CGS 16949A, a New Nonsteroidal Aromatase Inhibitor: Effects on Hormone-dependent and -independent Tumors in Vivo

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ABSTRACT

CGS 16949A is a very potent and highly selective inhibitor of the aromatase enzyme system in vitro and of estrogen biosynthesis in vivo. These characteristics are reflected in the marked efficacy with which it affects growth of estrogen-dependent 7,12-dimethylbenz(a)anthracene-induced mammary carcinomas in intact female Sprague-Dawley rats. Daily p.o. treatment of tumor-bearing rats for 42 days with CGS 16949A at doses of 1.0 to 8.0 mg/kg caused almost complete regression of palpable tumors and almost totally suppressed the appearance of new tumors. A dose of about 0.1 mg/kg corresponded to the 50% effective dose, and a fully effective dose was estimated to be about 2.0 mg/kg. Eight to 10 days after cessation of treatment, tumor regrowth was observed. No unexpected side-effects were noted during the course of treatment. Tumors, which were allowed to regrow after a first treatment with CGS 16949A, were similarly efficaciously suppressed with a second treatment with CGS 16949A. Continuous long-term treatment with 2.0 mg/kg for 27 wk caused complete regression of tumors, suppressed the appearance of new tumors completely, and significantly prolonged the survival time of the tumor-bearing rats. This treatment schedule caused no major hematological or blood chemistry changes and was very well tolerated.

CGS 16949A was ineffective against transplantable hormone-independent tumors such as R-3230AC mammary carcinoma, 11095 prostate carcinoma, leukemia L1210, and B16 melanoma.

INTRODUCTION

The role of aromatase, a microsomal cytochrome P-450-dependent enzyme system, as a key enzyme in the glandular and extraglandular biosynthesis of estrogens in males and in females has been well established (1–3). Aromatase is found predominantly in the premenopausal ovary and also in adipose tissue, liver, brain, placenta, and breast cancer tissue (4–10). Estrogen produced either by the ovary or through extraglandular biosynthesis is thought to be responsible for growth stimulation of hormone-dependent metastatic breast cancer in pre- and postmenopausal women. Thus, treatment of breast cancer patients with aromatase inhibitors [lowering the levels of circulating estrogen (11, 12)] or with antiestrogens [agonist-potentiation of estrogen's effects] is the most effective therapy for the treatment of hormone-dependent breast cancer in the preclinical setting (13). Results of clinical trials with antiestrogens indicate that a >80% reduction of estrogen levels is required for maximal inhibition of aromatase activity. In this paper we report on the antitumor effects of CGS 16949A which were studied extensively in the estrogen-dependent DMBA-induced mammary tumor model in female Sprague-Dawley rats and in a panel of transplantable hormone-dependent tumors in mice and rats.

MATERIALS AND METHODS

Test Compounds. CGS 16949A (4-(5,6,7,8-tetrahydroimidazo[1,5a]-pyridin-5-yl)benzonitrile monohydrochloride (Fig. 1) was synthesized by Dr. L. J. Browne at the Chemical Research Laboratories, CIBA-GEIGY, Summit, NJ. Being water soluble, it was administered p.o. as a suspension in a 0.5% aqueous solution of carboxymethyl-cellulose sodium (Tylose C 600; Hoechst, Germany) containing 20% propylene glycol. More recently, reports on the clinical efficacy of a steroidal aromatase inhibitor, 4-hydroxyandrostenedione, have appeared in the literature (19, 20). These results further support the concept that aromatase inhibition is a successful therapy for the treatment of estrogen-dependent breast cancer. Thus, it was of interest to develop other more selective aromatase inhibitors of even higher potency.

