

Comparison of the Effects of the New Orally Active Antiestrogen EM-800 with ICI 182 780 and Toremifene on Estrogen-Sensitive Parameters in the Ovariectomized Mouse

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ABSTRACT

The nonsteroidal antiestrogen EM-800 is approximately 10-fold more potent than ICI 182 780, the most potent known steroidal antiestrogen, at inhibiting estrone-stimulated uterine weight in ovariectomized mice (half-maximal inhibitory daily sc doses of 0.2 and 2.0 μg , respectively). At maximal doses, however, both compounds lead to a similar maximal 90% inhibition of estrone-stimulated uterine weight. A 10-fold higher activity of EM-800 compared with ICI 182 780 was also observed on estrone-stimulated vaginal weight, with maximal inhibitions of 96% and 90%, respectively, achieved by the two compounds. In addition, EM-800 injected sc or administered orally led to a marked loss of uterine and vaginal estrogen receptor levels measured by binding assay, whereas ICI 182 780 exerted no

inhibitory effect on this parameter under the experimental conditions used. Comparable effects were observed when estrogen receptor protein levels were measured by enzyme immunoassay. After oral administration, EM-800 exerted maximal 83% and 88% inhibitions of uterine and vaginal weight, respectively, whereas maximal inhibitions limited to 51% and 67% were achieved with toremifene. This limited inhibition by toremifene of the stimulatory effect of estrone on uterine and vaginal weight is probably due to the intrinsic estrogenic activity of the compound. The present data also show that the steroidal antiestrogen ICI 182 780 has less than 3% the activity of EM-800 when administered by the oral route. In fact, EM-800 administered orally is 2- to 3-fold more potent than ICI 182 780 injected sc. (*Endocrinology* **139**: 2486–2492, 1998)

ESTROGENS are recognized to play the predominant role in breast cancer development and growth (1). As the first step in the action of estrogens in target tissues is binding to the estrogen receptor (ER), a logical approach for the treatment of estrogen-sensitive breast cancer is the use of antiestrogens, or compounds that block the interaction of estrogens of all sources with the ER. Tamoxifen, the only antiestrogen widely used for the treatment of breast cancer in women, behaves as a mixed agonist/antagonist of estrogen action (2), thus potentially limiting its therapeutic potential for the treatment of breast cancer in women.

Recently, 7α -alkyl derivatives of estradiol (3–5), 11β -amidoalkoxyphenyl estradiols (6), or estradiol 7α -alkyl derivatives possessing additional changes designed to increase their affinity for the ER and/or increase their bioavailability (7–11) have been synthesized and shown to possess pure and potent antiestrogenic activity in the most rigorous *in vitro* and *in vivo* systems (3, 11), including human breast cancer cells *in vitro* (3, 7, 9, 10) and *in vivo* in nude mice (4, 8, 12, 13).

These 7α -alkyl and 11β -amidoalkoxyphenyl derivatives of estradiol, however, have low oral bioavailability, thus limiting their acceptability for the treatment of breast cancer. We have thus developed a series of even more potent estrogen antagonists that possess high oral bioavailability in the

mouse, rat, monkey, and human. The present study compares the characteristics of the new antiestrogen EM-800 (14–17) on well characterized estrogen-sensitive parameters in the mouse with the effects of ICI 182 780 (4, 12) and toremifene, an analog of tamoxifen (18–22).

Materials and Methods

Animals

Female BALB/c mice (BALB/cAnNCrIBR), approximately 50 days old and weighing 18–20 g, were obtained from Charles-River (St. Constant, Canada) and housed 4–5/cage in a temperature (23 ± 1 C) and light (12 h light/day, lights on at 0715 h)-controlled environment. The mice were fed rat chow and tap water *ad libitum*. The animals were ovariectomized (OVX) under general anesthesia (Avertin) via bilateral flank incisions and randomly assigned to groups of 9–10 animals. Ten mice were kept intact as controls.

