Antitumor Efficacy in Rats of CGP 19984, a Thiazolidinedione Derivative That Inhibits Luteinizing Hormone Secretion

Margot M. Ip, Paul W. Sylvester, and Lotte Schenkel

Department, Pharmaceuticals Division, CIBA-GEIGY, Ltd., CH-4002 Basel, Switzerland

ABSTRACT

The antitumor efficacy and the hormonal effects of the thiazolidinedione derivative [sodium methyl[3-methyl-2,5-methyl-3-(2-methylallyl)-4-oxo-2-thiazolidinyldiene]hydrazono]-4-oxo-5-thiazolidinyl(phosphate), CGP 19984, have been studied in vivo rat prostatic and mammary cancer models. CGP 19984 significantly inhibited growth of the androgen-dependent Dunning R3327 rat prostate adenocarcinoma. Concomitant with tumor inhibition, a significant decrease in circulating luteinizing hormone and testosterone levels was observed, suggesting that the antitumor effects of drug treatment resulted primarily from inhibition of luteinizing hormone release and subsequently decreased testosterone synthesis. Drug treatment had little effect on serum prolactin or corticosterone levels. Animals showed no adverse effects from CGP 19984 except for a modest loss of body weight. In female rats, growth of the estrogen-independent MTW-9B rat mammary tumor was also inhibited by CGP 19984 and uterine weight and tumor progesterone receptor levels were reduced. The latter suggests that CGP 19984 treatment decreases circulating estrogen in female rats. However, the inhibitory effect of CGP 19984 on the growth of the MTW-9B tumor does not appear to be mediated by the action of the drug to lower estrogen levels, since this tumor is not dependent on estrogen for growth, and lower doses of CGP 19984 were found to be equally effective in reducing uterine weight, but had no antitumor activity. The ability of CGP 19984 to suppress gonadal function and to inhibit tumor growth suggests that this drug may have potential clinical application in the treatment of both hormone-dependent and-independent prostate and breast cancers.

INTRODUCTION

CGP 19984 is a derivative of thiazolidinedione (sodium methyl[3-methyl-2,5-methyl-3-(2-methylallyl)-4-oxo-2-thiazolidinyldiene]hydrazono]-4-oxo-5-thiazolidinyl(phosphate) (Fig. 1) which has been shown to cause regression of the hormone-dependent DMBA-induced rat mammary tumor (2). In addition, moderate activity was demonstrated in vivo against a series of autonomous tumors, including the Walker 256 and colon 26 carcinomas, the R3230 AC mammary tumor [an estrogen-responsive, although estrogen-independent (3) tumor], and the Hardy-Passey melanoma (2). Inhibition of proliferation of several human cell lines in vitro has also been demonstrated (2). A predecessor drug to CGP 19984, the thiazolidinedione derivative GP 48989 (5-methyl-3-(2-methylallyl)-2-[3-methyl-4-oxo-2-thiazolidinyldiene]hydrazono]-4-thiazolidinone), was shown to inhibit the DMBA-induced mammary tumor, inducing regression of both estrogen-dependent (4) and estrogen-independent (5) forms of the tumor. In the former case it was suggested that GP 48989 caused tumor regression through an inhibition of gonadotropin release (6).

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1 This work was supported in part by a grant from CIBA-GEIGY, Ltd., Basel, Switzerland. A preliminary report of this work was presented at the Thirteenth International Congress of Chemotherapy in Vienna (1).

2 To whom requests for reprints should be addressed.

3 The abbreviations used are: LH, luteinizing hormone; LHRH, luteinizing hormone releasing hormone; DMBA, 7,12-dimethylbenz(a)anthracene; NIAID, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases.

In view of the combined activity of these thiazolidinedione derivatives against both hormone-dependent and -independent tumors, the hypothesis was advanced that these derivatives might be effective agents in the treatment of breast and prostate cancers. Both types of cancer are heterogeneous in nature, and contain both hormone-dependent and -independent cell types. Relapse after endocrine therapy as the result of the outgrowth of hormone-independent cells, still remains a serious problem. Therefore, treatments which suppress growth of both hormone-dependent and -independent tumor cells should be more effective in inhibiting breast and prostate cancer than are treatments which act strictly as antihormonal agents. CGP 19984 was selected for further study because of its greater solubility than that of GP 48989.