CGS 16949A is a new nonsteroidal inhibitor of aromatase which shows higher potency and much greater specificity in its inhibition of aromatase than AG. Steele et al. (21) have shown, using double reciprocal plots, that CGS 16949A competitively inhibits the conversion of androstenedione to estrone in vitro using aromatase enzyme preparations derived from human placenta and rat ovary. The IC₅₀ of CGS 16949A and AG were, respectively, 4.5 x 10⁻⁹ M and 1.7 x 10⁻⁶ M in human placental microsomes and 1.4 x 10⁻⁹ M and 2.2 x 10⁻⁷ M in rat ovarian microsomes. Thus CGS 16949A was between 200 and 400 times as potent as AG in vitro. Häusler et al. (22) have recently demonstrated the high selectivity with which CGS 16949A inhibits aromatase. In in vitro preparations using hamster ovarian slices, they were able to show that CGS 16949A only inhibited luteinizing hormone-induced progesterone production at concentrations which were at least 300 times those required for maximal inhibition of estradiol production. This was in contrast to AG which inhibited the production of both steroids equally at the same concentration. In vivo, Steele et al. (21) showed that estrogen production in pregnantmure's serum gonadotrophin-primed immature rats was inhibited by more than 90% with a single p.o. administration of either 260 µg/kg of CGS 16949A or 100 mg/kg of AG. To demonstrate a lack of effect on adrenal steroidogenesis, the same authors showed that 4 mg/kg of CGS 16949A given to adult female rats for 14 days did not induce any adrenal hypertrophy. Finally, doses up to 25 mg/kg in standard bioassays showed no androgenic or estrogenic activity. These results demonstrate that CGS 16949A is a very potent and highly selective inhibitor of the aromatase enzyme system both in vitro and in vivo.
Antitumor Effects of a Nonsteroidal Aromatase Inhibitor

Tumors and Animals. Mammary tumors were induced in 50-day-old female Sprague-Dawley (Mo:SPRD) rats by a single p.o. administration of 15 mg DMBA (Fluka, Switzerland) in 1 ml of sesame oil. The majority of the tumors appeared 5 to 7 wk after DMBA administration. Rats carrying 1 to 3 tumors of 8- to 12-mm diameter were selected and randomized into various treatment groups and vehicle-treated control groups of between 10 to 20 animals each. The transplantable tumors used were stored in our tumor bank in liquid nitrogen. Before the start of experimental studies, two in vivo passages were carried out to obtain a suitably constant rate of tumor growth. The estrogen-independent R-3230AC mammary carcinoma in female Fischer 344 rats [CDF(F344)/CrIbr], the androgen-independent 11095 prostate carcinoma in male Fischer 344 rats, and the B16 melanoma in female C57BL/6F1/Tif (specific pathogen free) mice. The estrogen-independent mammary carcinoma 2661/61 was transplanted by i.m. injection of 0.1 ml of tumor homogenate (1:10 in Hanks' solution), respectively, into the animals' left flank. The estrogen-independent mammary carcinoma 2661/61 was transplanted by i.m. injection of 0.1 ml of tumor homogenate into the left hind leg of female CBA/Rij mice, and the ascitic leukemia L1210/S2, by i.p. injection of $1 \times 10^6$ cells into female C57BL/6 $\times$ DBA/2 F1/Bom (specific pathogen free) mice.

Treatment Schedules. In the first dose-finding study and in the subsequent study to determine the ED50 in rats with DMBA-induced mammary tumors, the daily total dose of test compound was split into halves and administered p.o. by gavage at 8 a.m. and 3 p.m. for 42 consecutive days. In all other studies the drugs were administered p.o., once daily for the periods of time as indicated in the figures. Rats and mice with transplantable solid or ascites tumors were treated with CGS 16949A twice daily for 10 consecutive days, starting 24 h after tumor transplantation.

