Cancer Chemother Pharmacol (2005) 56: 415–420
DOI 10.1007/s00280-005-1016-1

ORIGINAL ARTICLE

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Exploratory study of drug plasma levels during bicalutamide 150 mg therapy co-administered with tamoxifen or anastrozole for prophylaxis of gynecomastia and breast pain in men with prostate cancer

Received: 15 June 2004 / Accepted: 15 December 2004 / Published online: 19 April 2005

Abstract *Objective*: A randomized multicenter (14 centers) trial was conducted in 114 men with prostate cancer to determine whether the antiestrogen tamoxifen ('Nolvadex') 20 mg or the aromatase inhibitor anastrozole ('Arimidex') 1 mg prevent gynecomastia and breast pain during treatment with the non-steroidal antiandrogen bicalutamide ('Casodex') 150 mg, without compromising efficacy, safety, or quality of life. Plasma samples were collected in a subgroup of these patients to investigate whether trough (pre-dose) concentrations of bicalutamide 150 mg are influenced by concomitant administration of tamoxifen 20 mg or anastrozole 1 mg; the results of this pilot study are reported in this article. *Methods*: A subpopulation of patients from a randomized placebo-controlled trial evaluating tamoxifen 20 mg and anastrozole 1 mg for the prevention of gynecomastia and breast pain in men receiving bicalutamide 150 mg for early or recurrent prostate cancer were selected on a voluntary basis from three of the trial centers. Plasma samples were collected on days 7, 14, 28, and 84 of therapy and analyzed to determine the plasma concentrations of (R)–bicalutamide and (S)-bicalutamide. In addition, plasma concentrations of tamoxifen, *N*–desmethyltamoxifen, and anastrozole were determined. *Results*: A total of 21 patients were selected. There was no significant difference between treatment groups with respect to the trough plasma concentrations of either bicalutamide enantiomer at any point during the study. Plasma concentrations of the enantiomers, and the relative proportion of the ®)- and (S)–enantiomers, were consistent with those reported in previous studies. Plasma concentrations of tamoxifen, *N*–desmethyltamoxifen, and anastrozole were also similar to those described elsewhere in the literature. *Conclusions*: The findings of this pilot study suggest that trough plasma concentrations of bicalutamide enantiomers following administration of bicalutamide 150 mg are not markedly influenced by concomitant administration of tamoxifen 20 mg or anastrozole 1 mg. However, an effect of tamoxifen on bicalutamide pharmacokinetics can not be completely excluded due to the size of this study. Further studies are needed to clarify the effect of tamoxifen on bicalutamide pharmacokinetics and prostate cancer control in bicalutamide-treated patients. 'Arimidex', 'Casodex', and 'Nolvadex' are trademarks of the AstraZeneca group of companies

Keywords Bicalutamide · Tamoxifen · Anastrozole · Prostate cancer · Gynecomastia

This trial was sponsored by AstraZeneca (Milan, Italy)

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Introduction

Bicalutamide ('Casodex') 150 mg is an orally active, non-steroidal antiandrogen that is an established monotherapy treatment option for locally advanced prostate cancer in patients who wish to avoid the adverse effects of surgical or medical castration. Bicalutamide 150 mg is currently being evaluated as an adjuvant to standard care (radical prostatectomy, radiotherapy, or watchful waiting) for non-metastatic prostate cancer in the ongoing early prostate cancer (EPC) program [8, 9, 13]. The second protocol-specified analysis of this trial program at a median follow-up of 5.4 years showed that

bicalutamide 150 mg significantly improves progression-free survival and reduces the risk of objective progression, with the greatest benefits seen in patients with locally advanced disease [13].

Bicalutamide 150 mg is generally well tolerated; however, breast pain and gynecomastia are common adverse events that may lead to treatment withdrawal. In the EPC program, breast pain, although mild to moderate in >90% of cases, had occurred in 73.6% of the bicalutamide 150 mg group at 5.4 years' median follow-up compared with 7.6% of the placebo group; corresponding incidences of gynecomastia were 68.3 and 8.3%, respectively [13]. Treatment withdrawal due to breast pain and/or gynecomastia occurred more frequently in the bicalutamide 150 mg group compared with the placebo group (16.7% vs. 0.7%).