Chemicals

EM-800 [(+)-7-pivaloyloxy-3-(4'-pivaloyloxyphenyl)-4-methyl-2-(4''-(2''-piperidinoethoxy)phenyl)-2H-benzopyran] (14) and ICI 182 780 were synthesized in the medicinal chemistry division of our laboratory. Both compounds analyzed under Good Laboratory Practice (GLP) conditions were more than 99% pure. Toremifene citrate was provided by Orion Corp. (Farmos, Finland). The structures of these antiestrogens are illustrated in Fig. 1.

Treatments

For the experiment described in Figs. 2–5, EM-800 and ICI 182 780 were injected sc once daily at different doses (0.1, 0.3, 1.0, 3.0, or 10 μg /injection), whereas in Figs. 6–9, EM-800, ICI 182 780 and toremifene were administered orally by gavage once daily at a dose of 0.3, 1.0, 3.0,

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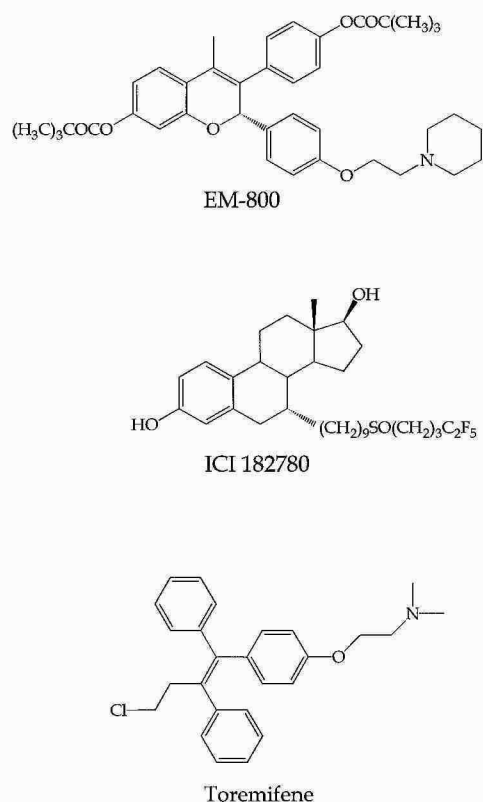


FIG. 1. Chemical structures of antiestrogens.

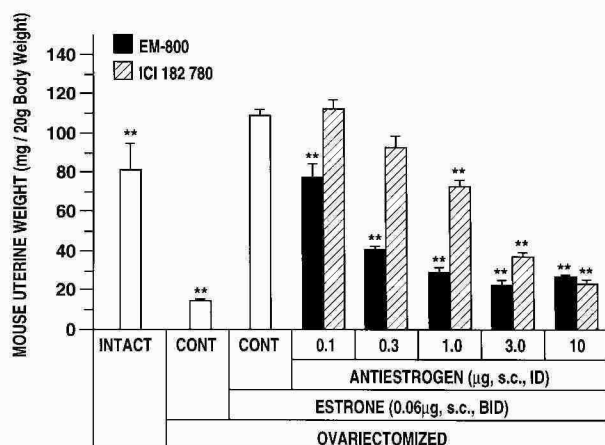


FIG. 2. Effect on uterine weight of increasing concentrations of EM-800 and ICI 182 780 injected sc for 9 days to ovariectomized mice simultaneously treated with estrone. **, $P < 0.0001$ vs. estrone-treated control.

or 10.0 μg /animal. Treatment with the antiestrogens was initiated 2 days after ovariectomy, whereas treatment with estrone (0.06 μg , sc, twice daily) was started 3 days later (5 days postovariectomy). Thereafter, estrone and antiestrogens were administered in combination for a 6-day period. Compounds were dissolved in a 50:50 (vol/vol) mixture of polyethylene glycol 600 and ethanol and administered in a 1% (wt/vol) gelatin-0.9% NaCl solution (final concentration of polyethylene glycol 600/ethanol was 8%). Mice in the intact and OVX control groups received the vehicle alone during the 9-day period. The animals were killed by cervical dislocation on the 11th morning after ovariectomy. The uteri and vagina were rapidly dissected and weighed, and then frozen in liquid nitrogen and stored at -80 C.

