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Flutamide Administration at 500 mg Daily Has Similar Effects on Serum Testosterone to 750 mg Daily

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ABSTRACT: A prior comparison of 750 mg flutamide daily to 500 mg daily with an LHRH analog or orchiectomy showed no difference in effect on prostate specific antigen (PSA). However, any difference was likely masked by hypogonadism from concomitant LHRH analog or orchiectomy. We sought to evaluate different flutamide dosing schedules without this confounding factor. We recruited 50 men with advanced prostate cancer who elected to receive hormonal therapy to be randomized to 1 of 3 flutamide treatment groups: 1) 250 mg once daily, 2) 250 mg twice daily, or 3) 250 mg 3 times daily for 3 months, after which the therapy of their choice was instituted. Serum samples at the initiation of therapy and at the 1- and 3-month time point were assessed for PSA, testosterone, liver function tests, hematology, and renal function. Prostate volume, androgen deficiency symptoms, and a compliance diary were also recorded. Testosterone and PSA levels show a dose-dependent response to flutamide monotherapy. Loss of libido and erectile dysfunction occurred in all 3 treatment groups, with a trend toward worsening sexual function with higher flutamide dosing, but this trend did not reach statistical significance. Prostate volumes decreased by an average of 34.3% in the patients receiving 250 mg flutamide 3 times daily, 27.8% in patients receiving 250 mg flutamide twice daily, and 19.2% in those receiving a once daily dose of 250 mg flutamide. There was a significant difference between the once daily group and the 3 times daily group ($P = .047$). Flutamide at 500 mg did not result in significant changes in testosterone, PSA, prostate volume, or androgen deficiency symptoms compared to 750 mg daily after 3 months.

Key Words: Prostate neoplasm, antiandrogen, hormone, PSA, androgen deprivation.

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As a result of the 5-hour to 6-hour serum half-life of flutamide, the original dosing schedule for this medication was established at 3 times daily (Belanger et al, 1988; Schulz et al, 1988; Neri, 1989). This 3 times daily dosing imparts a practical limitation to flutamide use. Pharmacokinetic data in animal models indicate that once daily dosing is equally effective (Luo et al, 1997). Based on this information, a subsequent clinical trial compared dosing with 250 mg of flutamide 3 times daily in conjunction with an LHRH analog or orchiectomy to dosing with 500 mg once daily in combination with an LHRH analog or orchiectomy in the treatment of advanced prostate cancer in 440 men aged 46 to 94 years (mean, 71 years) with confirmed stage M1 disease (Thrasher et al, 2000). In this trial, the prostate specific antigen (PSA) normalized by week 12 in 71% of the patients receiving the 500 mg dose and in 75% of those receiving the standard dose. The percent change in PSA was 89% and 96%, respectively. The treatment groups were not significantly different with respect to the incidence of adverse events: 71% vs 68% in the 500 mg and 750 mg arms, respectively ($P = .337$). These authors concluded that, when combined with castration, 500 mg of flutamide daily appears to be equally effective in lowering serum PSA and is not significantly more toxic than the conventional 3 times daily dosing and results in a cost savings of 30%. This study is limited, however, since any differences in the PSA effect of the two dosing schedules may have been masked by the profound hypogonadism caused by the concomitant LHRH analog or orchiectomy. To address this limitation, we designed the current study, evaluating flutamide at 3 dosing schedules (once daily, twice daily, and 3 times daily) administered as short-term antiandrogen monotherapy (Boccon-Gibod, 1998; Kolvenbag et al, 2001).

Materials and Methods

This study was approved by the Institutional Review Board on Human Subjects in Medical Research. Men were recruited for the study who were between 60 and 85 years of age who elected to receive hormonal therapy for prostate cancer in the following clinical situations: 1) clinically localized prostate cancer (T1, T2), to be treated primarily with hormonal therapy or with hormonal therapy for at least 3 months prior to planned prostatectomy, external radiation therapy, or brachytherapy; 2) locally

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extensive prostate cancer (T3), to be treated with hormonal therapy as primary therapy or for at least 3 months prior to planned external radiation therapy; or 3) metastatic prostate cancer to bones and/or lymph nodes, to be treated primarily with hormonal therapy. Exclusion criteria included the following: symptomatic prostate cancer (eg, obstructive symptoms, bone pain); metastatic lesions near the spinal cord or in weight-bearing areas of the skeleton; any other situation in which the treating physician felt that expeditious initiation of complete androgen deprivation was indicated; atypical metastatic sites (eg, liver, lung); life expectancy of less than 1 year; inability to give written, informed consent; major medical/psychiatric illness; hepatic or renal disease that might be exacerbated by flutamide; presence of an active neoplasm (except nonmelanoma skin cancers) other than prostate cancer; currently/previously receiving hormonal therapy for prostate cancer or finasteride; currently/previously receiving chemotherapy or immunotherapy for prostate cancer; abnormalities on screening blood tests (SGOT, SGPT, bilirubin, and/or creatinine of >1.5 times the upper limits of normal, and/or white blood cell count of <3000 cells/mm_2); history of hypersensitivity to antiandrogen drugs; patients who were unlikely to be compliant; or patients who could not be contacted in case of emergency.