The mechanisms involved in the development of gynecomastia during bicalutamide 150 mg monotherapy are related to the hypergonadotrophic effects of the drug, which increase the ratio of estrogenic:androgenic activity in the breast [5]. Estrogens induce the benign proliferation of male breast glandular tissue and, if proliferation is long standing, irreversible hyalinization and fibrosis may occur. The pathogenesis of gynecomastia during non-steroidal antiandrogen monotherapy provides the rationale for pharmacologic attempts to prevent glandular proliferation, either via inhibition of the peripheral aromatization of testosterone to estrogen or direct competition with estrogens at the tissue level.

The roles of tamoxifen ('Nolvadex', an antiestrogen) and anastrozole ('Arimidex', a non-steroidal aromatase inhibitor) in preventing the development of gynecomastia and breast pain during administration of bicalutamide 150 mg have recently been studied in patients with localized/locally advanced or biochemically recurrent prostate cancer [1]. The bicalutamide/tamoxifen group showed significantly lower incidences of gynecomastia (7% vs. 76%; $p < 0.001$) and breast pain (6% vs. 39%; $p = 0.001$) than the bicalutamide 150 mg monotherapy group. Also, the addition of tamoxifen to bicalutamide 150 mg monotherapy was not associated with any safety concerns or adverse influence on tumor response or patients' quality of life. The moderate reductions in the incidences of gynecomastia and breast pain in the bicalutamide/anastrozole group were not significant when compared with the incidences in the bicalutamide 150 mg monotherapy group.

Bicalutamide 150 mg has a low potential to interact with other drugs metabolized by the cytochrome P450 enzymes, including tamoxifen [6]. However, if tamoxifen is to be considered for use in the prophylaxis of bicalutamide 150 mg-induced gynecomastia or breast pain, it is important to explore the potential of either one of these drugs to modify plasma levels of the other [3, 4]. Bicalutamide 150 mg is a racemic mixture of two enantiomers, (R)-bicalutamide and (S)-bicalutamide, with the antiandrogenic activity residing almost exclusively in the (R)-enantiomer. At steady state, (R)-bicalutamide constitutes more than 99% of the circulating drug concentration [11]. Therefore, in a sub-population of our clinical trial we made an exploratory assessment of the plasma concentrations of ®)- and (S)-bicalutamide in the presence of tamoxifen or anastrozole.

Methods

Patients

The main clinical trial was a 48-week, multicenter, randomized, double-blind, placebo-controlled study designed to compare three bicalutamide 150 mg-based treatments: bicalutamide 150 mg once daily (od) monotherapy; bicalutamide 150 mg/tamoxifen 20 mg od combination therapy; and bicalutamide 150 mg/anastrozole 1 mg od combination therapy. The trial enrolled patients with localized/locally advanced or biochemically recurrent prostate cancer. Full details of the inclusion and exclusion criteria and other methodological details have been published elsewhere [1]. From this trial population, a sub-population consisting of 21patients, seven from each arm of the trial, were randomly selected from 3 of the 14 study centers (S. Anna Hospital, Como, Italy; City Hospital, Fidenza, Italy; City Hospital, Siena, Italy—these centers having volunteered to participate in this study) to undergo blood sampling to quantify concentrations of both enantiomers of bicalutamide, and tamoxifen, *N*-desmethyltamoxifen, or anastrozole.

Blood sampling and plasma assays

Blood samples (10 ml) were taken from each patient at baseline and prior to dosing on days 7, 14, 28, and 84 of randomized therapy. At each visit, samples were transferred into heparin tubes and centrifuged for 10–15 min at 1,000 G, and plasma was then extracted, stored between −25°C and −15°C, and analyzed within 1 year of storage. Plasma samples were analyzed for concentrations of (R)-bicalutamide and (S)-bicalutamide. Additional determinations of tamoxifen and its hydroxylated metabolite N-desmethyltamoxifen were made in plasma samples from the bicalutamide 150 mg/tamoxifen 20 mg group, and anastrozole in samples from the bicalutamide 150 mg/anastrozole 1 mg group. All analyses were undertaken by centralized laboratories: BAS Analytics (Kenilworth, Warwickshire, UK) for the bicalutamide enantiomers; and MDS Pharma Services (Blainville, QC, Canada) for tamoxifen, *N*-desmethyltamoxifen, and anastrozole.