ER assays

Binding assay. Preparation of cytosol: Vaginal and uterine tissues were minced and homogenized at 4 C with two 10-sec bursts of a Polytron PT 10-ST (Brinkmann Instruments, Westbury, NY) in 20 vol buffer A (25 mM Tris-HCl, 1.5 mM EDTA disodium salt, 10 mM α -monothioglycerol, 10% glycerol, and 10 mM sodium molybdate, pH 7.4). For each group, three different homogenates were used, and each homogenate was prepared from a pool of two or three uteri or vaginas. The homogenates were then centrifuged at $105,000 \times g$ for 60 min at 4 C. The steroid binding assay was performed with freshly prepared cytosol. The protein concentration of cytosol was determined using the method of Bradford (23) with BSA as standard.

Estrogen binding assay: [2,4,6,7- ^3H]Estradiol (SA, 87 Ci/mmol) was purchased from New England Nuclear (Boston, MA), whereas diethylstilbestrol was obtained from Sigma Chemical Co. (St. Louis, MO). [^3H]Estradiol binding was measured using the dextran-coated charcoal absorption technique, essentially as previously described (24–27). In brief, 0.2-ml aliquots of the cytosol preparation were incubated with 0.1 ml [^3H]estradiol (final concentration, 3–5 nM) in the presence or absence of a 100-fold excess of diethylstilbestrol for 3 h at room temperature. Unbound steroids were separated by incubation for 15 min at 4 C with 0.3 ml of 0.5% Norit-A and 0.05% dextran T-70 in buffer B (1.5 mM EDTA disodium salt, 10 mM α -monothioglycerol, and 10 mM Tris-HCl, pH 7.4) and centrifugation at $3000 \times g$ for 15 min. Aliquots of the supernatant (0.3 ml) were then taken for radioactivity measurement after the addition of 10 ml liquid scintillation cocktail.

Enzyme immunoassay (ER-EIA). Preparation of cytosol: Cytosols were prepared as described for the binding assay, except that vaginal tissue was homogenized in 10 vol of a different buffer (10 mM Tris-HCl, 1.5 mM EDTA disodium salt, 1 mM α -monothioglycerol, and 5 mM sodium molybdate, pH 7.4). For each group, only one homogenate prepared from a pool of three vaginas was used.

ER-EIA assay: The ER-EIA monoclonal kit from Abbott Laboratories (Diagnostics Division, North Chicago, IL) used for this assay is an enzyme immunoassay based on the sandwich principle, using monoclonal rat antibodies. A detailed description of the method used is given in the instruction manual supplied with the kit. In brief, cytosols (100 μl) were incubated at 4 C for 18 h with antibody (rat anti-ER; D547)-coated polystyrene beads that bind ER proteins. A second antibody (rat anti-ER; H222) conjugated to horseradish peroxidase was then incubated with the beads at 37 C for 1 h to label the bound receptor. A further incubation (30 min at room temperature) of the beads with the enzyme substrate hydrogen peroxide and the color reagent/electron donor *o*-phenylenediamine-2HCl produced a phenazine polymer chromophore that was measured at 492 nm. Each incubation step was completed by washing the beads with distilled water, and the enzyme reaction was stopped by the addition of 1 N sulfuric acid. A standard curve was obtained by plotting the ER concentration of ER standards (0 and dilutions of 500 fmol/ml ER stock, supplied in the Abbott kit) vs. their absorbance.

Statistical analysis

The effects of drugs and doses were analyzed using a two-factor nested ANOVA model. When main effects were significant ($P < 0.05$), *a posteriori* pairwise comparison between the control and treated groups was performed with Fisher's least significant difference test (LS-MEANS), requiring $P < 0.01$ to declare significance. Original scale values were used to analyze the variables with normally distributed residuals and respecting the hypothesis of homoscedasticity. If not, a log or a rank transformation was applied to the measurements before analysis. The two routes of administration (sc and oral) were analyzed separately using a common intact group. All data are presented as the mean \pm SEM.

