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Open Dose-Finding Study of a New Potent and Selective Nonsteroidal Aromatase Inhibitor, CGS 20 267, in Healthy Male Subjects

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ABSTRACT

The aim of this open, dose-finding study was to evaluate the effects of single dose CGS 20 267, a new oral nonsteroidal aromatase inhibitor, on the inhibition of estrogen production and also on the production of adrenal and testicular steroids in healthy male subjects. Nine dose levels ranging from 0.02–30 mg and placebo were tested, each dose being given to 3 subjects only. A total of 18 subjects were included; 12 of them received 2 single administrations, the remaining 6 were exposed only once to one of the 2 highest dose levels.

A reduction in serum estrogen levels when compared to baseline was already observed after 2 h, reaching maximum suppression between 10 and 48 h after administration. After 24 h, a suppression of estrone levels by 60–85% from baseline was achieved with all tested doses. A reduction in estradiol levels by about 30% from baseline was observed at the lowest dose (0.02 mg). This reduction was further enhanced dose dependently to a maximum of about 90% from baseline at 24 h after administration of the highest dose (30 mg). With the higher doses (10 and 30 mg), estrogen suppression was maintained up to 3 days. A dose-dependent increase of testosterone, LH, and FSH was observed and was most pronounced in the 10- and 30-mg dose groups, which can be considered as a consequence of the long-lasting aromatase inhibition achieved with these high doses.

No effect on serum cortisol and aldosterone levels was observed up to the highest dose. No clinically relevant changes were observed in blood chemistry and hematology tests. The systemic and subjective tolerability of CGS 20 267 was good at all doses.

This study has shown that CGS 20 267 is a well tolerated, potent, selective, and long-acting inhibitor of the aromatase enzyme after single administration. (*J Clin Endocrinol Metab* **77:** 319–323, 1993)

THE aromatase enzyme plays a key role in the biosynthesis of estrogens. Estrogen deprivation by means of aromatase inhibitors (AI) may be of value for treating estrogen-dependent diseases (1). Aminoglutethimide (AG), an inhibitor of the aromatase enzyme, is a well established treatment for advanced breast cancer in postmenopausal women (2). However, AG is a relatively nonselective inhibitor of the aromatase enzyme in that it also inhibits other enzymes involved in steroid biosynthesis at concentrations similar to those at which it inhibits aromatase (2). This, coupled with its moderate tolerability, spurred the search for AIs which are much more potent and selective in their action as inhibitors of estrogen biosynthesis than AG and better tolerated. Among the new AIs, 4-hydroxyandrostenedione (CGP 32 349), a highly selective steroidal compound (3), was the first of these new inhibitors to be used clinically. Its efficacy in the treatment of advanced breast cancer has been shown (4, 5). Fadrozole hydrochloride (CGS 16 949 A), an orally active, highly potent nonsteroidal AI, is not completely selective (6, 7). It is currently evaluated in advanced breast cancer (8, 9). Other steroidal AIs, exemestane (10) and atamestane (11), and the nonsteroidal, R76713, are in early clinical development.

CGS 20 267 [4-4'-(1H-1,2,4-triazol-1-yl-methylene)-bis-benzonitrile] is a new orally active, potent, and highly specific AI without intrinsic androgenic or estrogenic properties (12). *In vitro*, CGS 20 267 is about 200 times as potent as AG (12). It only inhibits adrenal steroidogenesis in rat adrenal preparations at concentrations from 6,000 (aldosterone) to 15,000 (corticosterone) times higher than those required for the inhibition of estrogen production in hamster ovarian slices (12). CGS 20 267 inhibits aromatase *in vivo* 10,000 times as potently as AG (12). In adult female rats bearing estrogen-dependent 7, 12-dimethylbenz(a)anthracene-induced mammary tumors, 0.1 mg/kg orally given daily for 42 days caused almost complete regression of tumours present at the start of treatment. Thus, the high potency and selectivity of this new AI warranted further evaluation in humans.

