on the CT scans, they had decreased to one third of the original size. After confirming the resolution of ureteral obstruction by antegrade pyelography, the bilateral nephrostomy tubes were removed.

Serum concentration of flutamide:

A 125 mg flutamide capsule was administered at 7 a.m., and blood samples were collected 4 hours later on days 1, 2, 3, 5, 6, 8, 12, 14, 17, 18 and 27. The blood samples were centrifuged, and separated plasma was immediately frozen to -20°C until assay. The OH-flutamide concentration was measured by a

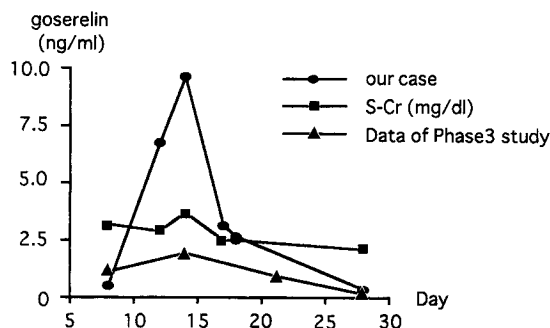


Fig. 1. The serum concentration of goserelin S-Cr: serum creatinine.

specific, sensitive, and reproducible gas-liquid chromatography method.

There was no significant correlation between serum creatinine and the OH-flutamide concentration, which remained between 200 and 500 ng/ml without reference to creatinine level (1.8–6.6 mg/dl) (analyzed by Pearson correlation, $p > 0.1$).

Serum concentration of goserelin:

After implantation of goserelin (3.6 mg depot), blood samples were obtained at 11 a.m. on days 8, 12, 14, 15 and 25. Blood was allowed to clot on ice before centrifugation for collection of the serum, which was stored at -20°C . The serum goserelin level was measured by a standard double antibody RIA.

The serum goserelin level increased to a peak on day 14, as described previously, but the peak value of 9.63 ng/ml was higher than that reported before¹⁾ (mean $\pm$ SD 2.848 ± 0.199) (Fig. 1).

DISCUSSION

Labrie et al.²⁾ reported the use of combined androgen blockade (CAB) therapy for prostate cancer in 1982, and prospective randomized studies of this treatment have subsequently been performed in Europe and America. In these studies, patients receiving CAB therapy showed a longer progression-free survival and an increased median survival time compared to those who had surgical castration or treatment with an LH-RH agonist alone^{3,4)} In Japan, flutamide received approval in 1994, and CAB therapy is now widely available for advanced prostate cancer.

Flutamide is a nonsteroidal antiandrogen used in the treatment of prostate cancer. Its efficacy as an antiandrogen is equal to or higher than that of cyproterone acetate and its hormonal side effects are weak. In Japan, a phase I study of orally administered flutamide was performed in patients with prostate cancer, and the drug received approval in November 1994. Goserelin is a luteinizing hormone-releasing hormone (LH-RH) analogue and is generally accepted as a useful treatment for prostate cancer.

In our department, CAB therapy with goserelin and flutamide was started in 1995. Compared with diethylstilbestrol phosphate, there are fewer side effects requiring hospital admission. However, since severe side effects have been reported⁵⁾, care is needed when treating patients with renal or hepatic insufficiency and the elderly. Since flutamide is mainly metabolized in the liver, administration to patients with hepatic insufficiency is dangerous. Care must also be taken when flutamide is administered to patients with renal insufficiency, because of the lack of data about the serum concentration of flutamide in such patients. Flutamide is rapidly absorbed after oral administration, and is mainly metabolized to the active plasma metabolite OH-flutamide. On the other hand, the main urinary metabolite at 24 hours after administration is a glucuronic acid. The percentage of each metabolite after hydrolysis by β -glucuronidase is as follows: flutamide-3 $26.3 \pm 13.1\%$, OH-flutamide $6.0 \pm 4.9\%$, flutamide-1 $2.6 \pm 2.2\%$, flutamide-5 $0.5 \pm 0.5\%$, and flutamide-6 $0.7 \pm 1.4\%$ ⁶⁾ Thus, very little OH-flutamide, an active metabolite, is found in the urine.

Swan et al.⁷⁾ examined the single oral dose pharmacokinetic parameters of flutamide in 4 patients with renal insufficiency (creatinine clearance of 5–29 ml/min). They reported no severe adverse reactions and concluded that the effect of renal insufficiency was slight, since $t_{1/2}$ was minimally prolonged when the creatinine clearance was < 30 ml/min. They concluded that dose adjustment in patients with renal insufficiency is not necessary for flutamide.

In our study, the serum concentration of OH-flutamide was not correlated with the serum creatinine level, and was similar to the data of the phase III study. This implies a low rate of renal metabolism of OH-flutamide and our data support the conclusion of Swan.

In 1971, Matsuo et al.⁸⁾ determined the structure of the natural LHRH, which is formed from 10 amino acids with 9 peptide bonds. Due to rapid hydrolysis of its peptide bond, the natural LHRH has a serum half-life of only a few minutes. Goserelin ([D-Ser(But)⁶AzGly¹⁰] LHRH) is a synthetic analogue of LHRH¹⁾ Structural changes have been made to reduce its susceptibility to peptidase activity, with an accompanying increase in the affinity for receptor proteins that gives goserelin a 100-fold greater potency than LHRH in inducing ovulation in rats. Goserelin is hydrolyzed by carboxylesterase in the blood, and this enzyme is also found in many organs, e.g., the liver, intestines, kidneys, and brain⁹⁾ If the kidneys are important for hydrolysis of goserelin, accumulation would occur in patients with renal insufficiency. However, the role of the kidneys in the

metabolism of goserelin remains unclear. Therefore, it cannot be concluded that the maximum serum concentration of goserelin in our patient, which was higher than that in the phase III study, was increased by renal dysfunction. Further investigation is needed to clarify this issue.

The main metabolite of goserelin is 5–10 peptide (Tyr-D-Ser(But)-Leu-Arg-Pro-Azagly·NH₂), which is principally excreted in the urine and feces. Therefore, accumulation of this metabolite in patients with renal dysfunction can be predicted. However, the LHRH activity and toxicity of this metabolite are thought to be very weak. Although we did not study this metabolite, its toxicity seemed to be low, because there were no severe adverse reactions in our patient despite possible metabolite accumulation.

In conclusion, further studies in more patients over a longer period are needed to confirm the safety of CAB therapy in patients with renal insufficiency.

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和文抄録

血中 Goserelin, Flutamide 濃度を測定しえた閉塞性腎機能障害の 1 例

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72歳，男性．頻尿を主訴に当科受診．初診時，前立腺はリンゴ大，石様硬で，血中 PSA 値は 73 ng/ml (RIA) であった．腹部 CT 検査では腫大した傍大動脈リンパ節と両側水腎症を認め，両側経皮的腎瘻造設と経直腸的前立腺針生検を施行した．診断は中分化型前立腺癌で，ただちに goserelin, flutamide 投与を開

始し，Cr とその血中濃度を経時的に測定した．血中 goserelin は治療開始後14日目で 9.6 ng/ml と，国内臨床試験データより高い値を示したが，血中 flutamide は400から 470 ng/ml と国内臨床試験データとほぼ同じ値であった．

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