The tumor models used in the experiments reported herein were the transplantable Dunning R3327 rat prostate adenocarcinoma and the MTW-9B rat mammary tumor. The former is a well-differentiated, slow-growing, androgen-dependent tumor that is histologically and histochemically similar to human prostate cancer (7, 8). It is composed of both hormone-dependent and -independent cells, with the former predominating, at least initially (7, 8). The tumor is responsive to castration (8), pharmacological doses of estrogens (8), the antiestrogen tamoxifen (9), as well as to LHRH agonists (10) and antagonists (11). The MTW-9B transplantable mammary tumor (12) grows in syngeneic Wistar-Furth rats. It is estrogen- and prolactin-dependent, as evidenced by the lack of effect of ovariectomy or hypophysectomy on its growth rate. The MTW-9B tumor also does not respond to tamoxifen therapy (13). However, the estrogen receptor in the tumor appears to be functional since synthesis of the progesterone receptor is dependent on the presence of estrogen (14). The studies reported in this paper demonstrate the effectiveness of CGP 19984 in inhibiting growth of both the androgen-dependent R3327 prostate tumor and the estrogen-independent MTW-9B mammary tumor.

MATERIALS AND METHODS

Animals and Tumors. Male Copenhagen X Fischer F1 rats bearing bilateral implants of the androgen-dependent well-differentiated R3327 Dunning rat prostate adenocarcinoma were kindly provided by Dr. Norman Altman of the Papanicolaou Cancer Research Institute in Miami, FL. Female Wistar-Furth rats were purchased from Harlan Sprague-Dawley (Indianapolis, IN), and were transplanted by trocar with the MTW-9B mammary tumor. Rats were housed in a temperature-controlled room with a 12-h light, 12-h dark, or 14-h light, 10-h dark schedule, and were fed rat chow (Teklad, Inc., Madison, WI) and water ad libitum.

Drug Preparation. CGP 19984 was supplied by CIBA-GEIGY, Ltd., Basel, Switzerland. It was dissolved in a vehicle of aqueous 0.5% carboxymethylcellulose (prostate experiments and mammary tumor experiment 3) or in aqueous 20% propylene glycol-0.5% carboxymethylcellulose (mammary tumor experiments 1 and 2). The drug was prepared fresh once or twice per week at concentrations of 5 or 50 mg/ml for the 25-mg/kg or 250-mg/kg dosage schedules, respectively. Each rat received 0.5 ml/100 g body weight of drug or vehicle, p.o., on a schedule of 5 times a week.

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CGP 19984: PROSTATE AND MAMMARY TUMORS

Table 1. Effect of CGP 19984 treatment in intact male Copenhagen-Fischer rats bearing the R3327 prostate adenocarcinoma

<table>
<thead>
<tr>
<th>Treatment period (wk after transplant)</th>
<th>N</th>
<th>Tumor wt (g)</th>
<th>Seminal vesicle wt (g)</th>
<th>Serum testosterone (ng/ml)</th>
<th>Carcass wt (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>12</td>
<td>3.19 ± 0.70 (14)</td>
<td>1.05 ± 0.09 (8)</td>
<td>3.36 ± 0.93 (8)</td>
<td>372 ± 12 (8)</td>
</tr>
<tr>
<td>CGP 19984</td>
<td>10</td>
<td>0.60 ± 0.15 (16)</td>
<td>0.23 ± 0.02 (8)</td>
<td>0.19 ± 0.05 (7)</td>
<td>307 ± 8 (8)</td>
</tr>
<tr>
<td>Control</td>
<td>13-26</td>
<td>26.3 ± 3.1 (15)</td>
<td>0.67 ± 0.04 (8)</td>
<td>1.51 ± 0.20 (8)</td>
<td>397 ± 12 (8)</td>
</tr>
<tr>
<td>CGP 19984</td>
<td>10</td>
<td>10.1 ± 1.3 (20)</td>
<td>0.46 ± 0.06 (10)</td>
<td>0.64 ± 0.08 (10)</td>
<td>390 ± 8 (10)</td>
</tr>
<tr>
<td>Control</td>
<td>14-25 and 18-29</td>
<td>4.43 ± 1.22 (11)</td>
<td>0.70 ± 0.05 (8)</td>
<td>ND*</td>
<td>346 ± 9 (8)</td>
</tr>
<tr>
<td>CGP 19984</td>
<td>10</td>
<td>2.42 ± 0.75 (16)</td>
<td>0.22 ± 0.02 (9)</td>
<td>ND</td>
<td>305 ± 5 (9)</td>
</tr>
<tr>
<td>Control</td>
<td>27-38</td>
<td>2.45 ± 0.74 (19)</td>
<td>0.65 ± 0.04 (10)</td>
<td>1.94 ± 0.19 (10)</td>
<td>407 ± 7 (10)</td>
</tr>
<tr>
<td>CGP 19984</td>
<td>11</td>
<td>0.81 ± 0.12 (17)</td>
<td>0.24 ± 0.02 (9)</td>
<td>0.32 ± 0.07 (9)</td>
<td>329 ± 6 (9)</td>
</tr>
</tbody>
</table>

* The dose of CGP 19984 used in all these experiments was 250 mg/kg, p.o., 5 times a week.