Results

To assess the relative efficacy of EM-800 and the steroidal antiestrogen ICI 182 780 under optimal conditions of bio-availability, the two compounds were first injected sc daily for 9 days, starting 2 days after ovariectomy and 3 days

before treatment with estrone. As illustrated in Figs. 2 and 3, EM-800 was approximately 10-fold more potent than ICI 182 780 in blocking the stimulatory effect of estrone (0.06 μg , sc, twice daily) on uterine (Fig. 2) and vaginal (Fig. 3) weight, respectively. The *P* values associated with the treatment and dose (treatment) nested effects are reported in Table 1 for both oral and sc routes. In fact, at the lowest daily dose used (0.1 μg or \sim 0.005 mg/kg), EM-800 caused a 33% decrease ($P < 0.0001$) in uterine weight, whereas doses of 0.3, 1.0, 3.0, and 10 μg caused respective 72%, 84%, 91%, and 87% decreases ($P < 0.0001$ for all doses *vs.* control) of estrone-stimulated uterine weight. ICI 182 780, on the other hand, had no significant effect at the two lowest doses used and caused 38%, 75%, and 90% decreases in uterine weight at doses of 1.0, 3.0, and 10 μg , respectively ($P < 0.0001$ at all doses *vs.* control).

A similar 10-fold higher activity of EM-800 compared with ICI 182 780 was observed on estrone-stimulated vaginal weight (Fig. 3). The daily 0.1- μg dose of EM-800 caused a 37% ($P < 0.0001$) inhibition of estrone-stimulated vaginal weight, whereas doses of 0.3, 1.0, 3.0, and 10 μg caused 66%, 91%, 98%, and 96% ($P < 0.0001$ for all groups *vs.* control) inhibitions of vaginal weight, respectively. ICI 182 780, on the other hand, had no detectable effect at the two lowest doses, whereas the 1.0-, 3.0-, and 10- μg daily sc doses caused respective 32%, 53%, and 90% inhibitions of estrone-stimulated vaginal weight ($P < 0.0001$ for all of these groups *vs.* control).

As illustrated in Fig. 4, treatment with EM-800 caused an almost complete loss of ER measured by binding assay in the uterus of mice supplemented with estrone. The daily 0.3- μg dose of EM-800 caused a 30% ($P < 0.01$) loss of uterine ER levels. With the daily 1.0- μg dose, a 70% loss of uterine

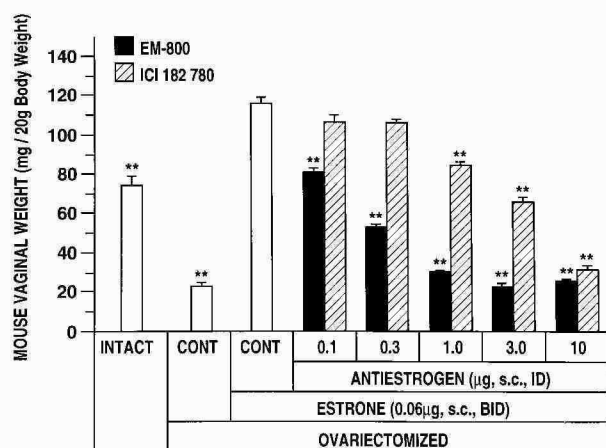


FIG. 3. Effect on vaginal weight of increasing concentrations of EM-800 and ICI 182 780 injected sc for 9 days to ovariectomized mice simultaneously treated with estrone. **, $P < 0.0001$ *vs.* estrone-treated control.

TABLE 1. *P* values associated with the treatment and dose (treatment) nested effects for both the oral and sc routes of administration

Route of administration	Source	Uterine wt	Vaginal wt	Uterine ER levels	Vaginal ER levels
sc	Treatment	<0.0001	<0.0001	<0.0001	<0.0001
	Dose (treatment)	<0.0001	<0.0001	0.0006	0.0029
Oral	Treatment	<0.0001	<0.0001	0.0010	<0.0001
	Dose (treatment)	<0.0001	<0.0001	0.0249	<0.0001

estradiol receptors from 426 ± 31 to 128 ± 14 fmol/mg protein ($P < 0.0001$) was observed, whereas further inhibition was observed at the 3.0- and 10- μg doses, thus decreasing uterine ER levels to 46 ± 3 fmol/mg protein (89% reduction; $P < 0.0001$) and 9 ± 3 fmol/mg protein (98% reduction; $P < 0.0001$), respectively. ICI 182 780, on the other hand, had no significant effect on the same parameter at the 0.3-, 1.0-, and 3.0- μg daily doses, whereas a 65% stimulation of uterine ER levels (705 ± 105 fmol/mg protein; $P < 0.001$) was observed at the highest dose used (10 μg). It can also be seen in Fig. 4 that ovariectomy increased uterine ERs from 418 ± 6 fmol/mg protein in intact animals to 1235 ± 163 fmol/mg protein ($P < 0.0001$ *vs.* intact) in ovariectomized rats, an increase that was completely reversed by the administration of estrone to ovariectomized animals.