This first clinical evaluation of the potency, selectivity, and tolerability of CGS 20 267 was conducted as an open single dose escalation study in healthy male subjects.

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Subjects and Methods

Subjects

Eighteen healthy male subjects (mean age: 28.4 yr, range: 20–48 yr, mean body weight: 75.3 kg, range: 60.4–95.1 kg) gave their written informed consent to participate in this study which was approved by an ethics committee from the University Hospital of Basel. The investigation was performed according to the Declaration of Helsinki, Venice Amendment 1983.

Study design

The study was an open dose-finding study with stepwise increasing doses of CGS 20 267 administered to healthy subjects. Nine dose levels

and placebo were each tested: 0.02, 0.1, 0.25, 0.5, 1.0, 2.5, 5.0, 10, and 30 mg. Each dose was tested in three subjects. CGS 20 267 was available as an oral solution. Each dose was given in a volume of 100 ml administered 1.5 h after a light breakfast. Twelve subjects received one low dose level and a 10 times higher dose with a treatment-free interval of at least 5 weeks. The remaining six subjects were exposed only once to one of the two higher doses (10 and 30 mg). The dose was increased only if the preceding dose level was well tolerated. The volunteers were required to keep to their normal diet during the whole study period. They were not allowed to consume alcohol or to take any other medication and had to avoid strenuous physical activity.

Experimental procedures

The study was conducted in the Human Pharmacology Department of CIBA-GEIGY Limited, Basel.

Blood samples for the measurement of serum estrone (E_1), estradiol (E_2), aldosterone (ALDO), cortisol, testosterone, LH, and FSH were collected 24 h before drug administration, immediately before drug intake and 2, 4, 8, 10, 24, 32, and 72 h after drug administration. Samples were collected 6, 8, 13, and 21 days after drug administration for the doses of 0.02, 0.1, 1.0, 2.5, 5.0, 10, and 30 mg. Samples taken on day 1 of the study were taken through an indwelling cannula (Venflon 18 gauge, Vigo AB, Sweden) inserted into a forearm vein and fitted with a three-way lock (model K96B, Bentley Laboratories, Netherlands). This system was kept open by flushing with heparinized saline (125 U/mL Liquemine Roche, Basel, Switzerland) after each withdrawal of blood. Other blood samples were drawn by separate vein punctures. They were drawn into ice-cooled containers (glass Venoject tubes, Terumo-Europe, Leuvin, Belgium) without additive, allowed to clot, and centrifuged at 3000 rpm at a temperature of +4 C for 5 min. The serum was removed and snap-frozen in polypropylene tubes on dry ice and kept at −18 C until analysis.

Measurement of serum sodium, potassium, calcium, phosphate, urea, creatinine, albumin, total protein, total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, amylase, red blood cells, hemoglobin, white blood cells with differential count, and platelets was performed before, and 24 and 48 h after drug intake. Blood samples were drawn into a Vacutainer tube without additive and transferred within 2 h for blood chemistry performed on a Hitachi 717 autoanalyser. Blood samples for hematology were drawn into an EDTA-Vacutainer for counts performed on an automatic Haemalog Counter (Technicon, New York, NY).

Body weight was registered with an electronic Seca Scale (model 708, Seca, Hamburg, Germany) 24 h and just before drug intake, and 24 and 48 h after drug administration. ECG was recorded before and 24 and 48 h after drug intake, in supine position with a six-channel recorder EK 36 (Hellige, Germany) and was evaluated on-line by means of the Hannover HES ECG program on a Digital Micro PDP-11 computer. Blood pressure and heart rate were measured as a mean of two consecutive readings with a Dinamap monitor model 1846 SX (Critikon Inc., Tampa, FL) after 15 min rest in supine position, and in orthostatic position after 3 min passive head-up tilting to an angle of 45°, before drug administration, and 2, 4, 8, 24, and 48 h after.