† Number of rats per group at initiation of therapy.

‡ Rats were implanted bilaterally with the R3327 tumor. The tumor weight value represents the average weight of each tumor in the group.

§ Mean ± SE.

∥ Numbers in parentheses, number of rats.

© Statistically different from corresponding control, P < 0.05.

‡ Rats were from 2 different transplant dates and were equally divided between the 2 groups.

∗ ND, not determined.

![Fig. 1. Structure of CGP 19984. The chemical name of this drug is sodium methyl][3-methyl-2-[5-methyl-3-(2-methylallyl)]-4-oxo-4-thiazolidinyl][hydrazono]-4-oxo-5-thiazolidinyl||phosphate. In some formulations, the sodium is replaced by ethanolammonium.](image)

Experimental Protocol. Four experiments were done with intact rats bearing the R3327 prostate adenocarcinoma and one with prostate tumor-bearing rats castrated or sham castrated 1 day prior to initiation of CGP 19984 therapy. The R3327 tumor contains a heterogeneous cell population and shows a variable growth rate from transplant to transplant. The time at which CGP 19984 treatment was started in each of the 5 experiments was based on average tumor size rather than on time after transplant. In 4 of the experiments, treatment was initiated when the average tumor diameter was 3.5–5 mm; in the other (Table 1, experiment 2), average tumor diameter was 10 mm at start of therapy. The effects of CGP 19984 were tested in tumors of fast (Table 1, experiment 2), slow (Table 1, experiment 4), and average (Table 1, experiment 2-4) in tumors of varying growth rate. The range of tumor growth inhibition in all 4 experiments was between 45 and 81%.

Hormone Assays. The effect of CGP 19984 therapy on serum levels of testosterone, LH, prolactin, and corticosterone was determined at several time periods after initiation of therapy in castrated and sham-castrated rats bearing the prostate tumor. Blood was obtained by orbital sinus puncture under light ether anaesthesia at 0, 2, 4, 8, and 12 weeks, and after decapitation at 15 weeks. The effect of CGP 19984 therapy on serum testosterone was also determined in intact rats, from blood taken after decapitation. In all experiments, blood was collected between the hours of 9 and 11 a.m.

Serum testosterone levels were measured in duplicates of 100 μl using the method of Schwartz and Justo (15). Testosterone antiserum directed against testosterone-11-BSA (GDN No. 250) was kindly provided by Dr. G. D. Niswender of Colorado State University, and [1,2,6,7,16,17-3H]testosterone (specific radioactivity, 135 Ci/mmol) was purchased from New England Nuclear (Boston, MA). Serum LH levels were measured in 50- and 100-μl aliquots using the NIADDK rat LH kit (National Hormone and Pituitary Program, Baltimore, MD) and were expressed as ng/ml in terms of NIADDK rat LH-RP-1. Serum prolactin levels are expressed as ng/ml in terms of NIADDK rat prolactin-RP-3. Serum corticosterone was measured using the procedure described by Henning (17), with [1,2,6,7-3H]corticosterone (105 Ci/mmol) purchased from New England Nuclear. This assay is based on corticosterone binding to rat corticosteroid-binding globulin.

Receptor Assays. Mammary tumors were removed, weighed, and frozen in liquid nitrogen. They were stored at −80°F until receptor assay within 2 weeks. Steroid receptors were measured in the cytosol according to methods described previously (14, 18). Estradiol and dihydrotestosterone receptor were assayed using a single saturating concentration of 10 nm; progesterone receptor was assayed using a single saturating concentration of 20 nm. Protein in the cytosol was determined according to the procedure of Lowry et al. (19).