A validated high-performance liquid chromatography-mass spectrometry method was used to determine the plasma concentrations of the bicalutamide enantiomers. The method involved liquid/liquid extraction of bicalutamide from the plasma samples followed by determination of the bicalutamide concentration using achiral reversed phase chromatography. The fraction

Table 1 Assay accuracy and precision

Assay	Accuracy (% bias)	Precision (% CV)
(R)-bicalutamide	−2.7 to 3.0	6.7–1 7.6
(S)-bicalutamide	−16.2 to 3.0	6.7–20.8
Tamoxifen	−5.4 to 0.6	4.8–10.4
N-desmethyltamoxifen	−2.7 to 11.1	3.0–10.7
Anastrozole	−1.8 to 1.2	3.0–11.5

CV coefficient of variation

containing bicalutamide was collected and the concentrations of R-bicalutamide and S-bicalutamide determined by chiral chromatography using the Ultron ES-OVM 150×4.6 mm column. The mobile phase was an aqueous ammonium formate (0.02 M)/acetonitrile mixture (85/15) and the flow rate was 1 ml/min. A Sciex tandem mass spectrometer was used for detection. Bicalutamide concentrations were measured by comparing the samples to be assayed against a set of calibration samples containing bicalutamide at concentrations of 0.2, 0.6, 1.2, 4.0, 8.0, 16, 24, 48, and 80 μg/ml. Standard curves were subsequently constructed by performing linear regression analysis, weighted $1/(x)^2$. Quality control samples consisting of bicalutamide (0.2, 30, and 60 μg/ml) were prepared by adding standard solutions of bicalutamide to heparinized drug-free plasma. Plasma used in calibration and quality control samples had been screened for hepatitisB and HIV and was stored between −25°C and −15°C prior to use. The lower limit of quantification of the assay was 0.1 μg/ml for each of the bicalutamide enantiomers. Assay accuracy and precision were within acceptable levels (Table 1).

Validated high-performance liquid chromatography–mass spectrometry methods were also used to determine the plasma concentrations of tamoxifen, *N*–desmethyltamoxifen, and anastrozole. These assays were conducted in two phases, due to the long time interval between receipt of the first and final plasma samples (April 2002 and January 2004), thus necessitating preparation of a new calibration standard curve and further quality control samples. Eight calibration standards were prepared for each compound during each phase: tamoxifen (phase 1: 0.500–60.0 ng/ml; phase 2: 0.499–59.9 ng/ml); *N*–desmethyltamoxifen (phase 1: 0.250–30.0 ng/ml; phase 2: 0.226–27.1 ng/ml); and anastrozole (phase 1: 1.00–60.0 ng/ml; phase 2: 1.01–60.6 ng/ml). The assay for tamoxifen and *N*-desmethyltamoxifen was validated to demonstrate that samples can be diluted into these ranges. Standard curves were subsequently constructed by performing linear regression analysis, weighted $1/(x)$ or $1/(x)^2$. Quality control samples consisting of tamoxifen (phase 1: 1.5, 20, and 45 ng/ml; phase 2: 1.4, 18.7, and 42 ng/ml), *N*–desmethyltamoxifen (phase 1: 0.75, 10, and 22.5 ng/ml; phase 2: 0.68, 9.06, and 20.4 ng/ml) or anastrozole (phases 1 and 2: 3, 20, and 45 ng/ml) were prepared by adding standard solutions to plasma, free from significant interference, using ethylenediamine tetra-acetic acid as an anticoagulant. Calibration and quality control samples were stored at −20°C prior to use. The lower limits of quantification of the assays were 0.5 ng/ml for tamoxifen, 0.249 ng/ml for *N*-desmethyltamoxifen, and 0.995 ng/ml for anastrozole. Assay accuracy and precision were within acceptable levels (Table 1).