Subjective tolerability was recorded on each study day by indirect questioning.

Assays

The serum levels of E_1 and E_2 were measured by a method whose details have been published previously (7). Specific RIA kits were used to measure serum cortisol, ALDO, testosterone, LH, and FSH (Diagnostics Products Corporation, Los Angeles, CA), tracers: ^{125}I-Cortisol, ^{125}I-aldosterone, ^{125}I-testosterone, ^{125}I-LH, and ^{125}I-FSH.

Statistical analyses

Due to the design of the study, no statistical tests for significance were performed. All parameters were analyzed arithmetically. Serum hormone levels are expressed as geometric means.

Results

Serum estrogen

A rapid suppression of serum estrogen levels was observed with all doses tested in this study, ranging from 0.02–30 mg CGS 20 267. The magnitude and duration of estrogen suppression was dependent on the dose. The decrease in serum E_1 levels was generally more pronounced and prolonged as compared to the decrease in serum E_2 concentrations.

The E_1 levels started to decrease within the first 2–4 h after administration of all doses. The maximum suppression of E_1 levels was observed in most cases between 24 and 48 hours after drug administration (Table 1). With the lowest dose of 0.02 mg, the reduction of E_1 levels was about 70% from baseline after 24 h. The next higher doses of up to 1 mg resulted in E_1 reduction from 0-h baseline levels by 60–70% at 24 h, with the exception of the 0.5-mg dose where suppression was about 80%. In the higher dose groups (2.5–30 mg) a reduction between 75% and 85% from baseline was observed at 24 h. With these higher doses, E_1 levels were at the detection limit of the assay (9 pmol/L) in 22 of 48 samples taken between 24 and 72 h after drug administration, which might consequently lead to an underestimation of E_1 suppression. The return of E_1 levels to baseline was very slow. With the 2.5-mg dose, suppression below 80% from baseline was sustained for 2 days, with 5, 10, and 30 mg for at least 3 days. In the 30 mg dose-group E_1 had not returned to baseline after 3 weeks (day 21 around 50% from baseline).

The E_2 levels started to decline within 2–4 h after drug administration and were maximally suppressed in most cases between 10 and 24 h after drug administration (Table 2). There was a clear dose-dependency of E_2 suppression which is shown in Fig. 1 at the 24-h time point. A reduction of about 30% from baseline was observed with the lowest dose of 0.02 mg after 24 h. Further suppression was achieved with increasing doses. E_2 levels decreased by about 50% from baseline within 24 h after 0.1 and 0.25 mg; by about 60% after 0.5 and 1 mg; and by about 75% after 2.5 and 5 mg. With the 10- and 30-mg doses, E_2 suppression was by 80% and 90% from baseline. Compared to E_1, the return of E_2 levels to baseline was faster, and only with the 10 and 30 mg doses was 80% suppression sustained for 2 and 3 days, respectively.

Testosterone, LH, FSH (Table 3, selected data)

A dose-related increase in testosterone, LH, and FSH levels was observed. Serum testosterone was elevated to about 150% of 0-h with all doses at 48 and 72 h after drug administration, except with 0.25 mg (130%) and 5 mg (210%). The increase reached 200% with doses between 2.5 and 30 mg. The values returned almost to normal after 21 days, except for the 30-mg dose. The dose-related increase of LH and FSH was very marked with doses of 1 mg and above, compared to baseline values and placebo. In these

TABLE 1. Serum E_1 levels [geometric mean; range in ( ) for selected time points; n = 3; expressed as picomoles per L]