Comparable effects were observed on vaginal ER levels measured by binding assay (Fig. 5). Thus, sc injection of 0.3, 1.0, 3.0, and 10 μg EM-800 caused 40% ($P < 0.01$), 82% ($P < 0.001$), 97% ($P < 0.0001$), and 99% ($P < 0.0001$) inhibitions of vaginal ER levels, respectively. ICI 182 780, on the other hand, had no significant effect on this parameter under the assay conditions used.

We next compared the activities of EM-800, ICI 182 780, and toremifene administered by the oral route. Whereas EM-800 caused an 18% ($P = \text{NS}$) inhibition of estrone-stimulated uterine weight at the daily oral dose of 0.3 μg (Fig. 6), doses of 1.0, 3.0, and 10 μg of the antiestrogen caused respective 46%, 71%, and 83% inhibitions of estrone-stimulated uterine weight ($P < 0.0001$ for all the three highest doses *vs.* control). Toremifene, a close analog of tamoxifen, caused 9% ($P = \text{NS}$), 25% ($P < 0.001$), 48% ($P < 0.0001$), and 51% ($P < 0.0001$) inhibitions of estrone-stimulated uterine weight at the 0.3-, 1.0-, 3.0-, and 10- μg doses, respectively. The only significant inhibitory effect of ICI 182 780, namely a 21% inhibition ($P < 0.01$), was observed at the highest dose used (10 μg daily), indicating at least a 30-fold lower activity of this compound compared with that of EM-800.

The daily oral administration of EM-800 led to respective 10% ($P = \text{NS}$), 38%, 64%, and 88% inhibitions of vaginal weight ($P < 0.0001$ for the three highest doses used *vs.* control) at the 0.3-, 1.0-, 3.0-, and 10- μg doses (Fig. 7), whereas ICI 182 780 exerted no significant inhibitory effect on this parameter. Toremifene, on the other hand, caused 4% ($P = \text{NS}$), 24%, 52%, and 67% inhibitions of vaginal weight at the 0.3-, 1.0-, 3.0-, and 10- μg doses, respectively ($P < 0.0001$ for the three highest doses used *vs.* control).

As illustrated in Fig. 8, only oral administration of the highest dose of EM-800 led to a significant decrease in uterine ER levels measured by binding assay (58% reduction; $P < 0.01$), whereas ICI 182 780 and toremifene had no effect on this parameter at any of the doses used.

Finally, as shown in Fig. 9, vaginal ER levels measured by

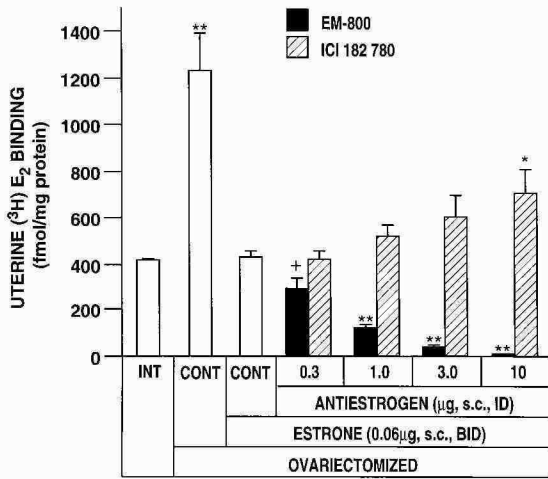


FIG. 4. Effect on uterine ER levels of increasing concentrations of EM-800 and ICI 182 780 injected sc for 9 days to ovariectomized mice simultaneously treated with estrone. +, $P < 0.01$; *, $P < 0.001$; **, $P < 0.0001$ (vs. estrone-treated control).

