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Pharmacokinetics and Dose Finding of a Potent Aromatase Inhibitor, Aromasin (Exemestane), in Young Males

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Suppression of estrogen, via estrogen receptor or aromatase blockade, is being investigated in the treatment of different conditions. Exemestane (Aromasin) is a potent and selective irreversible aromatase inhibitor. To characterize its suppression of estrogen and its pharmacokinetic (PK) properties in males, healthy eugonadal subjects (14–26 yr of age) were recruited. In a cross-over study, 12 were randomly assigned to 25 and 50 mg exemestane daily, orally, for 10 d with a 14-d washout period. Blood was withdrawn before and 24 h after the last dose of each treatment period. A PK study was performed (n = 10) using a 25-mg dose. Exemestane suppressed plasma estradiol comparably with either dose [25 mg, 38% ($P \leq 0.002$); 50 mg, 32% ($P \leq 0.008$)], with a reciprocal increase in testosterone concentrations (60% and 56%; $P \leq 0.003$ for both). Plasma lipids and IGF-I concentrations were unaffected by treatment. The PK properties of the 25-mg dose showed the highest exemestane concentrations 1 h after administration, indicating rapid absorption. The terminal half-life was 8.9 h. Maximal estradiol suppression of 62 ± 14% was observed at 12 h. The drug was well tolerated. In conclusion, exemestane is a potent aromatase inhibitor in men and an alternative to the choice of available inhibitors. Long-term efficacy and safety will need further study. (*J Clin Endocrinol Metab* 88: 5951–5956, 2003)

THE BIOLOGICAL ACTIONS of estrogens in males have begun to be unraveled via prismatic cases of estrogen deficiency in adults (1–3), gene knockout experiments in mice (4–6), and metabolic studies *in vivo* (7). Experiments in both animals and humans, for example, have clearly shown that epiphyseal fusion and the completion of final adult height are processes regulated by estrogen, even in the male. Male patients with functional mutations in either the estrogen receptor gene (1) or the aromatase gene (2, 3) have demonstrated continued linear growth into adulthood, tall stature, and osteopenia. This information has lead to the investigation of pharmacologically induced estrogen deficiency as an adjunct in delaying epiphyseal fusion in males with short stature and potentially increasing final adult height (8, 9).

The biosynthesis of estrogens from C_{19} steroids is regulated by the aromatase cytochrome p450 (CYP19), a product of a single CYP19 gene. This enzyme, which catalyzes the conversion of androstenedione and testosterone to estrone and estradiol, is widely expressed in numerous tissues, including bone (10, 11). We have conducted detailed studies of the metabolic effects of selective estrogen suppression in young eugonadal males using anastrozole, a potent and selective nonsteroidal aromatase inhibitor, and have shown that specific blockade of the aromatase enzyme for 10 wk did not have catabolic effects on protein metabolism, body composition, measures of muscle strength, and bone calcium metabolism (7). The data suggest that estrogens do not contribute significantly to the changes in body composition and protein synthesis observed with changing androgen levels in males. It also suggested that this level of aromatase inhibition does not negatively impact markers of bone calcium metabolism, at least in the short term.

A new irreversible aromatase enzyme blocker, exemestane (Aromasin), offers an alternative to suppress estrogen concentrations. It is structurally related to the natural substrate androstenedione, and it is metabolized to an intermediate that binds to the active site of the enzyme and inactivates it. It is excreted in the urine and feces. It decreases estradiol concentrations in postmenopausal women, but has no effect on the synthesis of glucocorticosteroids or aldosterone (12, 13). All pharmacokinetic (PK) data available to date are from postmenopausal women, as it is presently used in this population for the treatment of metastatic breast cancer (12–15). A daily dose of 25 mg has been shown to have no effect on circulating testosterone concentrations in females. This study was designed with two aims: first, to investigate the dose of exemestane that can be safely given in adolescent/young adult males with minimal or no side-effects, and second, to investigate the PK and pharmacodynamics of this aromatase inhibitor in males.

Subjects and Methods

These studies were approved by the Nemours Children's Clinic clinical research review committee and Baptist Medical Center/Wolfson Children's Hospital institutional review board. Healthy lean male volunteers between 14–26 yr of age were recruited after giving informed written consent to participate in study I or II (see below). Their clinical characteristics are summarized in Table 1.

Abbreviations: AUC, Area under the curve; CBC, cell blood count; HDL, high density lipoprotein; LDL, low density lipoprotein; PK, pharmacokinetic.