Test Parameters. During both the treatment and follow-up periods, rats with DMBA-induced mammary tumors were monitored weekly; body weights and the number of tumors were recorded. The size of the tumors was estimated by comparison with graded plastic balls and expressed in units of volume. In some experiments, 5 rats per group were sacrificed at the end of the treatment period, and the majority of the tumors appeared 5 to 7 wk after DMBA administration. The estrogen-independent mammary carcinoma 2661/61 was transplanted by i.m. injection of 0.1 ml of tumor homogenate (1:10 in Hanks' solution), respectively, into the animals' left flank. The estrogen-independent mammary carcinoma 2661/61 was transplanted by i.m. injection of 0.1 ml of tumor homogenate into the left hind leg of female CBA/Rij mice, and the ascitic leukemia L1210/S2, by i.p. injection of $1 \times 10^6$ cells into female C57BL/6 $\times$ DBA/2 F1/Bom (specific pathogen free) mice.

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Test Parameters. During both the treatment and follow-up periods, rats with DMBA-induced mammary tumors were monitored weekly; body weights and the number of tumors were recorded. The size of the tumors was estimated by comparison with graded plastic balls and expressed in units of volume. In some experiments, 5 rats per group were sacrificed at the end of the treatment period, and the remainder were maintained to the end of the follow-up period. At the end of the follow-up period, all the remaining animals were autopsied (in the control and some treatment groups, all animals did not survive through to the end of the follow-up period due to large tumor loads resulting in variable numbers of animals which could be evaluated at the end of the experiment). In some experiments, the tumors were excised and weighed along with the ovaries, uterus, adrenals, and liver. In the dose-finding study, blood was obtained retroorbitally under light ether anesthesia from all animals on Day 28 of the treatment schedule. Approximately 300 µl of blood were collected into heparinized tubes, and the plasma was separated by centrifugation and stored frozen at -20°C. Plasma estradiol concentrations were determined by a direct radioimmunoassay (estradiol radioimmunoassay kit; EIR, Würenlingen, Switzerland). Rats surviving after long-term treatment with CGS 16949A for 27 wk were sacrificed by decapitation immediately after cessation of treatment. Trunk blood was collected for determination of hematological and blood chemistry parameters.

Statistical Analysis. Data obtained in experiments with DMBA-induced mammary tumors were analyzed using a software package developed at the SAS Institute, Inc., Raleigh, NC (23, 24). Differences in mean tumor volumes were analyzed for significance by the Dunnett t test (25).

Results

Effects in Rats Bearing DMBA-induced Mammary Tumors. In a dose-finding study, randomized groups of animals were treated p.o. with each CGS 16949A at daily doses of 1.0, 2.0, 4.0, and 8.0 mg/kg or with vehicle at 0.5 ml/100 g of body weight. After the 42-day treatment period all doses caused an almost complete regression of tumors and suppressed the appearance of new tumors. Since the effects were maximal at all doses, no dose-response relationship could be observed. Eight to 10 days after cessation of treatment, tumor regrowth was observed in all animals (Fig. 2). The drug was well tolerated and caused no side-effects. Significantly increased body weights in the CGS 16949A-treated rats were observed, probably as a consequence of estrogen deprivation (Fig. 3). On Day 28 of the treatment schedule, blood was collected retroorbitally from all animals, and plasma estradiol concentrations were determined by radioimmunoassay. Serum estradiol was found to be significantly reduced ($P < 0.05$) as compared to controls in all the treatment groups (control = $18.4 \pm 3.3$; 1 mg/kg = $11.9 \pm 0.5$; 2 mg/kg = $12.0 \pm 0.5$; 4 mg/kg = $11.4 \pm 0.3$; 8 mg/kg = $11.5 \pm 0.7$ pg/ml). Just as with the effects on the mammary tumors, no dose dependency could be shown, as it appeared that a maximal effect on lowering serum estradiol was achieved even with the lowest dose.

To determine the ED50 for the antitumor effect of CGS 16949A, the same experiment as above was repeated using lower doses ranging between 0.05 and 1.0 mg/kg. The magnitude of the effect of 1.0 mg/kg seen in the first experiment could be reproduced. The ED50 was estimated to be about 0.1

\[ \text{Mean Tumor Volume (cc)} \]

- Control
- 1.0 mg/kg p.o.
- 4.0 mg/kg p.o.
- 2.0 mg/kg p.o.

\[ \text{Mean Body Weight (g)} \]

- Control
- 1.0 mg/kg p.o.
- 4.0 mg/kg p.o.
- 2.0 mg/kg p.o.
mg/kg/day; 0.05 mg/kg had no significant effect on tumor growth (Fig. 4).

