Sex Hormones and Antihormones in Endocrine Dependent Pathology: Basic and Clinical Aspects

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Editors:

Marcella Motta
Department of Endocrinology
University of Milan
Milan, Italy

Mario Serio
Endocrinology Unit
Department of Clinical Physiopathology
University of Florence
Florence, Italy

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Pure antioestrogens in breast cancer: experimental and clinical observations

R.I. Nicholson[1], J.M.W. Gee[1], C.L. Eaton[1], D.L. Manning[1], R.E. Mansel[2], A.K. Sharma[2], A. Douglas-Jones[2], M. Price-Thomas[3], A. Howell[4], D.J. DeFriend[4], N.J. Bundred[4], E. Anderson[4], J.F.R. Robertson[5], R.W. Blamey[5], M. Dowsett[6], M. Baum[6], P. Walton[7] and A.E. Wakeling[7]

[1]Tenovus Cancer Research Centre, Cardiff, UK; [2]Departments of Surgery (REM, AS) and Pathology (AD-J), UWCM, Cardiff, UK; [3]Royal Gwent Hospital, Newport, UK; [4]Withington and Christie Hospitals, Manchester, UK; [5]Department of Surgery, City Hospital, Nottingham, UK; [6]Royal Marsden Hospital, London, UK; and [7]Zeneca Pharmaceuticals, Macclesfield, UK

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Introduction

The last 10 years have seen the emergence of a new class of pharmacological agents termed pure antioestrogens (reviewed in [1]). These compounds, which were originally developed by ICI Pharmaceuticals Division in the UK, have the unique property of binding to the oestrogen receptor [2] and producing a receptor complex which lacks oestrogenic activity [3,4]. If we assume that the action of oestrogens on sensitive breast cancers favours cell proliferation and survival, and that they thereby act as a driving force for the growth and development of the disease [5], pure antioestrogens have the potential to fully negate these activities by producing a state of complete oestrogen withdrawal [6].

The perceived importance of pure antioestrogens, therefore, is as alternatives to antihormonal treatments which are designed to reduce the synthesis of oestrogens, but which currently fail to nullify oestrogenic signals arising from other sources [7,8], and as potential successors to "tamoxifen-like" antioestrogens, which although widely and successfully used in the therapy of primary and advanced disease [6], possess partial oestrogenic activity [9] which may negate aspects of their effectiveness as antitumour agents.

Since pure antioestrogens are now entering clinical development, the current paper seeks to outline some of their basic cellular and antitumour properties on human

Address for correspondence: R.I. Nicholson, Tenovus Cancer Research Centre, University of Wales, College of Medicine, Heath Park, Cardiff CF4 AXX, UK.

breast cancer cells in vitro [1,10] primarily using the lead compound ICI 164,384, and to compare this information with data derived from a phase I study of ICI 182,780 in primary breast cancer patients [11]. In each instance, emphasis will be placed on immunohistochemical data as it was our original hope that such an approach would facilitate an assessment of the degree to which pure antioestrogens were fulfilling their potential as complete antagonists of oestrogen action in clinical breast cancer and thereby aid in defining the importance of oestrogens in the regulation of breast cancer growth.

Figure 1 shows the structure of ICI 164,384 and ICI 182,780 which are 7α long-chain analogues of oestradiol. The ER binding affinity and potency of ICI 182,780 are greater than that observed for ICI 164,384 due to the substitution of the amide function by a sulphoxide group and the fluorination of the terminal chain [12]. Such differences, however, do not alter the intrinsic biological behaviour of the drugs which are identical to other pure antioestrogens, based on substitutions in the oestradiol nucleus [13,14] or nonsteroidal forms [15].

Properties of pure antioestrogens in vitro

One of the most important early observations arising from the functional disablement of ER signalling by pure antioestrogens in oestrogen-sensitive human breast cancer cell lines was that treated cells frequently became very efficiently growth-arrested [10,16,17]. This property is illustrated in Fig. 2a and shows the growth of MCF-7 cells in 10^{-9}M oestradiol in the presence or absence of a 100-fold excess of ICI