TABLE 1. Clinical characteristics of the study subjects

	Study I (n = 12)	Study II (n = 10)
Race, n (%)		
White	8	6
Black	1	1
Hispanic	3	1
Other		2
Age (yr)		
Mean ± SD	18.8 ± 3.5	19.4 ± 3.8
Range	14.0–25.0	14.0–26.0
BMI (kg/m^2)		
Mean ± SD	24.0 ± 2.9	25.4 ± 3.0
Range	20.0–29.0	20.9–29.1

Study I: dose finding

Two different doses of exemestane (Aromasin, 25-mg tablets) were administered orally in random order for 10 d with a 14-d washout in between. Twelve subjects were divided into 2 groups (treatment sequences): group I received 25 mg in period 1 and 50 mg in period 2, and group II received 50 mg in period 1 and 25 mg in period 2. Blood was withdrawn in the morning, between 0800–0900 h at the beginning of each treatment cycle and 24 h after the last dose of each treatment cycle (4 blood draws) for various pharmacodynamic assays. These included estradiol, estrone, estrone sulfate, androstenedione, testosterone, free testosterone, dehydroepiandrosterone sulfate, cortisol, SHBG, IGF-I, IGF-binding protein-3, and plasma lipid profiles [triglycerides, total cholesterol, high density lipoprotein (HDL) cholesterol, and low density lipoprotein (LDL) cholesterol]. Safety data, including general chemistries, cell blood count (CBC), urinalysis, and liver profiles, were measured as well. All adverse events were recorded.

Study II: PK study

Ten male volunteers participated in this study arm. They came to the Clinical Research Center at 0700 h after an overnight fast. An iv heparin lock was placed in a forearm vein for the blood drawing after numbing the skin with a topical anesthetic (EMLA, AstraZeneca, Wilmington, DE). In addition to safety laboratories (CBC, chemistry profile, and urinalysis), blood was withdrawn for determining exemestane, its metabolite 17-hydroexemestane, estradiol, testosterone, LH, and FSH concentrations. A regular breakfast was served that contained 30% of the total calories as fat, and a single dose of 25 mg exemestane was given with the meal. Blood was withdrawn at 0, 1, 2, 3, 4, 8, 12, 24, 48, 72, 144, and 240 h after the administration of exemestane for the same assays as at baseline. The subjects were fed a regular diet and were free to move around. After the 24 h sample was withdrawn, subjects were discharged home, and the 48, 72, 144, and 240 h samples were obtained as outpatients. LH and FSH were only measured up to 24 h.

Assays

As exemestane is a steroid, to eliminate any confounding interference of this compound and its metabolites on the assays of related endogenous steroidal hormones (androgens and estrogens), careful separation of the given compounds in the plasma samples was performed using HPLC, followed by RIA, as described by Johannessen *et al.* (16). Plasma estradiol, estrone, estrone sulfate, testosterone, and androstenedione concentrations were measured by a validated HPLC-RIA method at Aster-Cephac Laboratories (Saint-Benoit, Cedex, France). Briefly, a 2-ml plasma sample was loaded onto Amprep C_{18} cartridge and the fraction containing estrone sulfate or free steroids (estradiol, estrone, androstenedione, and testosterone) were eluted with 4 ml 24% acetonitrile in water or 100% acetonitrile, respectively. Estrone sulfate was hydrolyzed with arylsulfatase, and the deconjugated estrone was further extracted with a C_18 cartridge. The extracted fractions were injected into a reverse phase HPLC system. The eluates corresponding to estradiol, estrone, androstenedione, and testosterone or to deconjugated estrone (to measure estrone sulfate) were collected and subjected to specific RIAs using commercial kits. The collected fractions were evaporated and reconstituted using an assay buffer before RIA. Appropriate plasma samples, spiked with each of the tritiated hormones, were included in each analytical run to calculate overall recoveries to correct results measured by RIA. All extractions were performed singly, and all RIA analysis were performed in duplicate. The lower limit of sensitivity was 0.7 pg/ml for estradiol, 1.8 pg/ml for estrone, 6 pg/ml for estrone sulfate, 40 pg/ml for androstenedione, and 30 pg/ml for testosterone. The overall interassay coefficients of variation were: estradiol, 6.2%; estrone, 12.9%; estrone sulfate, 8.2%; androstenedione, 12.6%; and testosterone, 8.6%. Free testosterone was measured by a validated gas chromatography/mass spectrometry bioanalytical method at Taylor Technology, Inc. (Princeton, NJ). LH and FSH were measured by RIA at the Nemours Biomedical Research Laboratory using commercial kits from Diagnostic Systems Laboratories, Inc. (Webster, TX). All other hormones were measured at a contract laboratory by RIAs using commercial kits. All samples were run in the same assay run. Concentrations of plasma lipids, chemistry profile, and CBC were measured using automated analyzers at Baptist Medical Center (Jacksonville, FL). Exemestane and 17-hydroexemestane plasma levels were measured at Pharma Bio Research (Assen, The Netherlands) using a validated liquid chromatography method with tandem mass spectrometry detection (17). The lower limit of sensitivity was 0.1 ng/ml for both assays.