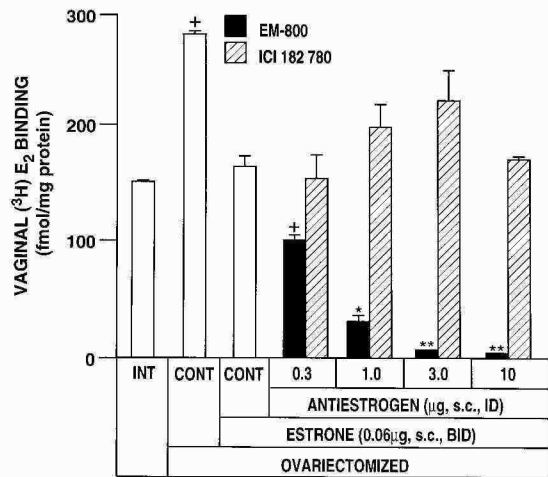


FIG. 5. Effect on vaginal ER levels of increasing concentrations of EM-800 and ICI 182 780 injected sc for 9 days to ovariectomized mice simultaneously treated with estrone. +, $P < 0.01$; *, $P < 0.001$; **, $P < 0.0001$ (vs. estrone-treated control).

binding assay decreased from 157 ± 12 fmol/mg protein in estrone-treated rats to 123 ± 5 fmol/mg protein ($P = NS$) in animals treated with the 0.3- μ g daily dose of EM-800, whereas daily treatment with the 1.0-, 3.0-, and 10- μ g doses reduced vaginal ER levels to 89 ± 0.1 fmol/mg protein (43% reduction; $P < 0.0001$), 87 ± 10 fmol/mg protein (45% reduction; $P < 0.0001$), and 30 ± 4 fmol/mg protein (81% reduction; $P < 0.0001$), respectively. Toremifene, on the other hand, caused 36% ($P < 0.001$), 21% (NS), 47% ($P < 0.0001$), and 45% ($P < 0.0001$) inhibitions of vaginal ER levels at daily doses of 0.3, 1.0, 3.0, and 10 μ g, respectively. ICI 182 780 had no significant effect on vaginal estradiol receptor levels under the experimental conditions used.

To ensure that the down-regulation of ER levels observed with EM-800 does not result from a failure of [3 H]estradiol to exchange with EM-800 [or its metabolite(s)], we evaluated the effects of treatments with EM-800, ICI 182 780, and

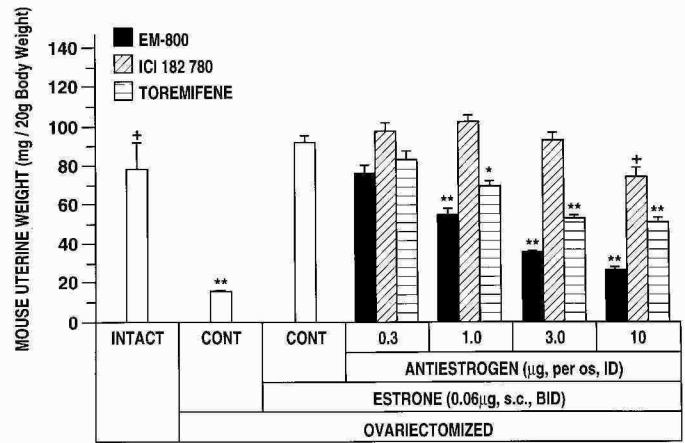


FIG. 6. Effect on uterine weight of increasing concentrations of EM-800, ICI 182 780, and toremifene administered orally for 9 days to ovariectomized mice simultaneously treated with estrone. +, $P < 0.01$; *, $P < 0.001$; **, $P < 0.0001$ (vs. estrone-treated control).