RESULTS

Effect of CGP 19984 on Growth of the Dunning R3327 Rat Prostate Adenocarcinoma in Intact Rats. The effect of CGP 19984 on growth of the prostate tumor was examined at a single dose of 250 mg/kg administered p.o., 5 times a week for 13 weeks. Growth of the tumor was markedly inhibited in animals treated with CGP 19984 (Fig. 2). At sacrifice, tumors from the treated group were only 19% of the size of those from the control group (Table 1, experiment 1). This inhibitory effect was confirmed in 3 additional experiments (Table 1, experiments 2-4) in tumors of varying growth rate. The range of tumor growth inhibition in all 4 experiments was between 45 and 81%.

No toxicity was apparent during treatment, except for some
loss in body weight (Table 1) varying between 2% (experiment 3) and 19% (experiment 4). Serum testosterone concentrations were markedly reduced, with an inhibition ranging between 54 and 94% in 4 separate experiments. Reflecting this decrease, seminal vesicle weights were also decreased by CGP 19984 in all experiments. There was no decrease in levels of androgen receptor in the tumor upon CGP 19984 treatment, with concentrations of $63.8 \pm 7.3$ (SE) ($n = 12$) and $71.0 \pm 5.7$ (SE) ($n = 15$) fmol/mg protein in control and CGP 19984-treated groups, respectively (data from tumors of rats in experiment 4).

Effect of CGP 19984 on Growth of the Dunning R3327 Rat Prostate Adenocarcinoma in Castrated Rats. It has previously been demonstrated that 10–30% of the cells within the R3327 tumor are androgen independent, and as a result, relapse is eventually observed after castration (8). Since CGP 19984 has previously been shown to be active in vitro and effective against the hormone-independent R3230 AC mammary tumor in vivo (2), it was considered possible that CGP 19984 might have activity against both the androgen-dependent and -independent cell populations within the R3327 prostate tumor. To test this, rats bearing the R3327 tumor were castrated or sham castrated, and 1 day later treatment with CGP 19984 or vehicle was initiated. As can be seen in Fig. 3, both CGP 19984 and castration inhibited growth of the tumor. The combination of both appeared to be most efficacious. Although tumors in this group did not regress, growth did not exceed 25% over the 15 weeks of treatment. Statistically, however, the tumor growth curves of the castrated, castrated plus CGP 19984, and sham castrated plus CGP 19984 groups were not different.

Table 2 shows the effect of CGP 19984 on tumor weight as well as on the relative weights of various tissues and organs determined at necropsy. In the intact rat, the relative weights of the seminal vesicles and epididymus were significantly decreased by CGP 19984 treatment; the weights of the testes, thyroid, anterior pituitary, adrenals, thymus, and liver were not significantly different. In the castrated rat, thyroid and liver relative weights were increased by CGP 19984 treatment. Carcass weights were significantly decreased by CGP 19984 in both sham-castrated and castrated rats; however, the decrease in tumor weight in sham-castrated rats treated with CGP 19984 was still statistically significant when tumor weights were expressed per 100 g carcass weight. The body weights of the rats throughout the experiment are presented in Fig. 4.

Effect of CGP 19984 on Serum Concentrations of LH, Testosterone, Prolactin, and Corticosterone in Castrated and Sham-Castrated Male Rats. The effect of CGP 19984 on plasma hormone concentrations was determined in the castrated and

Table 2: Effect of CGP 19984 in castrated and intact male Copenhagen-Fischer rats bearing the R3327 prostate adenocarcinoma