Statistical methods

As bicalutamide 150 mg was the only therapeutic agent common to each of the three treatment arms, only (R)-bicalutamide and (S)-bicalutamide plasma concentrations could be statistically compared among the treatment groups. Trough concentrations obtained on days 7, 14, 28, and 84 were examined using box-and-whisker plots to identify any outlying data points that could have a disproportionate effect upon subsequent statistical analysis. One data point (bicalutamide 150 mg group: day 28, [S]-bicalutamide concentration) was identified as lying >1.5 interquartile ranges above the upper level of the interquartile range. However, this outlier had no effect upon subsequent statistical analyses; therefore, the data and analyses presented in this paper describe the full data set. Plasma concentrations of the bicalutamide enantiomers were compared in each of the three treatment groups using discrete analyses of variance at each time point. All analyses were performed using the Minitab for Windows (Release 11.21) statistical package.

Results

Patient demography

The demography of the sub-population ($n=21$) for whom plasma samples were analyzed is presented in Table 2. The mean age and age range of the sub-population were similar to those of the overall study population [1]. While there were small differences between the sub-population and the overall population with respect to median prostate-specific antigen (PSA) levels and disease status at study entry, these were considered unlikely to influence the results of the drug plasma level assessments.

Concentrations of (R)- and (S)-bicalutamide enantiomers

Analyses of plasma samples showed that the proportion of (R)-bicalutamide to total concentration of enantiomers ([R]-bicalutamide plus [S]-bicalutamide) was 98.6% (19.43/[19.43 + 0.28] μg/ml) and 98.5% (28.52/[28.52 + 0.44] μg/ml) at days 28 and 84, respectively. The mean trough plasma concentrations of (R)-bicalu-

Table 2 Patient ($n = 21$) demography

	Bicalutamide 150 mg ($n = 7$)	Bicalutamide 150 mg/ tamoxifen 20 mg ($n = 7$)	Bicalutamide 150 mg/ anastrozole 1 mg($n = 7$)
Median age (range) (years)	74 (60–82)	74 (59–84)	73 (56–81)
grid Median PSA level (range) at entry, (ng/ml)	3.9 (2.9–8.9)	6.0 (3.2–82.2)	7.5 (3.1–36.8)
Disease status at entry, *n* (%)			
Localized/locally advanced	4 (57.1)	5 (71.4)	5 (71.4)
Biochemical failure following radical prostatectomy or radiotherapy	3 (42.9)	2 (28.6)	2 (28.6)

PSA prostate-specific antigen

tamide increased in all treatment groups during the study as they approached steady state (Table 3). There were no significant differences in (R)-bicalutamide concentrations between any of the treatment groups at any time point (Table 3). Mean plasma concentrations of the (S)-bicalutamide enantiomer remained relatively stable up to day 28 in all treatment groups, although these did increase slightly by day 84 in the bicalutamide 150 mg and bicalutamide 150mg/anastrozole groups (Table 4). There were no significant differences in (S)–bicalutamide concentrations between any of the treatment groups at any time point (Table 4).

In the bicalutamide 150 mg/tamoxifen 20 mg group, mean plasma concentrations of tamoxifen and its metabolite N-desmethyltamoxifen increased during the study (Table 5). Tamoxifen concentrations showed more moderate increases between days 28 and 84 than *N*-desmethyltamoxifen concentrations during the same period. In the bicalutamide 150 mg/anastrozole 1 mg group, the mean plasma concentration of anastrozole increased rapidly during the first 7 days and thereafter showed only moderate increases.

Discussion

In the main clinical study ($n = 114$) tamoxifen 20 mg od (but not anastrozole 1 mg od) was effective in reducing the incidence of bicalutamide 150 mg-induced gynecomastia and breast pain without compromising the efficacy of bicalutamide 150 mg, patient safety or quality of life [1]. However, as part of this clinical study, it was important to explore whether concomitant administration of tamoxifen or anastrozole might modify plasma levels of ®)- and (S)-bicalutamide. Obtaining this information represents the first step towards understanding the implications of concomitant administration in this setting, thus allowing the potential for an impact on cancer control and/or a need for modification of the bicalutamide 150 mg dosage to be assessed. However, a comprehensive pharmacokinetic study would be required to fully explore the interaction, or lack thereof, between these drugs.