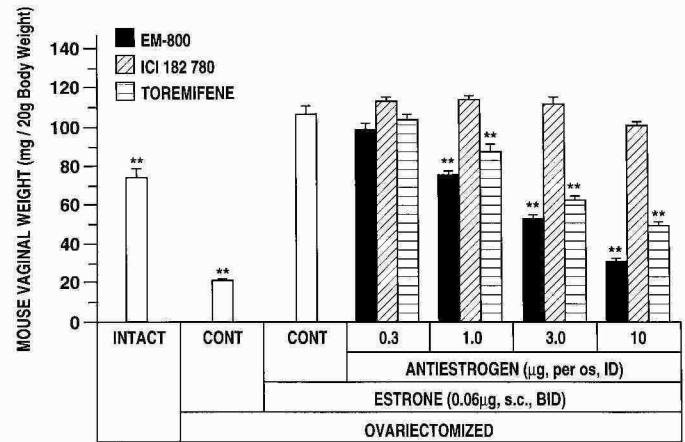


FIG. 7. Effect on vaginal weight of increasing concentrations of EM-800, ICI 182 780, and toremifene administered orally for 9 days to ovariectomized mice simultaneously treated with estrone. **, $P < 0.0001$ (vs. estrone-treated control).

toremifene (administered orally) on vaginal ER protein levels measured by ER-EIA. As shown in Table 2, treatment with increasing doses of EM-800 inhibited vaginal ER protein levels by 26%, 40%, and 71% at daily doses of 1.0, 3.0, and 10 μ g, respectively. As measurements of ER protein levels by EIA were performed on a pooled tissue homogenate, no statistical analysis could be performed. In animals treated with ICI 182 780, only a small 10–11% decrease in vaginal ER protein levels was observed at doses ranging from 1–10 μ g, whereas treatment with toremifene caused a 27% inhibition of this parameter only at the highest dose used (10 μ g).

Discussion

The present data show that EM-800 administered under conditions of maximal bioavailability (sc) is approximately 10 times more potent than ICI 182 780, the most potent of the known steroidal antiestrogens (4, 5, 12, 28, 29) previously studied in phase II clinical trials (4, 12, 30). In fact, a similar difference in the estimated potencies were obtained when the effects of the two antiestrogens were measured on estrone-

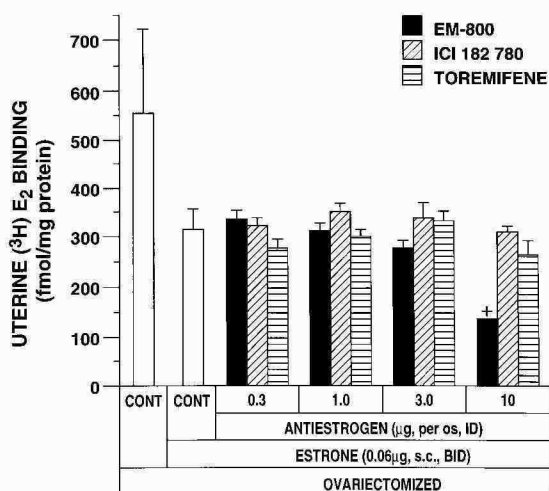


FIG. 8. Effect on uterine ER levels of increasing concentrations of EM-800, ICI 182 780, and toremifene administered orally for 9 days to ovariectomized mice simultaneously treated with estrone. +, $P < 0.01$ (vs. estrone-treated control).

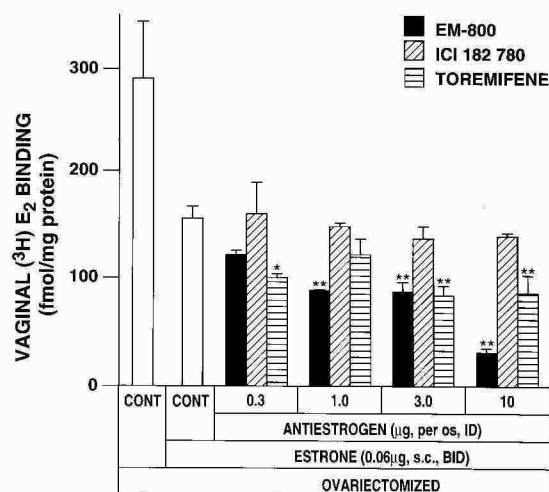


FIG. 9. Effect on vaginal ER levels of increasing concentrations of EM-800, ICI 182 780, and toremifene administered orally for 9 days to ovariectomized mice simultaneously treated with estrone. *, $P < 0.001$; **, $P < 0.0001$ (vs. estrone-treated control).

stimulated uterine and vaginal weights in ovariectomized mice. To eliminate the potential problem of variable absorption of the two compounds, both antiestrogens were initially administered by sc injection, a route of administration likely to lead to optimal exposure to the drugs.