Statistical analysis

For the pharmacodynamic results of study I, descriptive statistics were generated for the assays measured by group (sequence) and by treatment. The mean concentrations at baseline and at the end of treatment were summarized by period and by treatment group for all assays. A paired *t* test was used to test the difference between baseline and day 10 concentrations for each assay. A cross-over ANOVA with factors for period, treatment, group (sequence), and subject within group was conducted (18). A baseline value was added to the model. A paired *t* test was used to test the difference in concentrations at baseline and on d 10 for all assays. Significance was established at $P < 0.05$.

PK analysis

The PK of exemestane were determined by noncompartmental analysis (19) using the computer program WinNonlin (Pharsight Corp., Mountain View, CA). The maximum plasma concentration was the highest concentration observed for each individual. The area under the curve (AUC) was calculated using the linear trapezoidal rule up to the last quantifiable concentration and extrapolated to infinite time ($AUC_{0\text{-inf}}$). The half-life of the terminal decay phase, $t_{1/2,z}$, was determined by linear regression analysis of the natural log concentration *vs.* time curve, where $t_{1/2,z} = \ln^2/\text{Kel}$, where Kel is the slope of the regression line. Oral clearance was calculated as oral dose/$AUC_{0\text{-inf}}$. Analogous calculations were performed on ($c \times t$) *vs.* time plots to estimate the area under the first moment curve ($AUMC_{0\text{-inf}}$). The mean residence time was calculated as AUMC/AUC PK parameters were summarized with descriptive statistics.

Results

Study I: dose finding

Analysis of the data on hormone concentrations after the 25- and 50-mg doses showed no difference in any of the parameters measured due to an order effect; hence, the data were grouped for analysis by dose. The 25- and 50-mg doses of daily exemestane had comparable effects in suppressing circulating estrogen concentrations, with 38 ± 24% (mean ± SD; $P = 0.002$ *vs.* baseline) and 32 ± 29% ($P = 0.008$) decreases in estradiol concentrations, 71 ± 12% ($P < 0.0001$) and 74 ± 12% ($P < 0.0001$) decreases in estrone concentrations, and 45 ± 27% ($P = 0.004$) and 51 ± 20% ($P = 0.02$) decreases in estrone sulfate concentrations after doses of 25 and 50 mg, respectively. There was an increase in circulating testoster-

one concentrations after both 25 mg (60 ± 58%; $P = 0.001$) and 50 mg (56 ± 48%; $P = 0.003$) exemestane. Androstenedione concentrations were increased as well after 25 mg (32 ± 36%; $P = 0.004$) and 50 mg (47 ± 59%; $P = 0.052$) exemestane, respectively (Fig. 1 and Table 2). SHBG concentrations were decreased by 21 ± 7% ($P = 0.0003$) and 19 ± 39% ($P = 0.18$) at 25 and 50 mg exemestane, respectively. Free testosterone concentrations were increased by 117 ± 74% ($P = 0.0001$) and 154 ± 95% ($P < 0.0001$) at both doses, due to the decrease in SHBG and the increase in total testosterone. No effect on circulating dehydroepiandrosterone sulfate was observed at either dose. Serum cortisol concentrations increased significantly (38 ± 39%; $P = 0.008$) with the 25-mg dose, but not the 50-mg dose, yet the increase was well within the normal range of cortisol concentrations. Plasma IGF-I decreased significantly (−13 ± 11%; $P = 0.008$) after the 25-mg dose, but not the 50-mg dose. Similarly, IGF-binding protein-3 showed a trend toward lower concentrations after the 25-mg dose (−7 ± 13%; $P = 0.09$), but not the 50-mg dose. There were no changes in circulating serum triglycerides, cholesterol, or LDL or HDL cholesterol concentrations with either dose of exemestane. Table 2 summarizes the results of the hormonal and lipid data.

Study II: PK

As the level of suppression of circulating estrogens was comparable between doses, we elected to use 25 mg for the subsequent PK study. In all individuals, the highest concentrations of exemestane were observed in the first blood sample drawn 1 h after oral administration, indicating rapid absorption of the drug. Plasma concentration *vs.* time profiles