Within the study population of 21 patients, plasma concentrations of the bicalutamide enantiomers over the course of the study were similar in each of the treatment groups, suggesting that any pharmacokinetic interaction between bicalutamide 150 mg and tamoxifen or anastrozole is minimal or at least relatively small. While this study has insufficient scope to detect small to moderate differences in plasma drug levels among treatment groups, the current findings are in accordance with previous results that have shown bicalutamide 150 mg to have a low potential for drug–drug interactions.

The current findings expand upon those reported in a randomized, double-blind, placebo-controlled trial conducted in the US by Saltzstein et al. [7], in which patients with localized or locally advanced prostate cancer were

Table 3 Mean (SE/range) concentration of (R)-bicalutamide in plasma samples from each of the three treatment groups on days 7, 14, 28, and 84

Visit	Mean (SE/range) concentration (μg/ml) of (R)-bicalutamide following administration of:			*p* value
	Bicalutamide 150 mg ($n = 7$)	Bicalutamide 150 mg/tamoxifen 20 mg ($n = 7$)	Bicalutamide 150 mg/anastrozole 1 mg ($n = 7$)	
Day 7	9.71 (1.12/6.80–14.80)	13.65[b] (2.67/8.80–22.20)	9.07 (1.13/14–12.60)	0.158
Day 14	12.60 (1.64/7.75–19.00)	15.70[a] (2.25/10.30–23.60)	13.91 (0.71/11.90–16.30)	0.408
Day 28	19.43 (2.84/8.90–26.50)	23.35[b] (3.04/13.70–33.20)	16.62[b] (1.31/13.50–20.90)	0.224
Day 84	28.52[a] (4.05/13.20–35.50)	25.70[a] (3.27/17.40–32.50)	24.22[a] (4.30/15.60–38.60)	0.736

[a] $n = 5$, [b] $n = 6$ (remaining samples unavailable); *SE* standard error

Table 4 Mean (SE/range) concentration of (S)-bicalutamide in plasma samples from each of the three treatment groups on days 7, 14, 28, and 84

Visit	Mean (SE/range) concentration (μg/ml) of (S)-bicalutamide following administration of:			*p* value
	Bicalutamide 150 mg ($n=7$)	Bicalutamide 150 mg/tamoxifen 20 mg ($n=7$)	Bicalutamide 150 mg/anastrozole 1 mg ($n=7$)	
Day 7	0.26 (0.04/0.10–0.40)	0.26[a] (0.03/0.19–0.37)	0.22 (0.02/0.14–0.29)	0.515
Day 14	0.27[a] (0.06/0.10–0.54)	0.23[b] (0.04/0.16–0.31)	0.22[a] (0.04/0.11–0.38)	0.777
Day 28	0.28[a] (0.06/0.11–0.59)	0.25[b] (0.05/0.11–0.38)	0.19[a] (0.03/0.10–0.29)	0.381
Day 84	0.44[c] (0.09/0.27–0.68)	0.24[b] (0.06/0.10–0.43)	0.31[c] (0.04/0.20–0.38)	0.132

[a] $n=6$, [b] $n=5$, [c] $n=4$ (remaining samples unavailable); *SE* standard error

Table 5 Mean (SE/range) concentration of tamoxifen and N-desmethyltamoxifen in plasma samples from the bicalutamide 150 mg/tamoxifen 20 mg group, and anastrozole in plasma samples from the bicalutamide 150 mg/anastrozole 1 mg group, on days 7, 14, 28, and 84

