41

AROMATASE INHIBITORS IN THE TREATMENT OF BREAST AND PROSTATIC CANCER

M. Dowsett
Dept. of Biochemical Endocrinology, Royal Marsden Hospital, London SW3 6JJ, United Kingdom.

Numerous aromatase inhibitors are under development for breast cancer treatment. The major aims are to obtain a drug which at its dose of maximum efficacy has no effect on other endocrine systems, has no clinical side-effects and is convenient to administer. During the early clinical stages of development detailed endocrine and pharmacokinetic analyses are a valuable aid in the establishment of a drug's selectivity and its optimum dose, route and frequency of administration. The optimal dose may be defined as the minimum that will achieve maximal and sustained suppression of aromatase activity. This has generally been measured indirectly by comparing the suppression of plasma oestrogen levels at a selection of dosages. This approach has major advantages in speeding dose selection for therapeutic clinical trials. However, it also has some disadvantages including the unproven assumption that clinical response has a direct relationship with the degree of oestrogen suppression. In addition there are technical difficulties of analysis, of wide variability in endocrine response between patients and of demonstrating oestrogen suppression to be equivalent between doses (necessary to show maximal suppression). The direct measurement of aromatase inhibition in vivo by isotopic infusion analysis provides support to these indirect estimates. Its value will be shown by our recent results with CGS16949A. The additional value of collating pharmacokinetic and endocrine measurements is apparent from our investigations of 4hydroxyandrostenedione (4-OHA) and pyridoglutethimide. A consideration of our experience with these inhibitors may be helpful in directing the development of future agents.

Whilst the value of aromatase inhibition in breast cancer is established their value in prostatic cancer is in doubt: we have found that 4-OHA is only poorly efficacious in advanced prostatic cancer.

42

AROMATASE AND OTHER INHIBITORS IN BREAST AND PROSTATIC CANCER.

A.Brodie, C.Son, P.Banks, S.Inkster, J.Zhou.
University of Maryland, Dept. Pharmacology, School of Medicine, Baltimore, Maryland, USA.

Estrogens have an important role in regulating the growth of breast carcinomata. Synthesis of estrogens by aromatase occurs in a wide variety of tissues, including breast tumors. Thus, aromatase inhibitors could provide effective treatment by reducing estrogens produced in all tissues. We have demonstrated that 4-hydroxy-androstenedione (4-OHA) selectively inhibits aromatase in ovarian and peripheral tissues and reduces plasma estrogen levels in rat and non-human primate species. 4OHA was also found to inhibit gonadotropin levels and reduce estrogen and progesterone receptor levels in target tissues of treated animals. The mechanisms of these effects appear to be associated with the weak androgenic activity of the compound. In men, the role of estrogens in prostatic disease is unclear. Although estradiol is produced by the testis, we have not detected the presence of aromatase in prostatic tissue from patients with BPH or cancer. However, 4OHA was found to inhibit 5α-reductase to some extent but less than 4MA, N,N-diethyl-4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxyamide (L636028). Our results suggest that 4OHA may act by several mechanism which could contribute to beneficial effects in patients with hormone dependent cancers. (Supported by NIH grants CA27440 & HD13909).

43

New non-steroidal inhibitor of cytochrome P450-mediated biosynthesis

R. De Coster, W. Wouters, H. Vanden Bossche, J. Bruynseels, C.R. Bowden, R.W. Tuman, R. Van Ginckel, H. Vanderpas, D. Janssens, P. Van Rooy. and P.A.J. Janssen. Janssen Research Foundation, 2340, Beerse, Belgium and Spring House, PA 19477, USA

R 76713 is a new triazole derivative about 1000 times more potent than aminoglutethimide, the aromatase inhibitor presently used in the endocrine therapy of breast cancer. In the nanomolar range, R 76713 blocks estradiol biosynthesis in rat and human ovarian granulosa cells, human stromal cells of adipose tissue and human placenta microsomes. It is also very potent *in vivo*, completely inhibiting peripheral aromatase activity at very low doses (≤0.05 mg/kg) and ovarian estradiol production at higher doses in rats (about 1 mg/kg). Other enzymatic reactions of testicular, ovarian, glucocorticoid, mineralocorticoid and liver steroid metabolism or binding of steroids to their receptors are not at all affected by R 76713, even at concentrations at least 500-fold higher than those needed for estrogen suppression.
R 76713, to the same extent as ovariectomy, reduced the growth of estrogen-sensitive mammary adeno-carcinomas in rats (NMU, DMBA) and inhibited the appearance of new tumors.
In male volunteers, 2.5 or 5 mg of R 76713 rapidly lowered estradiol levels to the detection limit of the assay. This effect lasted for almost 24 hours. In young female volunteers, higher doses up to 2 x 20 mg were required to block estradiol biosynthesis for 24 hours. Daily administrations of both doses of 10 and 20 mg bid for 1 week reduced plasma estradiol to levels observed in postmenopausal women.

44

RELATIONSHIP BETWEEN TUMOUR AROMATASE ACTIVITY, TUMOR CHARACTERISTICS AND RESPONSE TO THERAPY;

WR Miller, Dept. of Clinical Oncology, Western General, Edinburgh EH4 2XU.

Aromatase activity has been measured in 270 human breast cancers by incubating tumour minces with [7α^{3}H] testosterone for 2h and characterizing purified oestradiol fractions by chemical derivative formation. Of the tumours, 188 (70%) showed evidence of oestrogen biosynthesis, levels varying between 0.5 and 12.5 fmol E2 produced/h/g tissue. Qualitative and quantitative relationships have been sought between aromatase activity and tumour histology, steroid receptor status, clinical characteristics of the patients, prognosis in 'early' disease and endocrine responsiveness in 'advanced' disease with the aim of defining the role and significance of local oestrogen biosynthesis within breast cancers.