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PYRIDOGLUTETHIMIDE: A New Aromatase Inhibitor.
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Aminoglutethimide [3-(4-aminophenyl)-3-ethylpiperidine--2,6-dione, AG] is widely used in the treatment of estrogen-dependent metastatic breast carcinoma. However, together with its desired aromatase inhibitory activity, AG also inhibits the cholesterol side-chain cleavage enzyme, desmolase,necessitating concomitant hydrocortisone therapy. AG is extensively converted into the inactive metabolite N-acetylAG, whilst also stimulating its own metabolism to N-hydroxyAG. AG also possesses dose-limiting CNS toxicity.

In an attempt to develop a more specific and metabolically stable aromatase inhibitor we have undertaken a chemical synthesis programme for analogues of AG. Of the compounds tested to date in our in vitro aromatase and desmolase assays, pyridoglutethimide [3-ethyl-3-(4-pyridyl)--piperidine-2,6-dione, PyG] was found to be a specific and potent inhibitor of aromatase. In the rat and the rabbit PyG shows more favourable pharmacokinetics than AG, exhibiting good bioavailability together with a prolonged plasma half-life ($t_{\frac{1}{2}}$ rat = 6 h, $t_{\frac{1}{2}}$ rabbit = 16.4 h). PyG is less extensively metabolised than AG with only the N-oxide (inactive vs aromatase) being detected to date (rat, rabbit, human).

Since PyG does not possess the CNS toxicity associated with AG, is more specific in action, undergoes less adverse metabolism and exhibits well maintained plasma levels, this new compound may be useful as an improved therapy for hormone-dependent breast cancer.

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INHIBITION OF HUMAN PLACENTAL AROMATASE AND RAT PROSTATIC 5α-REDUCTASE BY 4-FLUOROANDROSTENEDIONE
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The aromatase and 5α-reductase enzymes are respective target enzymes for the development of drugs to treat hormone dependent breast and prostate tumours. The most effective in vitro inhibitors of aromatase activity are analogues of the endogenous substrate, androstenedione. Clinical studies with 4-hydroxyandrostenedione (4-OHA), a potent irreversible inactivator of the aromatase enzyme have been encouraging. We have now identified 4-fluoroandrostenedione as a potent (apparent Ki of 15 nM, compared with 43 nM for 4-OHA) reversible inhibitor of aromatase activity in microsomes from human placentae. Both steroids were tested on rats bearing the nitrosomethylurea (NMU) induced mammary tumour. There was a 67% response rate with 4-OHA and a 44% response rate with 4-fluoroandrostenedione. In addition, 4-fluoroandrostenedione is a strong in vitro inhibitor of the 5α-reductase enzyme from rat prostatic tissue (apparent Ki = 0.48 μM, progesterone, under similar conditions, has a Ki value of 0.41 μM). In conclusion, 4-fluoroandrostenedione, as an inhibitor of steroidogenic enzymes, may be useful in treating hormone dependent tumours.

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PHARMACOKINETICS AND METABOLISM OF MEDROXYPROGESTERONE ACETATE (MPA) IN PATIENTS WITH ADVANCED BREAST CANCER.
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To study the pharmacokinetics and metabolism of MPA, radioactive MPA (100 μCi) was administered intravenously or orally to three patients with advanced breast cancer. Serum samples were drawn sequentially and the total radioactivity measured in serum, in an ether extract, and in the residual aqueous phase.

After intravenous injection the ether extract contained only MPA and showed a three-phasic disappearance curve, which indicated that MPA was distributed in three compartments. In the initial phase the halflife of MPA was less than 5 min, thereafter the slope of the curve showed a halflife of approximately 45 min. In the third phase the curves revealed halflifes of 4 to 7 hours, an apparent distribution volume of 241.7 ± 32.3 litre, and a metabolic clearance rate of 735.9 ± 205.8 litre/day (mean ± SD).

The radioactivity in the aqueous phase rose rapidly and was higher than in the ether extract within 15 min. Treatment of the aqueous phase with β-glucuronidase gave rise to a compound which with TLC cromatography and crystallization to constant specific activity was identified as MPA. This strongly suggests that a major metabolite of MPA following i.v. administration was a glucuronide of the 3-enol form of MPA.

After oral administration the total radioactivity in serum increased rapidly and reached a plateau after approximately two hours, at a level of 0.8-1.0% of the total dose/litre serum. More than 90% of the total radioactivity could not be extracted by ether, and treatment with β-glucuronidase and subsequent TLC demonstrated a metabolite slightly more polar than MPA. TLC of the ether extract also revealed a slightly more polar metabolite in addition to MPA. The metabolites have not been further characterized.

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ESTROGEN TREATMENT OF HUMAN ENDOMETRIAL ADENOCARCINOMA HETEROTRANSPLANTED TO NUDE MICE.
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Eight weeks old oophorectomized nude mice with heterotransplanted human endometrial carcinomas (estrogen receptor positive ER^+ and progesterone receptor negative PgR^-) were treated in the 8th passage with 8 mg/kg Estraduring (R) (Polyestradiol phosph) in group 1. Group 2 0,8 mg/kg Estradurin (R) (Polyestradiol phosph) and group 3 normal saline as control Tumor volume was measured 2 times weekly. Fourteen days after the start of treatment the tumor growth ingroups 1 and 2 was inhibited up to day 36 compared to group 3. At that day cytosol ERc, nuclear estrogen receptor (ERn), PgR and H^3TdR incorporation into DNA were analysed.

	Median ER_k fmol/mg DNA	Median ER_c fmol/mg DNA	DNA incorp median	Median PgR fmol/mg DNA
Tumor in passage 7	20	900	178	-
Group 1	48,5	770	112	1350
Group 2	21	1100	156	290
Group 3	20	1100	181	-

Estrogen treatment increased ER_k and decreased ER_c levels in heterotransplantated adenocarcinoma corporis uteri and in these may PgR to be induced. H_3thymidin incorporation to DNA decreased.
These changes seem to be dose dependent.