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TREATMENT OF EXPERIMENTAL BREAST CANCER WITH NEW ANTI-PROGESTINS (ORG31710, ORG31806)

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We have used two new antiprogestins ORG31710 and ORG31806 in a 3-week treatment of rats bearing DMBA-induced mammary tumors. Dosages used were: 0.4, 1 and 2.5 mg/kg, twice daily p.o. The ORG31806 dosages caused inhibition of tumor growth by 38% (not significant), 90% ($p<0.004$) and 78% ($p<0.008$), respectively. However, increasing ORG31710 dosages caused not only tumor inhibition by 82% ($p<0.008$), but also tumor remission by 20% and 19% (both $p<0.001$), respectively. With the exception of the lowest dosage of ORG31806, its higher dosages caused significantly increased plasma levels of prolactin (PRL) and estradiol (E_2). In contrast, no effect of ORG31710 treatment was found on E_2 levels, whereas PRL plasma levels were significantly increased only after treatment with the highest dosage ($p<0.005$; 2.5 mg/kg). Effects of treatment on organ weights of the pituitary, adrenals, ovaries and uterus were also investigated. It was found that treatment with these antiprogestins resulted in increased pituitary weight of 29% (highest dosage ORG31710; $p<0.0001$) and 46% (highest dosage ORG31806; $p<0.001$). Treatment with the highest ORG31806 dosage (2.5 mg/kg) gave rise to increased uterine weight (17%; $p<0.01$). In conclusion, treatment with relatively low doses of these new antiprogestins resulted in strong tumor inhibition, and even in tumor remission. The endocrine effects appear promising in sense of negligible antiglucocorticoid side-effects.

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EFFECTS OF LONG TERM ORAL TREATMENT WITH RU486 ON UNRESECTABLE MENINGIOMA

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Since meningiomas are often progesterone receptor positive, we studied treatment of this tumor with the progesterone receptor blocker RU486. 14 patients (8 female/6 male) with median age 54 (range 23-80) years received 200 mg daily for median 12 (range 2-26) months. 5 patients had minor objective regression accompanied in 3 cases by subjective improvement. Side effects included fatigue (11), hot flashes (5), gynecomastia (3), and partial alopecia (2). Menses ceased in 2/2 premenopausal patients. Cortisol rose from basal level (mean $\pm$ SEM) 13.12 $\pm$ 1.69 to 26.48 $\pm$ 3.84 ug/dl ($p=0.004$) due to the antiglucocorticoid properties of RU486. Other endocrine changes included increase in TSH from basal level 1.93 $\pm$ 0.40 to 4.37 $\pm$ 0.72 mIU/ml ($p=0.0003$) and corresponding decrease in T4 from basal level 5.77 $\pm$ 0.43 to 4.47 $\pm$ 0.44 ug/dl ($p=0.006$). No significant change in androstenedione, testosterone, or progesterone was seen. Thus RU486 has activity against meningioma. However chronic RU486 treatment results in additional endocrine alterations.

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RESPONSE OF MENINGIOMA TO MIFEPRISTONE

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Meningiomas contain progesterone receptors. Growth of meningioma might be stimulated by progesterone, whereas mifepristone (anti-progestational drug) inhibits tumour growth in vitro. We treated two patients with recurrent, inoperable meningiomas with mifepristone 200 mg/day for 6 months and 400 mg/day for the next 6-8 months. Dexamethasone was administered because of glucocorticoid receptor blocking activity. Patient 1 (46 yr) had a fast growing left medial sphenoid wing meningioma infiltrating the sellar area, the right cavernous sinus and the posterior fossa causing brainstem compression. Besides hypopituitarism she has a diminished visual acuity, partial paralysis of N 3, 4, 5, and 6 of the left side and temporal visual field defect on the right side. During treatment her wellbeing improved, while tumour growth on CT scan appeared less. Neurological defects remained stable. Visual field and acuity decreased less. After withdrawal of mifepristone the clinical and neurological situation deteriorated with a significant tumour growth on CT scan. Patient 2 (51 yr) has a tuberculum sellae meningioma with en-plaque extension into the optical canals with impaired vision of the right and blindness of the left eye. During treatment deterioration of vision stopped or slowed down. After stopping mifepristone visual field and acuity decreased markedly. In both patients no side effects of mifepristone were found. We conclude that mifepristone, stopping or slowing down growth of meningioma in our patients, may be of value in treatment of recurrent, inoperable meningiomas.

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IMPORTANCE OF ESTRONE SULFATASE IN HORMONE-DEPENDENT AND HORMONE-INDEPENDENT HUMAN MAMMARY CANCER CELL LINES.

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Estrogen sulfates are quantitatively the most important form of estrogens in breast cancer tissues. Estrone sulfate (E_1-S) accounts for 250-2800 pg/-tissue (n=10) and estradiol sulfate for 150-2100 pg/g. These values are 3-6 times those of the corresponding unconjugated estrogens. Estrone sulfate is largely converted to estradiol (E_2) in the hormone-dependent mammary cancer cell lines (MCF-7, T47D) and various anti-estrogens (Tamoxifen and derivatives), the full anti-estrogen ICI 164,384 as well as progesterone, decrease very significantly the level of E_2 originated from E_1-S. On the other hand, after incubation of the hormone-independent mammary cancer cell lines (MDA-MB-231 or MDA-MB-436) with [^{3}H]-E_1-S, very little of the radioactive material was associated with the cell and no effect was observed with the various anti-estrogens. The data indicate that the estrone sulfatase activity is very low in these cell lines. However, after homogenization of cells, the sulfatase activity (Vmax or Km) is similar to, or more intense than, that in the hormone-dependent cells, suggesting different mechanisms (or co-factors) for the estrogen sulfatase activity in breast cancer.

In conclusion, estrogen sulfates can play an important biological role in breast cancer and the control of estrone sulfatase activity can open new possibilities in the treatment of this disease.