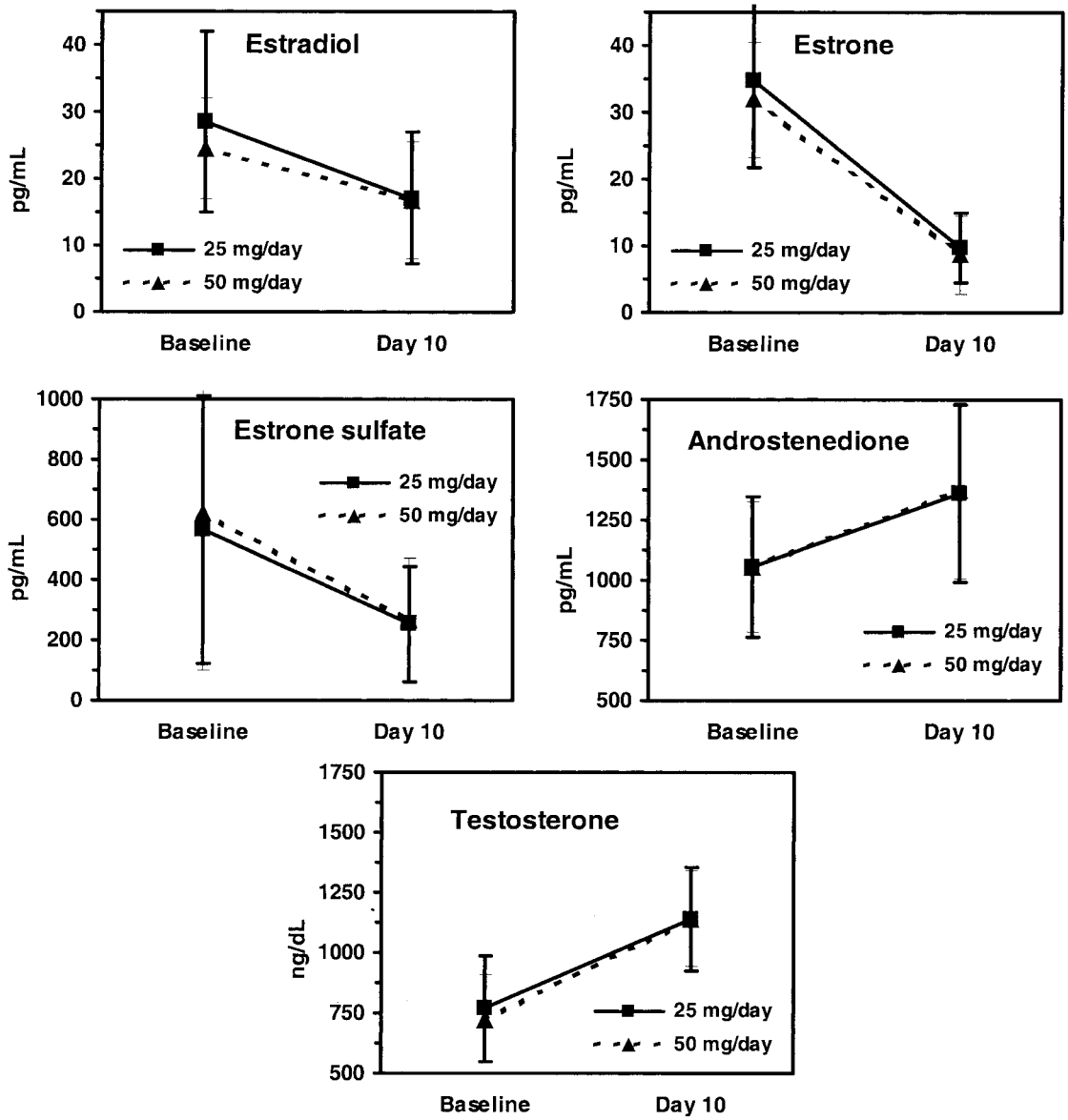

FIG. 1. Estrogen and androgen plasma levels after 10 d of daily exemestane (25 or 50 mg) in healthy young males (mean ± SD; n = 9–11). To convert to Systeme International units: estradiol, picomoles per liter (×3.671); estrone, picomoles per liter (×3.699); androstenedione, nanomoles per liter (*0.003492); and testosterone, nanomoles per liter (×0.03467).

TABLE 2. Changes in hormone and lipid concentrations in study I: young male subjects received 25 or 50 mg exemestane daily for 10 days