<table>
<thead>
<tr>
<th>Tumor wt</th>
<th>Control</th>
<th>CGP 19984</th>
<th>Control</th>
<th>CGP 19984</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham-castrated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g</td>
<td>2.94 ± 0.76*</td>
<td>0.44 ± 0.35*</td>
<td>0.41 ± 0.22</td>
<td>0.39 ± 0.22</td>
</tr>
<tr>
<td>mg/100 g</td>
<td>799 ± 200</td>
<td>136 ± 77</td>
<td>112 ± 58</td>
<td>123 ± 69</td>
</tr>
<tr>
<td>Carcass wt (g)</td>
<td>371 ± 16</td>
<td>321 ± 77</td>
<td>353 ± 11</td>
<td>298 ± 88</td>
</tr>
<tr>
<td>Seminal vesicle wt (mg/100 g)</td>
<td>158 ± 6</td>
<td>103 ± 11</td>
<td>29 ± 3</td>
<td>35 ± 3</td>
</tr>
<tr>
<td>Testes wt (mg/100 g)</td>
<td>864 ± 19</td>
<td>873 ± 23</td>
<td>15.5 ± 0.6</td>
<td>15.1 ± 0.9</td>
</tr>
<tr>
<td>Epididymus wt (mg/100 g)</td>
<td>309 ± 15</td>
<td>255 ± 9</td>
<td>48.1 ± 3.6</td>
<td>43.0 ± 4.6</td>
</tr>
<tr>
<td>Thyroid wt (mg/100 g)</td>
<td>8.9 ± 0.7</td>
<td>7.7 ± 0.5</td>
<td>7.4 ± 0.2</td>
<td>9.2 ± 0.6</td>
</tr>
<tr>
<td>Anterior pituitary wt (mg/100 g)</td>
<td>2.5 ± 0.2</td>
<td>2.9 ± 0.2</td>
<td>3.1 ± 0.3</td>
<td>3.1 ± 0.2</td>
</tr>
<tr>
<td>Adrenal wt (mg/100 g)</td>
<td>16.1 ± 0.7</td>
<td>16.5 ± 0.7</td>
<td>15.5 ± 0.6</td>
<td>15.1 ± 0.9</td>
</tr>
<tr>
<td>Thymus wt (mg/100 g)</td>
<td>28.8 ± 22</td>
<td>31.8 ± 3.7</td>
<td>48.1 ± 3.6</td>
<td>43.0 ± 4.6</td>
</tr>
<tr>
<td>Liver wt (g/100 g)</td>
<td>3.2 ± 0.11</td>
<td>3.6 ± 0.2</td>
<td>2.6 ± 0.1</td>
<td>3.9 ± 0.1</td>
</tr>
</tbody>
</table>

* CGP 19984 was administered at a dose of 250 mg/kg, p.o., 5 times a week.
* Mean ± SE. Sample size is 14, 9, 12, and 12 for the tumor weights in the sham-castrated control and CGP 19984-treated groups, respectively. For all other weights, sample size is 7, 6, 6, and 6 for the 4 groups, respectively.
* Statistically different from the corresponding control, $P < 0.05$.
* All tissue weights are expressed per 100 g carcass weight.
Serum LH levels were significantly reduced in rats treated with CGP 19984 (Fig. 5). Two weeks after initiation of therapy, serum LH was decreased in sham-castrated rats to 11% of control values. LH levels remained suppressed in CGP 19984-treated rats for at least 1 month after the start of treatment, but thereafter there appeared to be a slow rise, with LH concentrations increasing to 38% of control at 8 weeks, 51% of control at 12 weeks, and 60% of control at 15 weeks. In castrated rats, LH concentration showed the characteristic increase in the weeks following castration to levels approximately 10-fold higher than those observed in intact rats. Strikingly, in castrated rats treated with CGP 19984, LH concentrations were reduced to 6–10% of the castrated control values for at least 3 months after initiation of therapy.

In response to the decreased levels of LH, serum testosterone levels also showed a marked reduction following CGP 19984 therapy (Table 3). Two weeks after the start of treatment, testosterone was reduced to 14% of control levels in intact rats, and at 4 and 8 weeks, the levels were below the minimum detectable in the assay. At later time periods, parallel to the increase of LH, testosterone concentrations began to rise again, reaching levels of 24 and 46% of control, respectively, at 12 and 15 weeks.

Figs. 6 and 7 show the concentrations of serum prolactin and corticosterone, respectively, at various times during treatment. Although there appear to be some changes at particular time points, no consistent pattern is evident with either hormone, and it appears as if CGP 19984 has no major effect on either prolactin or corticosterone.

Effect of CGP 19984 on Growth of the MTW-9B Mammary Tumor. Since previous data had suggested that CGP 19984 had cytotoxic or cytostatic activity (2), the drug was also tested in vivo against the MTW-9B rat mammary tumor. Fig. 8 shows that the 250-mg/kg dose of CGP 19984 partially inhibited the growth of the MTW-9B mammary tumor in 3 separate experiments. This inhibition was observed independent of the time of initiation of drug administration and did not appear to be a nonspecific effect resulting from loss of body weight (Table 4).

Interestingly, uterine weight was decreased by both doses of CGP 19984 (Table 4), suggesting that estrogen levels are reduced by this treatment. Further evidence for this is given by the fact that tumor progesterone receptor levels were reduced from 62.3 ± 10.3 fmol/mg protein (n = 11) in the control to 34.4 ± 10.5 (n = 6) and 26.7 ± 6.1 (n = 9) fmol/mg protein in the 25- and 250-mg/kg CGP 19984 treatment groups, respectively (Fig. 8, experiment 2). Tumor levels of estrogen and androgen receptor were measured, but were not significantly altered by either dose of CGP 19984 (data not shown).