	Placebo	CGS 20 267 (mg)								
		0.02	0.1	0.25	0.5	1.0	2.5	5.0	10	30
0 h	107.3	73.0	102.1	65.8	83.0	61.9	67.7	80.5	71.6	90.3
	(75.5–137.6)	(39.9–108.3)	(90.3–124.7)	(52.9–80.6)	(69.2–93.6)	(56.2–71.8)	(61.8–76.2)	(67.0–97.3)	(54.4–101.4)	(88.8–91.4)
2 h	122.9	52.9	69.4	44.4	54.0	36.7	43.6	43.5	48.8	52.0
4 h	112.8	43.8	51.2	34.3	38.7	42.4	40.8	29.5	49.2	37.4
8 h	91.0	33.2	35.7	29.7	31.7	27.6	29.3	24.5	30.8	29.1
10 h	88.3	21.8	35.0	31.3	33.9	30.5	25.2	23.6	30.8	24.2
	(70.3–104.7)	(10.7–39.6)	(27.4–39.9)	(29.2–33.3)	(30.7–38.5)	(22.9–38.5)	(22.6–27.7)	(19.3–32.6)	(24.0–37.7)	(18.1–29.6)
24 h	126.2	21.8	31.3	25.0	16.0	20.6	9.8	10.4	18.8	11.1
	(90.3–155.0)	(11.1–38.5)	(22.6–38.1)	(22.9–27.7)	(10.4–27.0)	(18.5–22.6)	(9.0[a]–10.7)	(9.0[a]–15.9)	(15.9–22.2)	(9.0[a]–12.6)
32 h	96.6	23.6	29.6	23.6	18.1	22.2	9.3	11.3	15.4	10.7
48 h	105.9	34.4	34.6	28.2	17.1	19.6	9.6	10.0	12.8	9.0
	(86.9–121.7)	(25.9–42.2)	(25.9–46.2)	(24.8–35.5)	(9.0[a]–30.3)	(15.2–29.2)	(9.0[a]–9.9)	(9.0[a]–11.5)	(11.8–14.8)	(9.0)[a]
72 h	130.5	31.8	43.1	32.4	17.6	26.2	13.4	10.1	10.4	9.0
	(99.1–155.7)	(16.3–66.2)	(37.3–55.5)	(31.1–33.3)	(9.0[a]–31.8)	(20.3–33.3)	(11.5–14.8)	(9.0[a]–12.2)	(9.6–11.8)	(9.0)[a]
Day 6		92.0	47.2				21.2	29.7	31.8	21.1
Day 8		76.5	65.0				27.5	30.0	43.8	20.7
Day 13		86.5	86.2				35.3	55.0	44.3	39.6
Day 21		94.3	98.6			73.4	57.0	79.3	66.4	44.6
		(76.9–106.2)	(84.0–115.8)			(46.3–122.8)	(38.8–83.6)	(52.2–146.9)	(48.8–114.7)	(36.6–55.1)

[a] Values at the detection limit of the assay.

TABLE 2. Serum E_2 levels [geometric mean; range in ( ) for selected time points; n = 3; expressed as picomoles per L]