Assay	Dose (mg)	n	Baseline (mean ± SD)	End of 10-d treatment (mean ± SD)	% Change from baseline (mean ± SD)	*P* value (end − baseline)
Free testosterone (ng/dl)	25	11	9.5 ± 3.3	19.1 ± 4.7	117.0 ± 73.9	0.0001
	50	10	8.2 ± 2.9	19.4 ± 4.5	153.6 ± 94.6	0.0000
DHEAS (ng/ml)	25	11	1561 ± 826	1662 ± 726	18.6 ± 39.9	0.4227
	50	9	1771 ± 909	1876 ± 840	2.8 ± 12.5	0.7804
Cortisol (μg/dl)	25	9	10.2 ± 3.4	13.1 ± 2.7	37.9 ± 39.5	0.0080
	50	9	11.8 ± 6.6	11.3 ± 3.5	34.2 ± 104.0	0.7781
SHBG (nmol/liter)	25	10	22 ± 7	18 ± 5	−20.6 ± 7.0	0.0003
	50	10	28 ± 20	19 ± 5	−18.9 ± 39.2	0.1756
IGF-I (ng/ml)	25	11	533 ± 137	455 ± 80	−12.5 ± 11.1	0.0075
	50	10	491 ± 149	471 ± 118	2.0 ± 19.4	0.8197
IGFBP-3 (ng/liter)	25	11	5.0 ± 0.9	4.6 ± 0.6	−7.0 ± 12.5	0.0878
	50	10	4.8 ± 0.5	4.7 ± 0.6	0.2 ± 8.1	0.9776
Triglycerides (mg/dl)	25	11	89.9 ± 57.8	86.2 ± 49.4	−0.8 ± 26.4	0.5821
	50	10	118.5 ± 145.1	93.6 ± 51.1	28.0 ± 60.3	0.5634
Cholesterol (mg/dl)	25	11	144 ± 11	142 ± 17	−1.3 ± 9.3	0.6513
	50	10	139 ± 15	145 ± 14	4.2 ± 6.3	0.0725
Cholesterol HDL (mg/dl)	25	11	42 ± 11	42 ± 12	−1.0 ± 7.4	0.6938
	50	10	43 ± 11	41 ± 11	−4.1 ± 13.0	0.2796
Cholesterol LDL (mg/dl)	25	11	107 ± 16	106 ± 15	0.4 ± 15.6	0.8423
	50	10	96 ± 25	108 ± 13	20.7 ± 48.1	0.1381

DHEAS, Dehydroepiandrosterone sulfate; IGFBP-3, IGF-binding protein-3. To convert to Systeme International units: free testosterone, nmol/liter (×0.03467); DHEAS, μmol/liter (×0.002714); cortisol, nmol/liter (×27.59); IGF-I, mg/liter (×1); triglycerides, mmol/liter (×0.01129); cholesterol, mmol/liter (×0.02586).

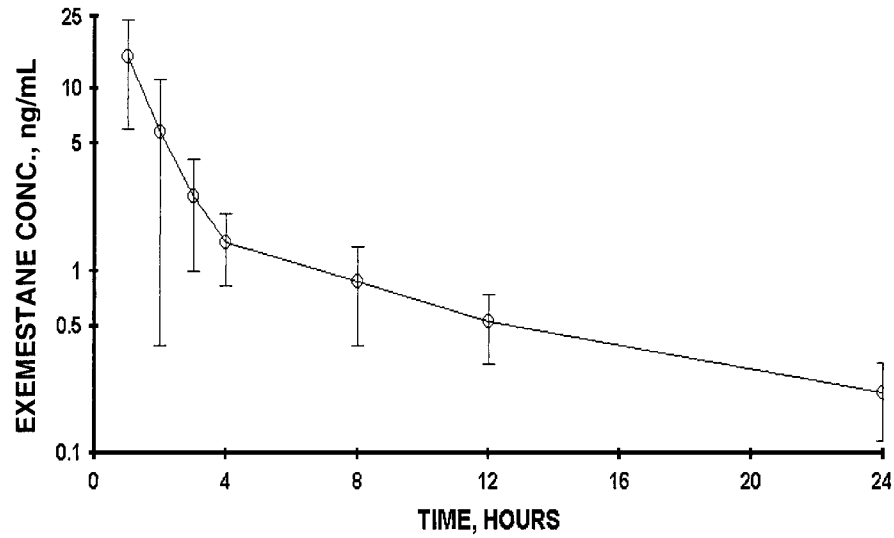

FIG. 2. Mean ± SD exemestane plasma concentrations *vs.* time in 10 young males receiving a single 25-mg oral dose.

in all subjects were characterized by a biexponential decline in exemestane (Fig. 2), with terminal half-life of 8.9 h. The other PK parameters are listed in Table 3. The mean maximal plasma concentration of the metabolite 17-hydroexemestane was 1.16 ± 0.36 ng/ml, a concentration achieved 1 h after the exemestane dose. These levels rapidly declined, and concentrations below the lower limit of sensitivity (0.1 ng/ml) were observed at a median time of 12 h (range, 4–24 h).

The mean baseline levels of estradiol and testosterone were 24.5 ± 8.8 pg/ml and 581 ± 165 ng/dl, respectively. Maximal suppression of estradiol (62 ± 14%) was observed 12 h after a single 25-mg dose of exemestane. Estradiol remained suppressed by 58 ± 21% at 24 h and returned to baseline 3–6 d after treatment (Fig. 3). At the time of maximal estradiol suppression, plasma testosterone levels were unchanged and thereafter tended to increase by 32% between 2–3 d; however, contrary to the significant increase in testosterone observed after 10-d daily dosing, this change did not achieve statistical significance after a single oral dose. Serum LH and FSH concentrations were measured up to 24 h at the same time intervals as the exemestane samples for the PK analysis. The mean baseline levels of LH and FSH were 4.8 ± 2.2 and 1.3 ± 0.7 mIU/ml, respectively. The percent change from baseline up to 24 h is reported in Fig. 4. The LH levels initially decreased by 26% at 2 h; thereafter, there was a tendency for an increase to a maximum of 81% at 24 h. The levels of FSH were unchanged up to 12 h and increased by 49% at 24 h.