Fifty men who elected to receive hormonal therapy, met the inclusion criteria, and agreed to participate in this study were randomized to 1 of 3 treatment groups: 1) flutamide 250 mg once daily, 2) flutamide 250 mg twice daily, and 3) flutamide 250 mg 3 times daily. Patients received the flutamide as monotherapy for 3 months, after which the therapy of their choice was instituted (eg, addition of LHRH analog, orchiectomy, continued flutamide monotherapy, radiation therapy, or intermittent hormonal therapy). Blood samples were drawn at the initiation of therapy and at the 3-month time point for measurement of testosterone, PSA, liver function tests, hematology, and renal function. Transrectal ultrasound for prostate volume estimation was performed at the initiation of study and at the end of the 3-month study. At the initiation of therapy and at 3 months, patients were weighed, evaluated for performance status, and completed a questionnaire regarding side effects of the medication (hot flashes, breast pain, gynecomastia, gastrointestinal symptoms) as well as the Androgen Deficiency in Aging Males (ADAM) questionnaire, which includes qualitative questions about libido, erectile dysfunction, fatigue, and depression (Morley et al, 2000). Throughout the study period, patients also completed a compliance diary.

Tests for statistically significant differences were performed with the Student's 2-tailed *t* test. Statistical significance was considered to be a *P* value of less than .05.

Results

The patients had a mean age of 73.4 years (range 54–79 years of age), with an average PSA of 16.4 ng/dL (range, 8.2–27.6 ng/dL). There were 15 patients randomized to the 250-mg flutamide once daily treatment, 13 patients randomized to the 500-mg daily (250 mg twice a day) treatment, and 14 patients randomized to the 750 mg daily (250 mg 3 times a day) treatment.

Results are shown in the Table. At the time of initiation of therapy, there was no significant difference in the pretreatment testosterone levels for the 3 dosing groups, with a mean testosterone for the 250 mg/d group of 348 mg/dL; for the 500 mg/d group, the mean testosterone was 398 mg/dL; and for the 750 mg/d group, the mean testosterone level was 324 mg/dL. With flutamide monotherapy, testosterone levels rose with therapy in a dose-dependant fashion. Patients receiving 250 mg daily of flutamide demonstrated a mean testosterone level of 497 mg/dL at 1 month and 508 mg/dL at 3 months of therapy. The patients in the 500 mg daily group had a mean testosterone level of 538 mg/dL at 1 month and 654 mg/dL at 3 months. With 750 mg of flutamide daily, the mean testosterone level was 533 mg/dL after 1 month and 679 mg/dL after 3 months. There was no statistically significant difference in testosterone levels at each time point between the 3 dosage groups at 1 month. There was, however, a statistically significant difference between the testosterone levels of the 250 mg daily group and both the 500 mg daily group ($P = .042$) and the 750 mg daily group ($P = .011$) after 3 months of therapy.

There was no significant difference in the weight gain and symptoms of depression between any of the 3 treatment groups or between treatment groups and pretreatment values. Loss of libido and erectile dysfunction occurred in all 3 treatment groups, with a trend toward worsening sexual function with higher flutamide dosing, but this trend did not reach statistical significance. Those patients taking flutamide 250 mg 3 times daily felt significantly more fatigued than those on 250 mg once daily ($P = .040$) or 250 mg twice daily ($P = .043$) after 3 months of therapy. However, there was no significant change in the performance status.

No patient failed to have a decrease in PSA level in response to therapy. There was no significant difference in the pretreatment PSA levels for the 3 dosing groups, with a mean PSA for the 250 mg/d group of 15.4 ng/mL; for the 500 mg/d group, the mean PSA was 17.2 ng/mL; and for the 750 mg/d group, the mean PSA was 16.7 ng/mL. There was a statistically significant difference between the PSA decrease experienced by the patients receiving 250 mg of flutamide compared to those receiving the standard dose of 750 mg at both the 1 month ($P = .013$) and 3 month ($P = .007$) time points. Patients receiving 250 mg daily had a mean PSA at 1 month of 10.7 ng/mL and a mean PSA level at 3 months of 8.1 ng/mL. Men receiving 750 mg of flutamide daily had a mean PSA at 1 month of 6.4 ng/mL, and at 3 months the mean PSA was 3.5 ng/mL. There was no statistically significant difference, however, between the PSA decrease in patients receiving 500 mg daily compared to those receiving 750