	Placebo	CGS 20 267 (mg)								
		0.02	0.1	0.25	0.5	1.0	2.5	5.0	10	30
0 h	118.1	78.9	94.2	69.7	65.6	84.7	77.1	73.7	81.8	132.9
	(103.5–137.7)	(52.9–111.2)	(84.4–105.7)	(54.0–84.8)	(52.5–99.5)	(71.2–106.5)	(67.9–90.7)	(60.9–92.1)	(74.9–94.0)	(106.5–161.9)
2 h	141.6	72.2	70.2	46.5	45.7	51.6	49.2	48.9	51.8	58.8
4 h	126.0	52.6	43.3	41.0	35.0	41.4	35.9	38.2	42.7	35.2
8 h	100.0	46.7	35.7	34.4	25.6	33.7	28.9	25.1	30.7	26.7
10 h	90.0	49.8	35.3	33.0	30.2	31.4	22.0	21.1	29.0	23.0
	(86.6–117.8)	(31.2–88.5)	(30.1–41.5)	(26.1–38.2)	(27.5–35.2)	(29.7–34.9)	(20.6–25.3)	(17.6–26.4)	(21.3–34.9)	(18.7–26.1)
24 h	122.6	52.3	49.6	33.0	23.9	31.9	19.5	18.5	16.8	11.4
	(92.1–151.6)	(34.5–87.4)	(36.3–60.6)	(24.6–39.6)	(16.2–33.8)	(27.9–39.6)	(17.6–21.7)	(12.8–22.8)	(15.4–19.5)	(8.4–15.8)
32 h	96.1	55.6	55.4	43.0	34.5	41.0	26.9	20.6	17.3	12.6
48 h	99.5	62.4	67.6	50.8	42.7	44.8	29.1	23.5	19.0	10.4
	(71.2–120.0)	(41.8–94.7)	(36.3–125.9)	(34.1–80.4)	(30.5–62.8)	(36.0–52.9)	(20.9–37.8)	(15.4–25.3)	(15.8–19.1)	(11.4–15.1)
72 h	122.2	69.0	87.7	54.1	44.0	58.4	53.4	33.2	29.2	12.1
	(82.6–168.9)	(47.0–106.8)	(49.2–157.9)	(41.8–65.7)	(27.9–60.2)	(43.0–91.4)	(48.1–61.3)	(29.0–36.7)	(27.5–31.2)	(11.4–12.5)
Day 6		110.4	88.5				74.4	67.1	123.0	28.4
Day 8		89.6	112.1				72.3	65.8	155.8	38.9
Day 13		89.9	122.7				85.0	54.4	135.8	152.0
Day 21		91.5	142.5			77.1	88.8	71.3	141.7	135.3
		(72.3–120.8)	(122.6–165.6)			(55.4–117.1)	(84.8–92.9)	(42.2–107.6)	(107.2–244.5)	(91.4–167.8)

dose groups, the values did not completely return to baseline by day 21.

Cortisol, ALDO (Fig. 2 - selected data)

No drug-related changes of serum cortisol or ALDO levels were observed during the study period with any of the doses tested. Serum levels of both hormones showed a classical diurnal pattern and the curves of every group were very similar to the placebo curves.

Subjective tolerability

After 5 of the 30 single administrations (27 times CGS 20 267 and 3 times placebo), clinical symptoms were recorded in 4 out of the 18 subjects.

In one subject who received the 0.5 mg dose a drop of blood pressure (22 mm Hg for the systolic and 15 mm Hg for the diastolic) was observed during tilting at baseline and only for the systolic blood pressure after drug administration. A similar phenomenon occurred in the same subject before and after the administration of a 10-times higher dose. The existence of the phenomenon before drug administration

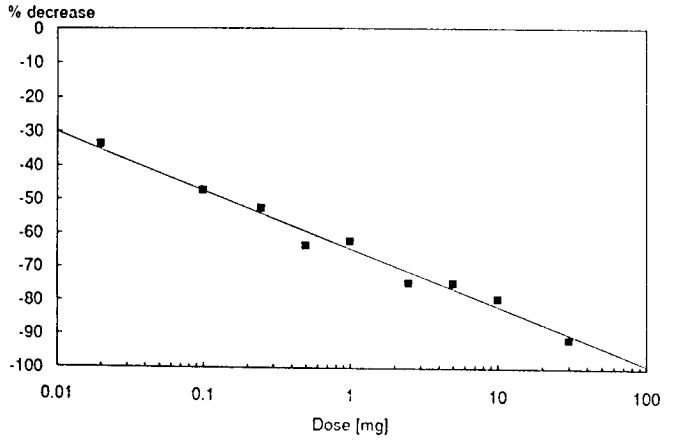

FIG. 1. Dose-response relationship between orally administered single doses of CGS 20 267 and suppression of serum E_2 concentrations. (E_2 suppression is expressed as percent decrease of baseline 24 h after administration of each dose. Each data point is the geometric mean of three observations.)

ruled out a causal relationship with the study medication. This subject reported a moderate headache 12 h after the administration of the high dose and a severe migraine 48 h later. Two other subjects reported headache 12 h after administration of the 0.02 mg dose, which was not reported when they received the higher dose of 1 mg CGS 20 267. Slight headache was reported by one subject 12 h after receiving the 0.1-mg dose.