TABLE 3. Pharmacokinetic parameters after a single 25-mg oral dose of exemestane in 10 young males

PK parameter	Mean ± SE
Cmax (ng/ml)	16.1 ± 8.0
AUC (ng/ml·h)	36.4 ± 8.8
Kel (h^{-1})	0.0955 ± 0.0363
Half-life (h)	8.9 ± 5.3
MRT (h)	7.0 ± 3.7
Oral clearance (liter/h)	725 ± 186

Cmax, Maximum plasma concentration; Kel, slope of the regression line; MRT, mean residence time.

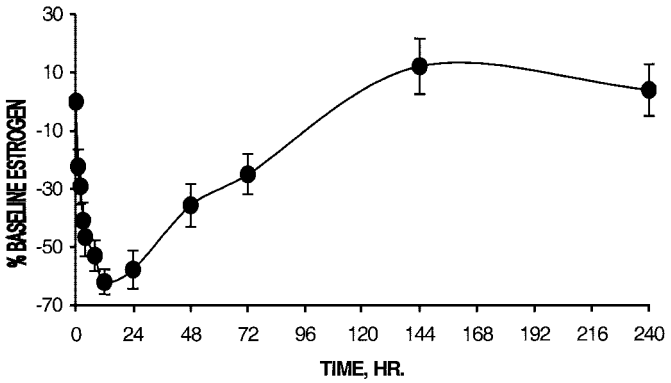

FIG. 3. Percent change from baseline (mean ± SD) in plasma estradiol concentrations after a single 25-mg dose of exemestane in 10 young males.

Safety

Exemestane was well tolerated by the study subjects, with no serious adverse events reported. General chemistries, CBC, and differential urinalysis and liver profiles were measured and were unchanged during administration.

Discussion

We report the first detailed study of the pharmacological effects of exemestane in male subjects. Doses of 25 and 50 mg were comparable in suppressing all circulating estrogens and had similar effects of increasing serum androstenedione and testosterone concentrations. There were 38%, 71%, and 45% decreases in estradiol, estrone, and estrone sulfate concentrations, respectively, after 10 d, approximately 24 h after administration of the last dose of 25 mg exemestane, coupled with 60% and 32% increases in testosterone and androstenedione concentrations. The rise in the aromatase substrates, testosterone and androstenedione, is probably secondary to substrate accumulation and/or to the feedback increase in gonadotropins caused by aromatase blockade. The 21% decrease in SHBG concentrations caused by 25 mg exemestane confirms the observation in postmenopausal women (20).

The maximum plasma concentration, time to achieve maximal concentrations and oral clearance for exemestane after oral administration of a single dose of 25 mg in the present study of males were similar to those reported for females (21–23). The terminal half-life in the present study (8.9 h) was considerably shorter than the published value of 27 h (23). The reason for this difference is not clear, but may be related

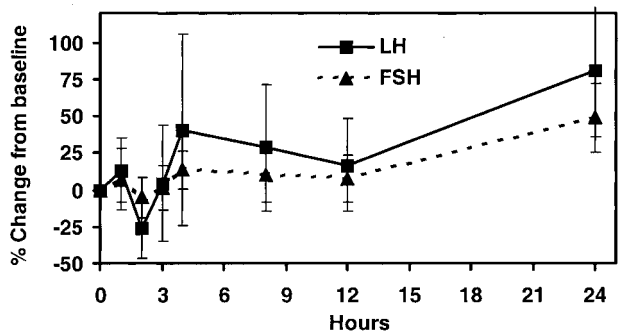

FIG. 4. Percent change from baseline (mean ± SD) in plasma LH and FSH concentrations after a single 25-mg dose of exemestane in 10 young males.

to a true gender dependency possibly involving the volume of distribution (lower in males than females) and plasma or tissue protein binding (respectively, higher and lower in males). This finding may also be due to the lower sensitivity of the analytical methodology used in the previous studies (14 pg/ml by HPLC/RIA) (21).