Comparison of the effects of flutamide monotherapy at 250 mg, 500 mg, and 750 mg daily

Features Assessed	All Patients Pretreatment (n = 42)	Flutamide Dose 250 mg (250 mg QD) (n = 15)	500 mg (250 mg BID) (n = 13)	750 mg (250 mg TID) (n = 14)	*P* Value 250 mg vs 500 mg	500 mg vs 750 mg	250 mg vs 750 mg
Age, (y)†	73.4	72.8	74.2	69.5	NS*	NS	NS
Baseline testosterone (mg/dL)†	355	348	398	324	NS	NS	NS
1-month testosterone (mg/dL)†	522	497	538	533	NS	NS	NS
3-month testosterone (mg/dL)†	610	508	654	678	.042	NS	.011
Baseline PSA (ng/mL)†	16.4	15.4	17.2	16.7	NS	NS	NS
1-month PSA (ng/mL)†	8.2	10.7	7.3	6.4	NS	NS	.013
3-month PSA (ng/mL)†	6.6	8.1	5.0	3.5	NS	NS	.007
Prostate volume decrease‡	53.5 mL	19.8%	28.7%	34.7%	NS	NS	.047
Decreased libido§	21.4%	60.0%	69.2%	78.6%	NS	NS	NS
Erectile dysfunction§	35.7%	73.3%	76.9%	85.7%	NS	NS	NS
Decreased mood§	7.1%	20.0%	15.4%	21.4%	NS	NS	NS
Fatigue§	2.4%	13.3%	15.4%	42.8%	NS	.040	.043
Weight gain‖	90.7 kg	1.9%	2.4%	2.3%	NS	NS	NS
Hot flashes§	0.0%	20.0%	38.5%	50.0%	NS	NS	NS
Breast pain/enlargement†	0.0%	0.0%	7.7%	7.1%	NS	NS	NS
Gastrointestinal symptoms§	2.4%	20.0%	7.7%	14.3%	NS	NS	NS
Doses missed¶	NA	19.8%	23.4%	34.7%	NS	NS	.041

* NS, indicates not significant; OD, once daily; BID, twice daily; and TID, three times/day.
† Average of patients in the respective group.
‡ Average pretreatment volume (mL) and mean % decrease after 3 months of therapy.
§ Percent of patients after 3 months of therapy.
‖ Average pretreatment weight (kg) and mean % increase after 3 months of therapy.
¶ Average percent of doses missed after 3 months of therapy; NA = not applicable.

mg daily ($P = .19$). After 1 month of 500 mg flutamide daily, the patients in this group had a mean PSA of 7.3 ng/mL and a PSA of 5.0 ng/mL after 3 months.

Two patients in the 250 mg daily group and one patient in the 750 mg daily group dropped out of the study because of gastrointestinal discomfort. One additional patient in each treatment group complained of some gastrointestinal discomfort, but symptoms were not substantial enough to stimulate them to withdraw from the study. This difference in gastrointestinal complaints did not reach statistical significance. No patients in any of the 3 groups demonstrated elevation of liver enzymes or change in hematocrit values.

Prostate volume measured by transrectal ultrasound at the initiation of the study ranged from 18.6 to 96.2 cc (mean, 53.5 cc). There were no significant differences in prostate volume among the 3 treatment groups. After 3 months of therapy, prostate volumes decreased by an average of 34.3% in the patients receiving 250 mg flutamide 3 times daily, 27.8% in patients receiving 250 mg flutamide twice daily, and 19.2% in those receiving a once daily dose of 250 mg flutamide. There was no significant difference between the size decrease demonstrated in the 3 times daily vs 2 times daily groups; however, there was a significant difference between the 1 time daily group and the 3 times daily group ($P = .047$).

The patients on 250 mg of flutamide 3 times daily missed an average of 34.7% of their doses, whereas those on twice daily and once daily dosing regimens missed 23.4% and 19.8% of their doses, respectively. This represented a significant difference in compliance between patients on 3 times daily dosing compared to those on once daily dosing ($P = .041$), but no significant difference between once and twice daily dosing was noted.

