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Inhibitors: Class of Drugs Used in the Off Label Treatment

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Abstract

In bone, aromatase is expressed primarily in osteoblasts and chondrocytes. Aromatase activity in cultured osteoblasts is comparable to that present in adipose stromal cells.

Keywords: Tumours; DHEA; Testosterone; Aromatases; Cytochrome; Human breast

Introduction

For both breast tumours and bone, it is likely that circulating estrogen levels are only partly responsible for the relatively high endogenous tissue estrogen levels. The circulating levels reflect the sum of local formation in its various sites. This is a fundamental concept for interpreting relationships between circulating estrogen levels in postmenopausal women and estrogen insufficiency in specific tissues. The second important point is that estrogen production in these extra-gonadal sites is dependent on an external source of C19 androgenic precursors, since these extragonadal tissues are incapable of converting cholesterol to the C19 steroid. As a consequence, circulating levels of testosterone and androstenedione as well as dehydroepiandrosterone (DHEA) and DHEA become extremely important in terms of providing adequate substrate for estrogen biosynthesis in these sites [1]. It should be pointed out that, in the postmenopausal woman, circulating testosterone and androstenedione levels are an order of magnitude greater than circulating estradiol and estrone levels. Differences in the levels of circulating androgens are likely to be important determinants for maintenance of local estrogen levels in extragonadal sites. Moreover, in men, circulating testosterone levels are an order of magnitude greater than those in postmenopausal women. In postmenopausal women, the ovaries secrete 25–35% of the circulating testosterone. The remainder is formed peripherally from androstenedione and DHEA produced in the ovaries and from androstenedione, DHEA, and DHEAS secreted by the adrenals. However, the secretion of these steroids and their plasma concentrations decrease markedly with advancing age [2]. In this context, it is appropriate to consider why osteoporosis is more common in women than in men and why it affects women at a younger age in terms of fracture incidence. We have suggested that uninterrupted sufficiency of circulating testosterone in men throughout life supports the local production of aromatase inhibitors & breast cancer therapy estradiol by aromatization of testosterone in estrogen-dependent tissues. This affords on-going protection against the so-called estrogen deficiency diseases. This appears to be important in terms of protecting the bones of men against mineral loss and also may contribute to the maintenance of cognitive function and prevention of Alzheimer's disease. A large number of aromatase inhibitors have been developed and utilised in clinical studies over the last 20 years [3]. The most successful are now being licensed mainly for breast cancer treatment. This development was prompted by the recognition that the cytochrome P450 inhibitor aminoglutethimide is an aromatase inhibitor and exerts its therapeutic effectiveness in postmenopausal women with advanced breast cancer via the inhibition of aromatase. This recognition validated aromatase as a new target for treatment of breast cancer patients with hormone-dependent disease. The widespread acceptance that aminoglutethimide was anything but a perfect drug and the need for combination with glucocorticoid led to the development of numerous new drugs. These have generally been categorised as first-, second-, and third-generation inhibitors [4]. Categorises the structures of a selection of the most prominent. Aminoglutethimide is recognised as the dominant first-generation compound. The second generation showed improved potency but either metabolic or symptomatic side effects limited the dose at which these inhibitors could be used. Therefore, overall pharmacological efficacy of the compounds was no greater than that of aminoglutethimide itself [5]. In contrast, the third-generation compounds have been found to be highly specific and well tolerated such that they have been usable at dosages that effectively obliterate the activity of aromatase. Many pathological states at least partly depend on continued estrogen stimulation and, thus, in principle, might be expected to be good targets for aromatase inhibition. However, most of these diseases (e.g., endometriosis, fibroids) are almost entirely limited to premenopausal women and are not subject to targeting with aromatase inhibitors alone. Thus, the clinical application of inhibitors has been confined almost entirely to the main estrogen-dependent disease in postmenopausal women [6]. All type 2 inhibitors have a basic nitrogen atom that allows them to interact with the iron atom of the hemeprosthetic group of the enzyme. Their specificity for inhibition of the aromatase enzyme (as opposed to the very large number of other cytochrome P450 enzymes) is determined by the other structural aspects of the drugs and the way that these allow a close fit to the substrate-binding site of aromatase. This results in high-affinity binding and limits the fit into the substrate-binding site of other enzymes.