The maximal suppression evoked by exemestane at the single dose of 25 mg in the present study was similar to published results in postmenopausal women, but the time course differed (24). Evans *et al.* (24) reported that a single 25-mg oral dose of exemestane maximally suppressed estradiol concentrations by 72% 3 d after administration, and estradiol levels returned to baseline only 8–11 d after drug administration. In the present study maximal suppression of estradiol of 62% was observed 12 h after exemestane administration and returned to baseline 3–6 d after administration. The reason for this difference is not clear, but may be related to the shorter half-life of exemestane in males, the lower exposure to exemestane, and the higher levels of the aromatase substrates androstenedione (~1 ng/ml in young males *vs.* ~0.5 ng/ml in postmenopausal women), particularly the much higher testosterone concentrations in young males than in postmenopausal women (~700 ng/dl *vs.* ~20 ng/dl, respectively) (25). This is supported by the observation that in the 10-d study in young males reported here, the suppression of estradiol is weaker (due to the very high levels of the precursor testosterone) than that of estrone (due to androstenedione levels not very different from those in postmenopausal women). A limited suppression of circulating estradiol (~50%) has been reported in a similar study in young males treated with 1 mg daily anastrozole (7), a dose that reduces estradiol by 85% in postmenopausal women (23).

Aromatase inhibitors are being investigated in a variety of clinical situations besides breast cancer. As estrogen is the principal factor responsible for epiphyseal fusion, aromatase blockers are being studied in the treatment of severe short stature in boys (8, 9). This class of compounds has a theoretical advantage over using LHRH analogs to delay puberty, because they allow for progressive virilization while decreasing estrogens, potentially extending the time of epiphyseal fusion and thus the time for linear growth. Trials have not yet been performed in adolescent females due to the concerns that increased circulating gonadotropins, decreased estrogens, and increased testosterone could precip-

itate ovarian dysfunction and virilization, as is seen in the aromatase-deficient female (3, 26). Because of its properties of increasing circulating gonadotropins, it has been used as a treatment for oligospermic men with low testosterone/estradiol ratios with initial preliminary success (27). This class of compounds also has a theoretical application in the treatment of gynecomastia in those individuals with overexpressed aromatase activity as recently reported (28). In addition, studies conducted using estrogen receptor blockade in the treatment of gonadotropin-independent precocious puberty have shown encouraging results (29); hence, the use of aromatase blockers seems like a natural alternative worthy of clinical trials as well.

We conclude that exemestane is a potent aromatase inhibitor in men. Exemestane appears to be an alternative in the choice of inhibitors of the aromatase enzyme available for human studies. Further studies are underway to estimate dose and dosing intervals that will provide therapeutic suppression of estrogen concentrations in males. Long-term safety will also require further investigation.