In addition, the present data confirm the low oral bioavailability of the steroidal antiestrogen ICI 182 780 (4, 5). Although much higher doses of ICI 182 780 would need to be used to achieve an accurate assessment of the potency of this antiestrogen by the oral route, the present data indicate that ICI 182 780 has less than 3% the activity of EM-800 after oral administration.

On the other hand, the intrinsic estrogenic activity of toremifene, a close analog of tamoxifen (19, 20), is likely to be responsible for the limited maximal ability of this compound to reverse the stimulatory effect of estrone on mouse uterine and vaginal weight. In fact, the maximal inhibitory

TABLE 2. Vaginal estrogen receptor levels measured by enzyme immunoassay (ER-EIA) after oral administration for 9 days of increasing doses of EM-800, ICI 182 780, and toremifene to ovariectomized mice supplemented with estrone

Treatment	ER levels (fmol/mg protein)
OVX (control)	414
OVX + E ₁	238
OVX + E ₁ + EM-800 (1 µg)	175
OVX + E ₁ + EM-800 (3 µg)	143
OVX + E ₁ + EM-800 (10 µg)	69
OVX + E ₁ + ICI 182 780 (1 µg)	211
OVX + E ₁ + ICI 182 780 (3 µg)	212
OVX + E ₁ + ICI 182 780 (10 µg)	216
OVX + E ₁ + toremifene (1 µg)	262
OVX + E ₁ + toremifene (3 µg)	240
OVX + E ₁ + toremifene (10 µg)	173

Ovariectomized mice receiving the vehicle alone were used as additional controls.

effect achieved with the daily 10-µg dose of toremifene on uterine weight is limited to about 51% compared with an inhibitory effect of 83% observed for EM-800 at the same dose. The maximal inhibitory effects achieved by toremifene and EM-800 on vaginal weight at the highest dose used (10 µg) were 67% and 88%, respectively ($P < 0.0001$ between the two compounds). Thus, in addition to its lower potency to neutralize the stimulatory effect of estrone, toremifene at high doses exerts a lower maximal inhibitory effect than can be achieved with EM-800. This situation is analogous to that observed with tamoxifen.

Tamoxifen has long been known not to completely prevent binding of estrogen to the ER (31, 32). In agreement with the present *in vivo* data, the pharmacology of toremifene has been found to be similar that of tamoxifen (33, 34). In the mouse uterus, toremifene has relatively potent estrogenic activity, whereas its estrogenic activity is weaker in the rat uterus (18, 33). Tamoxifen and toremifene have also shown cross-resistance in the clinic (35).

It can be seen in the present study that the maximal inhibitory effects of EM-800 and ICI 182 780, administered sc, are of similar magnitude, namely 87% and 90% inhibitions of estrogen-stimulated uterine weight and 96% and 90% inhibitions of estrogen-stimulated vaginal weight, respectively. In the rat, at the highest dose used (1 mg/kg-day), treatment with ICI 182 780 for 14 days led to a 92% inhibition of uterine weight compared with the effect of ovariectomy (5). Such data are in agreement with the present finding of a 90% inhibition at the daily 0.5 mg/kg-dose. As mentioned above, the present data achieved with EM-800 and ICI 182 780 are very different from those observed with tamoxifen and toremifene, where the maximal inhibition obtained on uterine weight is about 50%, whereas it is limited to 67% for vaginal weight. As mentioned above, the much lower maximal blockade of estrogen action on these two parameters by tamoxifen and toremifene can be explained by the intrinsic estrogenic activity of these two compounds.

The present study shows that a half-maximal inhibitory effect of estrogen action on mouse uterine weight by ICI 182 780 administered sc is obtained at a dose of 2–3 µg/day or 0.1–0.2 mg/kg-day. These data can be compared with a half-maximal inhibitory dose of 0.5 mg/kg obtained in a recent

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