Body weight, blood pressure, heart rate, and ECG

No effect of the test drug on resting blood pressure, heart rate, or the reaction to passive tilting (except for the subject mentioned above) and ECG was observed. The body weight of the subjects remained stable throughout the study period and was unaffected by CGS 20 267.

Blood chemistry and hematology

No clinically relevant changes were observed with any of the doses or placebo during the study.

Discussion

Demonstration of aromatase inhibition requires documentation of decreases in serum and/or urinary estrogen levels without a concomitant reduction in serum testosterone and androstenedione levels, the androgen substrates for this enzyme. This open dose-finding study has shown that CGS 20 267 reduced serum E_1 and E_2-levels and did not suppress serum testosterone levels. The reduction in estrogen levels from baseline was already observed after 2 h, reaching maximum suppression between 10 and 48 h after drug administration. CGS 20 267 appears very potent with a dose-dependent suppression starting with a 30% reduction from baseline at the lowest dose of 0.02 mg and reaching a 90% reduction after 24 h with 30 mg CGS 20 267, if serum E_2, the major active estrogenic steroid, is considered. This level of suppression has never been reported after multiple application of high doses in postmenopausal patients with other aromatase inhibitors such as AG (13), fadrozole, or CGP 32 349 (14, 15), or multiple application of fadrozole in healthy men (16). Estrogen suppression was sustained over 24 h or more for all doses tested and was more pronounced for E_1, levels of which were reduced to 75–85% from baseline for 2–3 days with doses from 2.5–30 mg, showing that CGS 20 267 is a long-acting aromatase inhibitor. In this study, doses of up to 30 mg did not affect serum cortisol and ALDO levels, suggesting that CGS 20 267 is highly selective as predicted by the experimental models (12).

Dose-dependent increases in testosterone, LH, and FSH were observed and expected as a consequence of sustained inhibition of the aromatase enzyme in men. Results with fadrozole hydrochloride in healthy males indicated that the aromatization pathway is also of major importance in the regulation of gonadotropin secretion by aromatizable androgens in humans (16). After 10 days of 1 mg fadrozole twice daily, an E_2 suppression of 60% from baseline was observed with a significant increase of FSH and testosterone. The marked increase in serum testosterone and LH in the presence of suppressed estradiol levels seen in the present study is convincing evidence that aromatization does play a major

TABLE 3. Serum levels (geometric mean; n = 3) of LH, FSH, and testosterone (TEST) (expressed in international units per L for FSH, LH, and nanomoles per L for TEST)

		Placebo	CGS 20 267 (mg)								
			0.02	0.1	0.25	0.5	1.0	2.5	5.0	10	30
Pretreatment	LH	6.4	10.4	5.3	5.5	7.1	11.7	6.5	7.8	5.6	7.1
	FSH	8.7	10.5	9.5	8.3	9.7	10.4	8.7	8.8	6.2	7.1
	TEST	24.6	23.3	23.2	17.9	16.6	22.2	19.1	19.1	21.0	21.1
Day 2	LH	7.2	13.5	7.3	11.4	11.4	18.0	17.1	16.0	19.3	17.9
	FSH	10.7	12.9	10.1	13.6	13.5	16.1	15.2	16.5	12.7	14.3
	TEST	25.4	32.3	26.9	22.6	24.2	31.4	29.2	23.8	28.4	31.2
Day 3	LH	7.6	12.1	9.1	13.4	9.5	18.0	16.3	13.6	21.9	27.1
	FSH	10.4	12.7	13.7	13.1	14.1	16.1	17.0	17.5	16.4	18.8
	TEST	23.7	33.8	34.7	23.2	24.6	31.4	30.8	37.7	33.5	35.0
Day 6	LH		10.8	12.2				17.7	11.7	17.6	33.6
	FSH		29.9					15.2	14.8	23.9	29.9
	TEST		31.9	31.1				33.4	32.7	40.5	45.1
Day 21	LH		10.2	9.1			8.4	9.3	7.5	8.6	10.3
	FSH		28.2	6.5			16.3	8.2		13.1	9.7
	TEST		26.4	25.4			23.7	24.0	22.5	26.3	37.5