Discussion

A full understanding of these molecular interactions has been restricted by the unavailability of a crystallized aromatase preparation for structural analysis of the inhibitor-enzyme interaction. Thus, computer-generated models have depended largely on the structural analogies that can be surmised between aromatase and the few cytochrome P450 enzymes whose structure has been determined. Use of such models has illustrated the much-better fit to the substrate-binding site of aromatase by the triazole compounds anastrozole, letrozole, and vorozole than by aminoglutethimide, with letrozole and vorozole apparently having a somewhat more complete space-filling

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effect. The potency of these drugs generally has been assessed in vitro using human placental microsomal aromatase preparations. In this type of assay, fadrozole is one of the most potent drugs known, having an IC50 of 5 nM. However, its potency in vivo has been compromised by very rapid metabolism such that its in vitro activity has not been matched in in vivo studies. Letrozole and anastrozole appear to have relatively similar IC50s to each other [7]. But when these compounds have been tested on intact cells including hamster ovarian tissue, human breast fibroblasts, and aromatase-transfected human breast cancer cells difference in effectiveness has been found, with letrozole being the more potent. The explanation for the difference in the measurements made in intact cell and cell-free systems is not clear but may be related to uptake of the respective compounds. It might be expected that the intact cell systems would more accurately predict the likely effectiveness of these compounds in the in vivo setting. Until recently, preclinical modelling of the use of aromatase inhibitors in rodents has been largely limited to premenopausal systems because rodents appear to have little peripheral aromatase activity. In these models, the aromatase inhibitors generally have been shown to have good antitumour activity on carcinogen-induced mammary tumour. However, the compounds also have had a marked effect on ovarian morphology, with the induction of multiple follicles due to the increase in gonadal stimulation from loss of estrogen feedback on the hypothalamic-pituitary axis. More recently, model systems have focused on the use of aromatase transfected human MCF7 breast cancer cells in a xenograft model employing athymic nude mice [8]. These are more representative of the situation in postmenopausal women and rely on tumour aromatase as their primary source of estrogen. Using such models, it has been possible to show the effectiveness of contemporary aromatase inhibitors and compare them with tamoxifen.

Recommendations

In general, the inhibitors show greater efficacy than tamoxifen. As always, the interpretation of these data depends on the comparative pharmacology of the compounds in the mouse and human and the degree to which the experimental tumour represents the range of biological characteristics of human breast cancer. D. Pharmacological effectiveness Peripheral Effects Two methodologies have been used to estimate the clinical pharmacological effectiveness of aromatase inhibitors. Most studies have accumulated data on the effects of the compounds on plasma estrogen levels [9]. This methodology, however, suffers from a number of deficits. First, it cannot distinguish between effects on production and those that changes in clearance may have. However, a more important issue is the limited sensitivity of plasma estrogen assays: in effect, the maximum degree of suppression that can be shown of primary estrogens levels using the most sensitive immunoassays available is about Aromatase Inhibitors & Breast Cancer Therapy 325 85%. Many assays lack the sensitivity to show even this degree of efficacy [10]. Thus, comparing results between different studies and approaches has little validity. Of substantially greater value has been application of the more complicated methodology used to measure aromatase activity directly. This involves the injection of [3 H]-androstenedione and [14C]-estrone before and during the treatment of women with the respective inhibitor. Collecting urine over a 72-hour period and establishing the [3 H]: [14C] ratio in the purified estrogen fractions allow calculation of the peripheral aromatase activity in the patient and the degree of inhibition exerted.

Conclusion

An advantage of this methodology is that the inclusion of [14C]-estrone provides an internal standard that permits better comparability of results between studies and over time.

Acknowledgement

None

Conflict of Interest

None

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