Under the same experimental conditions, aminoglutethimide given p.o. in doses of 10, 30, and 100 mg/kg inhibited the growth of existing tumors only marginally (Fig. 5), caused only a few complete and partial tumor regressions, and weakly suppressed the appearance of new tumors, even at the maximally tolerated dose. In parallel, vaginal smears showed that the estrus cycle of the treated animals was undisturbed, even at the highest dose tested (data not shown). At the end of the treatment period, immediately after the last drug administration, 10 of 20 of both the drug-treated and control rats were sacrificed. Uterine weights of the aminoglutethimide-treated rats were only marginally lower (not statistically significant) than those of vehicle-treated control rats. This finding, along with the marginally increased body weights, was another indication of the relatively poor efficacy of aminoglutethimide in this model.

A 42-day p.o. treatment course of mammary tumor-bearing rats with the antiestrogen tamoxifen showed results which were comparable to those achieved with aminoglutethimide. No activity was observed when 0.1 mg/kg of test compound were given for 42 consecutive days. The tumor growth inhibition achieved in rats treated with 0.3 to 3.0 mg/kg was not dose related (Fig. 6). Partial regression of tumors was seen, and the mean number of new tumors per rat was reduced less than 50% compared with that of controls.

The effects of CGS 16949A, aminoglutethimide, and tamoxifen on the regression of palpable DMBA-induced mammary tumors and on the suppression of newly appearing tumors after a 6-wk treatment period are summarized in Table 1.

To evaluate whether DMBA-induced mammary tumors responding to a first treatment with CGS 16949A would respond again after regrowth following cessation of treatment, a second treatment schedule with CGS 16949A was initiated. Twenty-one days after cessation of the first 42-day p.o. treatment schedule with 0.1, 0.5, and 1.0 mg/kg/day, rats bearing regrown tumors were randomized into a treatment and a control group (n = 22 each). Despite the large size (up to 4-cm diameter) of regrown tumors (median, 6 tumors/rat) at the start of the second 42-day treatment course, 2.0 mg/kg of CGS 16949A again significantly reduced the mean tumor volume (Fig. 7).

Continuous long-term p.o. treatment with 2.0 mg of CGS 16949A/kg for 27 wk of rats bearing DMBA-induced mammary tumors caused complete regression of tumors and totally suppressed the appearance of new tumors. This pronounced effect of CGS 16949A is also reflected in a significant prolongation of survival time (Fig. 8). The last survivor of 15 vehicle-treated control rats died 25 wk after the start of the experiment due to a large tumor burden. In the group treated with 2.0 mg/kg of CGS 16949A, only 1 of 15 rats died bearing a large, presumably hormone-independent tumor. Two other drug-treated rats which died for unknown reasons had no tumors, though an injury by the stomach tube during drug administration could not be excluded. All survivors from this experiment were sacrificed at the end of the 27-wk treatment period. Since all vehicle-treated control rats died before the end of the experiment, a comparison between control and CGS 16949A-treated rats was not possible. The values for hematological parameters including WBC, RBC, platelets, hemoglobin, and hematocrit were all in the normal range as described by Ringler et al. (26).

The same was true for biochemical constituents of serum including glucose, urea nitrogen, creatinine, bilirubin, total serum protein, iron, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and D-glutamyltransferase (data not shown). All animals tolerated this long-term treatment very well with no overt signs of sedation or other side-effects being observed.