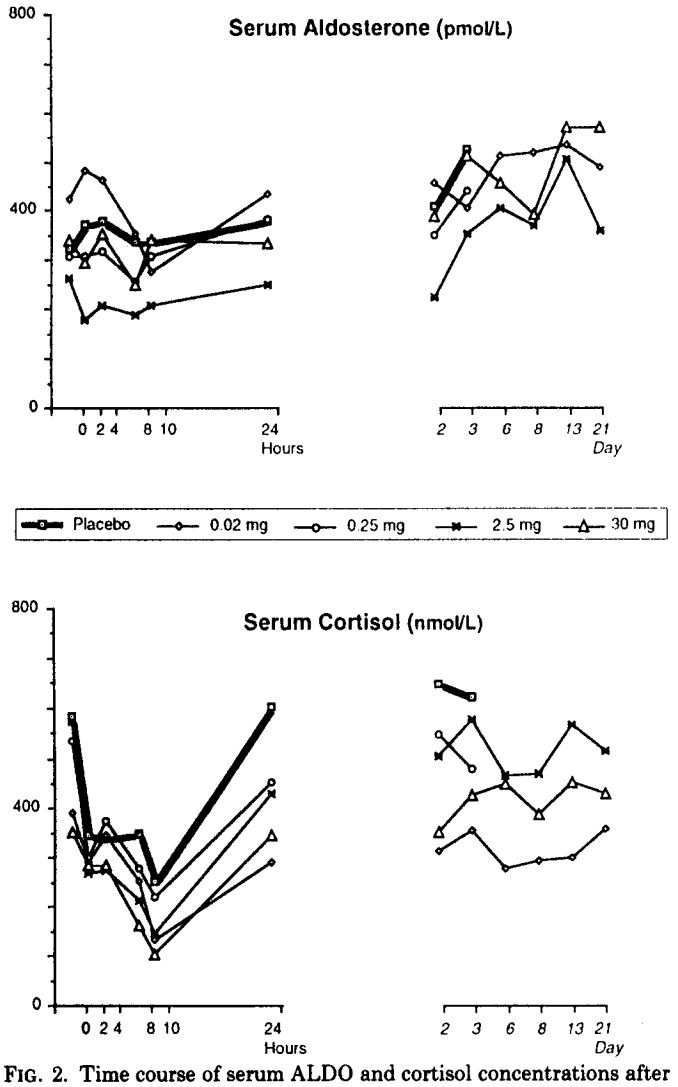

FIG. 2. Time course of serum ALDO and cortisol concentrations after oral administration of a single dose of CGS 20 267. (Each data point is the geometric mean of three observations.)

role in mediating the regulation of LH secretion by testosterone in men.

In conclusion, CGS 20 267 is a very potent inhibitor of estrogen biosynthesis in healthy males. CGS 20 267 is very selective in its inhibition of estrogen biosynthesis, as it does not affect serum concentrations of cortisol or ALDO. The effects of CGS 20 267 on testosterone, LH, and FSH are similar to those seen previously in healthy men with another nonsteroidal AI, fadrozole hydrochloride, and further support the premise that in men aromatization of testosterone to estrogens is a prerequisite for the regulation of gonadotropin secretion.

Thus, CGS 20 267 appears to be a well tolerated, potent, selective, and long-acting inhibitor of estrogen biosynthesis and presents itself as a promising compound for the treatment of breast cancer and other estrogen-dependent diseases.

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