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References

1. **Smith EP, Boyd J, Frank GR, Takahashi H, Cohen RM, Specker B, Williams TC, Lybahn DB, Korach, KS** 1994 Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med 331:1056–1061
2. **Carani C, Qin K, Simoni M, Faustini-Fustini M, Serpente S, Boyd J, Korach KS, Simpson ER** 1997 Effect of testosterone and estradiol in man with aromatase deficiency. N Engl J Med 337:95
3. **Morishima A, Grumbach MM, Simpson ER, Fisher C, Qin K** 1995 Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. J Clin Endocrinol Metab 80:3689–3698
4. **Simpson ER** 1998 Genetic mutations resulting in estrogen insufficiency in the male. Mol Cell Endocrinol 145:55–59
5. **Fisher CR, Graves KH, Parlow AF, Simpson ER** 1998 Characterization of mice deficient in aromatase (ArKO) because of targeted disruption of the cyp19 gene. Proc Natl Acad Sci USA 95:6965–6970
6. **Hewitt SC, Korach KS** 2002 Estrogen receptors: structure, mechanisms and function. Rev Endocr Metab Disord 3193–3200
7. **Mauras N, O'Brien KO, Oerter Klein K, Hayes V** 2000 Estrogen suppression in males: metabolic effects. J Clin Endocrinol Metab 85:2370–2377
8. **Wickman S, Sipila I, Ankarberg-Lindgren C, Norjavaara E, Dunkel L** 2001 A specific aromatase inhibitor and potential increase in adult height in boys with delayed puberty: a randomized controlled trial. Lancet 357:1743–1748
9. **Mauras N, Rini A, Welch S, Oerter-Klein K,** Long term effects of combined treatment with an aromatase blocker (Arimidex®) and GH in GH deficient (GHD) boys in puberty: preliminary results [Abstract OR-9-99]. LWPES/ESPE 6th Joint Meeting of the Society for Pediatr Research, Montréal, Canada, 2001
10. **Simpson ER, Zhao Y, Agarwal VR, Michael MD, Bulun SE, Hinshelwood MM, Graham-Lorence S, Sun T, Fisher CR, Qin K, Mendelson CR** 1997 Aromatase expression in health and disease. Recent Prog Horm Res 52:185–214
11. **Sasano H, Uzuki M, Sawai T, Nagura H, Matsunaga G, Kashimoto O, Harada N** 1997 Aromatase in human bone tissue. J Bone Miner Res 12:1416–1423
12. **Clemett D, Lamb HM** 2000 Exemestane: a review of its use in postmenopausal women with advanced breast cancer. Drugs 59:1279–1296
13. 2003 Aromasin. In: Physicians desk reference, 57th ed. Montvale, NJ: Thomson PDR; 2692–2695
14. **Lonning PE, Bajetta E, Murray R, Tubiana-Hulin M, Eisenberg PD, Mickiewicz E, Celio L, Pitt P, Mita M, Aaronson NK, Fowst C, Arkhipov A, di Salle E, Polli A, Massimini G** 2000 Activity of exemestane in metastatic breast cancer after failure of non steroidal aromatase inhibitors: a phase II trial. J Clin Oncol 18:2234–2244
15. **Kaufmann M, Bajetta E, Dirix LY, Fein LE, Jones SE, Zilembo N, Dugardyn JL, Nasurdi C, Mennel RG, Cervek J, Fowst C, Polli A, di Salle E, Arkhipov A, Piscitelli G, Miller LL, Massimini G** 2000 Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomized double-blind trial. J Clin Oncol 18:1399–1411
16. **Johannessen DC, Engan T, Di Salle E, Zurlo MG, Paolini J, Ornati G, Piscitelli G, Kvinnsland S, Lonning PE** 1997 Endocrine and clinical effects of exemestane (PNU 155971), a novel steroidal aromatase inhibitor, in postmenopausal breast cancer patients: a phase I study. Clin Cancer Res 3:1101–1108
17. **Cenacchi V, Barattč S, Cicioni P, Frigerio E, Long J, James C** 2000 LC-MS-MS determination of exemestane in human plasma with heated nebulizer interface following solid-phase extraction in the 96 well plate format. J Pharmacol Biom Anal 22:451–460
18. **Hills M, Armitage P** 1979 The two-period cross-over clinical trial. Br J Clin Pharmacol 8:7–20
19. **Gibaldi M, Perrier D** 1982 Pharmacokinetics, 2nd Ed. New York: Marcel Dekker
20. **Zilembo N, Noberasco C, Bajetta E, Martinetti A, Mariani L, Orefice S, Buzzoni R, Di Bartolomeo M, Di Leo A, Laffranchi A** 1995 Endocrinological and clinical evaluation of exemestane, a new steroidal aromatase inhibitor. Br J Cancer 72:1007–1012
21. **Poggesi I, Jannuzzo MG, di Salle E, Piscitelli G, Rocchetti M, Spinelli R, Broutin F, Ornati G, Massimini G** 1999 Effect of food and formulation on the pharmacokinetics (PK) and pharmacodynamics (PD) of a single oral dose of exemestane (Aromasin®, EXE) [Abstract 741]. Proc Am Soc Clin Oncol 18:193a
22. **Spinelli R, Jannuzzo MG, Poggesi I** 1999 Pharmacokinetics (PK) of Aromasin (Exemestane, EXE) after single and repeated doses in healthy postmenopausal volunteers (HPV) [Abstract 1185]. Eur J Cancer 35:S295
23. **Buzdar AU, Robertson JFR, Eiermann W, Nabholtz JM** 2002 An overview of the pharmacology and pharmacokinetics of the newer generation aromatase inhibitors anastrozole, letrozole and exemestane. Cancer 95:2006–2016
24. **Evans TR, Di Salle E, Ornati G, Lassus M, Benedetti MS, Pianezzola E, Coombes RC** 1992 Phase I and endocrine study of exemestane (FCE 24304), a new aromatase inhibitor in postmenopausal women. Cancer Res 52:5933–5939
25. **Kvinnsland S, Anker G, Dirix LY, Bonneterre J, Prove AM, Wilking N, Lobelle JP, Mariani O, di Salle E, Polli A, Massimini G** 2000 High activity and tolerability demonstrated for exemestane in postmenopausal women with metastatic breast cancer who had previously failed on tamoxifen treatment. Eur J Cancer 36:976–982
26. **Mullis PE, Yoshimura N, Kuhlmann B, Lippuner K, Jaeger P, Harada H** 1997 Aromatase deficiency in a female who is compound heterozygote for two new point mutations in the P450arom gene: impact of estrogens on hypergonadotropic hypogonadism, multicystic ovaries, and bone densitometry in childhood. J Clin Endocrinol Metab 82:1739–1745
27. **Raman JD, Schlegel PN** 2002 Aromatase inhibitors for male infertility. J Urol 167:624–629
28. **Shozu M, Sebastian S, Takayama K, Hsu WT, Schultz RA, Neely K, Bryant M, Bulun SE** 2003 Estrogen excess associated with novel gain-of-function mutations affecting the aromatase gene. N Engl J Med 348:1855–1865
29. **Eugster E, Rubin S, Reiter E, Plourde P, Jou HC, Pescovitz O** 2003 Tamoxifen treatment for precocious puberty (PP) in McCune-Albright syndrome: multicenter trial. J Pediatr 143:60–66