Effects on Hormone-independent Tumors. The pronounced activity of CGS 16949A against estrogen-dependent DMBA-
ANTITUMOR EFFECTS OF A NONSTEROIDAL AROMATASE INHIBITOR

Table 1 Effects of continuous p.o. treatment with CGS 16949A, aminoglutethimide, and tamoxifen on regression of established and suppression of new DMBA-induced mammary carcinomas in female Sprague-Dawley rats at the end of 6 wk of treatment

The number of tumors which showed complete regression, partial regression, stabilization, or progression is expressed as a percentage of the number of tumors present at the start of treatment in each of the groups.

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<th>Compound</th>
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<th>No. of tumors at start of treatment</th>
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<th>PR (%)</th>
<th>SD (%)</th>
<th>P (%)</th>
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* CR, complete regression, tumors not palpable; PR, partial regression, reduction of 51-99% of initial size; SD, stable disease, no change; P, progression, larger than 10->100% of initial size.

DISCUSSION

The primary aim of this study was to evaluate the antitumor effects of CGS 16949A on estrogen-dependent DMBA-induced mammary tumors in female Sprague-Dawley rats and to compare the effects of this compound with those of another aromatase inhibitor aminoglutethimide and of the antiestrogen tamoxifen. The DMBA-mammary tumor model resembles human breast cancer in its histology (27, 18), response to surgical ablative therapy (29), and hormonal therapy (30) and is widely used for evaluation of antitumor effects of endocrine agents (31, 33). However, it should be emphasized that the DMBA-mammary tumor model uses intact cycling rats which are able to correct suppressions in circulating estradiol concentrations by compensatory increases in gonadotrophins achieved through a functional feedback system. Thus the endocrine characteristics of this model are more comparable to those seen in premenopausal rather than postmenopausal women.

The present study demonstrates that the new nonsteroidal aromatase inhibitor CGS 16949A markedly and dose-dependently not only inhibits growth but also causes more than 80% regression of palpable DMBA-induced mammary tumors and suppresses almost totally the appearance of new tumors during
the treatment period. The reduced levels of circulating estradiol found in drug-treated rats could be taken to indicate reduced ovarian estrogen production probably caused by inhibition of ovarian aromatase; however, further studies involving the measurement of ovarian aromatase activity in drug-treated animals will be necessary to confirm this hypothesis. The marked anti-tumor efficacy of this drug was also shown by the fact that not only small but also large (up to 4-cm diameter) multiple and pretreated mammary tumors responded to subsequent treatments. The efficacy of aminoglutethimide and tamoxifen was clearly lower; at maximally tolerated doses the former achieved efficacy which, even at doses about the ED50 dose of CGS 16949A. These results are in accord with the findings of Wing et al. (34) who also observed only marginal effects on tumor growth, uterine weights, and serum estradiol levels in tumor-bearing rats with aminoglutethimide. Furthermore, when compared with 4-hydroxyandrostenedione (a steroidal aromatase inhibitor), CGS 16949A seems to be more efficacious. Wing et al. (34) reported that a daily s.c. dose of 50 mg/kg of 4-hydroxyandrostenedione resulted in a 75% reduction in total tumor volume. However, their data are expressed in such a way that a direct comparison is not possible. Nevertheless, it was found here that 2 mg/kg was a maximally effective dose with CGS 16949A, 4-hydroxyandrostenedione has at best 1/25 the potency of CGS 16949A. This compares well with in vitro potency estimates reported recently by Bhatnagar et al. (35). They showed that CGS 16949A was about 10 to 15 times more potent than 4-hydroxyandrostenedione in vitro. CGS 16949A thus is a highly efficacious antitumor agent against estrogen-dependent mammary tumors whose efficacy is probably related to its high in vitro and in vivo potency as an aromatase inhibitor.

Besides the marked efficacy and high potency, CGS 16949A was also seen to be well tolerated at therapeutically effective doses in tumor-bearing female Sprague-Dawley rats. No mortality was observed during a 27-wk uninterrupted treatment period. The blood chemistry values stayed in the range of normally observed values, and the weight gain which was observed in drug-treated animals can be explained to have occurred by estrogen deprivation (36).

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