DISCUSSION

The results presented here demonstrate that the orally active thiazolidinedione derivative, CGP 19984, effectively inhibits growth of the androgen-dependent R3327 rat prostate adenocarcinoma. Concomitant with this tumor inhibition, serum LH and testosterone concentrations were decreased, suggesting that CGP 19984 is acting via a chemical castration. The ability of CGP 19984 to decrease circulating testosterone concentration most likely results from inhibition of testosterone synthesis by the testes, secondary to a decreased circulating LH. It is unlikely that CGP 19984 affects the testes directly, since in this case LH levels would be elevated because of the loss of negative feedback, as is seen in castration. Additionally, a marked effect of CGP 19984 on serum LH was also noted in rats whose testes had been removed (Fig. 5).

Table 3 Effect of CGP 19984 on serum testosterone concentration in intact and castrated Copenhagen-Fischer male rats at various times after initiation of therapy

<table>
<thead>
<tr>
<th>Serum testosterone (ng/ml) at following times after start of treatment</th>
<th>Sham-castrate</th>
<th>Sham-castrate + CGP 19984</th>
<th>Castrate</th>
<th>Castrate + CGP 19984</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 wk</td>
<td>2.40 ± 0.46</td>
<td>1.51 ± 0.20</td>
<td>2.97 ± 0.92</td>
<td>3.32 ± 0.76</td>
</tr>
<tr>
<td>2 wk</td>
<td>1.86 ± 0.28</td>
<td>0.21 ± 0.05</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>4 wk</td>
<td>2.69 ± 0.54</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>8 wk</td>
<td>1.56 ± 0.31</td>
<td>0.37 ± 0.14</td>
<td>1.03 ± 0.41</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>12 wk</td>
<td>2.26 ± 0.65</td>
<td>0.37 ± 0.14</td>
<td>1.03 ± 0.41</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>15 wk</td>
<td>0.37 ± 0.14</td>
<td>1.03 ± 0.41</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

* Mean ± SE of 6–10 rats per group.
* * Significantly different than sham-castrated control (P < 0.01).
Our results also demonstrate that CGP 19984 has moderate activity against the estrogen-independent MTW-9B rat mammary tumor. This finding, in conjunction with the report of Schieweck et al. (2) that the drug shows activity against a variety of hormone-independent tumors in vivo and of human cell lines in vitro suggests that CGP 19984 has cytostatic or cytotoxic activity as well as hormonal activity. Schieweck et al. (2) have also demonstrated that CGP 19984 shows marked antitumor activity against the estrogen-dependent DMBA-induced rat mammary tumor, an effect which is probably mediated by decreased ovarian estrogen synthesis secondary to decreased LH. That estrogen levels are in fact decreased after CGP 19984 therapy is supported by our finding that uterine weight and tumor progesterone receptor levels were decreased in treated rats. However, the inhibitory effects of CGP 19984 on the growth of the MTW-9B tumor do not appear to be mediated by the action of this drug to lower estrogen levels, since lower doses of CGP 19984 were found to be equally effective in reducing uterine weight, but had no antitumor activity. Moreover, the inhibition of growth of either the MTW-9B or R3327 tumors does not appear to be the result of inhibition of body growth, since body weight loss was relatively modest in comparison with the marked antitumor activity.

LHRL antagonists and agonists, chemically quite different from CGP 19984, have been shown to inhibit growth of both

![Graph](image-url)
the Dunning R3327 prostate tumor (10, 11) and a variety of estrogen-dependent mammary tumors (20). Currently, some of the agonists are in clinical trial, where at least in the case of prostate cancer, the results to date are highly encouraging (20). The more traditional therapy for disseminated prostate cancer, which has included castration, hypophysectomy, adrenalectomy, and diethylstilbestrol administration, has been reasonably successful in retarding disease (21). The limitations and disadvantages of ablative therapy are obvious, however, and estrogen administration, while avoiding the drastic surgical procedures, has undesirable side effects, the most severe of which is an increased incidence of cardiovascular disease. Inhibitors of LH release, which have been shown to be relatively nontoxic (20), appear to be superior to the above types of hormonal therapy.

The results reported herein suggest that the thiazolidinedione derivative CGP 19984 has potential clinical application in the treatment of prostate and breast cancers through its ability to decrease serum LH concentrations. Although the mechanism by which it suppresses LH is not yet understood, CGP 19984 appears to offer a distinct advantage over LHRH agonists and antagonists since, unlike the LHRH derivatives, it is orally active.

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