Visit	Mean (SE/range) concentration (ng/ml)		
	Bicalutamide 150 mg/tamoxifen 20 mg ($n=7$)		Bicalutamide 150 mg/anastrozole 1mg ($n=7$)
	Tamoxifen	N-desmethyltamoxifen	Anastrozole
Day 7	82.32[a] (20.36/45.3–175.0)	44.23[a] (16.58/19.8–126.0)	29.84 (2.49/19.0–38.4)
Day 14	105.65[a] (15.77/78.5–181.0)	66.58[a] (10.74/46.5–115.0)	38.33 (3.83/28.7–57.8)
Day 28	185.29 (35.60/111.0–375.0)	150.81 (33.17/98.7–346.0)	41.93[a] (2.79/30.5–50.9)
Day 84	198.25[b] (29.87/140.0–268.0)	211.75[b] (30.06/139.0–279.0)	47.30[c] (5.95/35.4–53.6)

[a] $n=6$, [b] $n=4$, [c] $n=3$ (remaining samples unavailable); *SE* standard error

treated with tamoxifen 20 mg, anastrozole 1 mg, or placebo in addition to bicalutamide 150 mg for 3 months. In that study, the population geometric mean plasma concentration (16.4 μg/ml; range 2.4–44.6) of (R)-bicalutamide at 3 months was similar in each of the three treatment groups [7]. In the current study, the day 84 mean (R)-bicalutamide plasma concentrations within treatment groups were also similar (28.5, 25.7, and 24.2 μg/ml). Across all treatment groups, the geometric mean plasma concentration of (R)-bicalutamide at day 84 was higher (approximately 26.1 μg/ml) than that reported by Saltzstein et al.; however, the upper end of the range (13.2–38.6) was lower [7]. The data from both the Saltzstein et al. study [7] and the current study are consistent with the observed plasma concentrations of bicalutamide and/or its enantiomers during multiple dosing in previous studies [11].

Based on the terminal half-life of (R)-bicalutamide (approximately 7 days), steady-state concentrations were expected to be achieved in the average patient after approximately 35 days, i.e. between the sampling visits on days 28 and 84. Although the sampling schedule did not permit determination of when, or indeed if, steady state was achieved, the concentrations of (R)-bicalutamide (mean [range] on days 28 and 84: 19.43 μg/ml [8.9–26.5] and 28.52 μg/ml [13.2–35.5], respectively) in the bicalutamide 150 mg monotherapy group were similar to previously published data. For example, in a study by Tyrrell et al. [11] of bicalutamide 150 mg monotherapy in advanced prostate cancer, the geometric mean concentration at steady state of (R)–bicalutamide was 21.6 μg/ml (range 13.3–45.1).

Steady-state concentrations of tamoxifen (half-life 5–7 days) and its active metabolite *N*–desmethyltamoxifen (half-life 14 days) can be expected at approximately 4 and 8 weeks, respectively, after starting treatment [10, 12]. The ascents to steady-state concentrations of tamoxifen and *N*–desmethyltamoxifen observed in the current study were broadly consistent with these published half-lives; however, as described earlier, times to achieving steady-state concentrations could not be estimated from these data. Anastrozole has a half-life of approximately 2 days and plasma concentrations could thus be expected to reach steady state after approximately 7 days [2]; these data are consistent with data on anastrozole concentrations in the current study.

Conclusions

Our findings from this pilot study suggest that circulating plasma concentrations of ®)- and (S)-bicalutamide are not markedly influenced by the concomitant administration of tamoxifen 20 mg or anastrozole 1mg. The observations in the overall patient population [1], which showed no significant differences in the incidence of adverse events or the PSA response between the bicalutamide 150 mg and bicalutamide 150 mg/tamoxifen groups, support the findings reported here. However, given the small sample size, an effect of tamoxifen on

bicalutamide pharmacokinetics cannot be completely excluded. Our findings should therefore be viewed as preliminary, as should the PSA response data from the main clinical study. Further studies are needed to clarify the effect of tamoxifen on bicalutamide pharmacokinetics and prostate cancer control in bicalutamide-treated patients.

Acknowledgements The authors gratefully acknowledge the assistance of BAS Analytics (Kenilworth, Warwickshire, UK) and MDS Pharma Services (Blainville, QC, Canada) in determining the drug plasma levels reported in this paper.

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