Discussion

Nonsteroidal antiandrogens, such as flutamide, have been employed to augment the effectiveness of the standard androgen deprivation therapies, surgical castration, and LHRH agonists, in the treatment of advanced prostate cancer. Antiandrogens are also gaining popularity as potential monotherapy for select prostate cancer patients (Anderson, 2003). Although monotherapy rarely results in reduction of PSA to undetectable levels, survival outcome has not been found to be significantly different to that observed after castration in men with locally advanced, nonmetastatic disease (Iversen et al, 2000). The value of antiandrogen monotherapy over LHRH agonists or castration appears to be in the quality-of-life benefits. Nonsteroidal agents offer significant advantages with respect to sexual function, libido, overall energy, and bone mineral density when compared to LHRH agonists or castration (Iversen et al, 2001). Flutamide, the first nonsteroidal antiandrogen released in the United States, was ini-

tially recommended to be administered 3 times daily, but subsequent studies indicate that less frequent dosing is adequate. Clinical investigations have confirmed the effectiveness of a lower and less frequent dosing schedule when flutamide is used in combination with castration or an LHRH agonist in prostate cancer patients (Thrasher et al, 2000). Our study was designed to determine if similar results are also observed when the drug is administered as a monotherapy.

We found that serum testosterone increased in a dose-dependant fashion with flutamide monotherapy. However, a daily dose of 500 mg of flutamide, administered as 250 mg twice daily, did not result in a statistically different testosterone level compared to a dosing regimen of 750 mg daily, administered at the standard 250 mg 3 times daily dosing schedule. There was no significant difference in the androgen influenced quality-of-life issues (weight gain, loss of libido, erectile dysfunction, depression) for the 3 dosing groups. Despite the lack of difference in performance status, the perception of fatigue was greater in patients receiving flutamide 250 mg 3 times daily after 3 months.

We also found that PSA and prostate volume decreased in a dose-dependant fashion. After 3 months, a daily dose of 500 mg of flutamide, administered as 250 mg twice daily, did not result in a statistically different decrease in PSA compared to a dosing regimen of 750 mg daily, administered as a 250 mg 3 times daily dosing schedule. The lack of significant differences between treatment groups may be due to the fact that our study is limited by the short duration of the study and the small number of patients. The lack of a significant difference between the PSA level decrease of patients on twice daily vs patients on a 3 times daily regimen may also be influenced by the decreased compliance noted in patients taking the medication 3 times daily (Greenberg, 1984). The 34.7%, 23.4%, and 19.8% rates of missed doses for the once, twice, and 3 times daily dosing schedules observed in our patients is similar to rates observed in other studies of compliance. Although these compliance rates are probably higher than the compliance of nonstudy patients, as the exercise of completing a compliance record has been shown to improve compliance (Cornelis, 1976; Cheston, 1978), the differences between the 3 treatment groups might have been more pronounced had compliance been better. However, the efficacy of once daily dosing of flutamide compared to 3 times daily dosing has also been shown in animal studies negating the effect of compliance on efficacy (Luo et al, 1997). These data indicate that, although the serum levels of flutamide imply the need for multiple daily doses (Belanger et al, 1988; Shulz et al, 1988; Neri, 1989), androgen receptor binding may be maintained for longer periods of time (Wakeling et al, 1981; Teutsch et al, 1994; Singh et al, 2000). There may also be metabolites of flutamide that have a more prolonged effect. For example, the active plasma metabolite hydroxyflutamide has been shown to have a serum half-life of 10 hours (Radwanski et al, 1989).

Estradiol levels were not measured as part of this study, but it should be noted that as serum testosterone levels rise, an increase in peripheral aromatization will occur and will elevate estradiol levels. This increase in estradiol may be responsible for some of the PSA and prostate volume changes observed in our study.

As was the case in the study by Thrasher et al (2000), we saw a slightly higher incidence of gastrointestinal discomfort in the patients receiving once daily dosing of flutamide, despite the fact that the once daily dose in our study (250 mg) was half the dose employed by the prior investigators (500 mg). This difference did not reach statistical significance in either study. The 6% dropout rate due to diarrhea remains less than the 10% rate of diarrhea requiring discontinuing of therapy that has been reported in the literature (Yagoda, 1989; McLeod, 1997). Although some of the diarrhea has been attributed to flutamide-induced lactose intolerance, our data supports the theory by Thrasher et al (2000) that the gastrointestinal symptoms may be due, in part, to variations in serum drug levels rather than peak drug levels. In our study, none of the patients receiving flutamide as 500 mg in 2 divided doses dropped out of the study due to diarrhea, compared to a dropout rate of 5.4% when 500 mg flutamide was administered by Thrasher et al as a single dose.

Unlike the prior comparison of 500 mg of flutamide daily to 750 mg daily, we chose to administer the 500 mg dose in 2 divided doses rather than as a single dose. Although the divided doses appear to decrease the associated gastrointestinal symptoms, it is unclear whether this had an effect on the PSA response. Further evaluation of 500 mg of flutamide monotherapy administered once daily compared to 500 mg administered in 2 divided doses of 250 mg each should clarify the impact of frequency of administration on response and side effects.

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