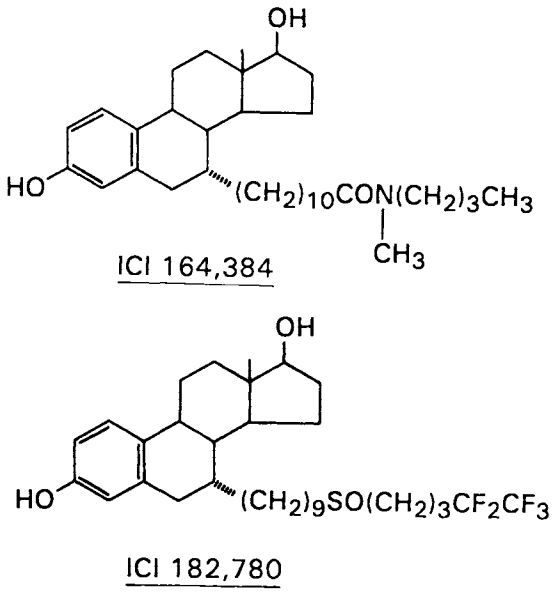

Fig. 1. Structures of ICI 164,384 and ICI 182,780.

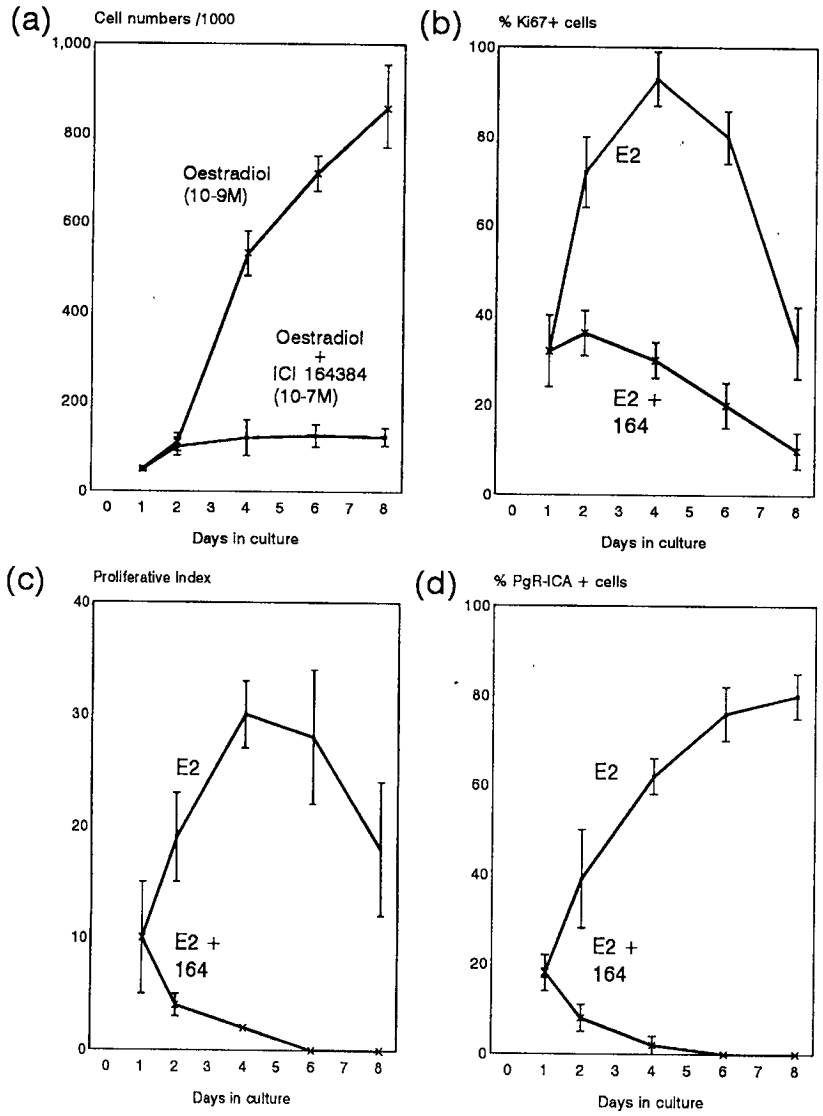

Fig. 2. Growth and immunohistochemical characterisation of MCF-7 cells. The cells were grown in white RPMI tissure culture medium with 5% DCC-stripped FCS (medium A) containing oestradiol ± ICI 164,384. (a) Cell numbers were assessed using a Coulter Counter; (b,c) Ki67; and (d) PR assays were performed according to the methods of Bouzubar et al. [19] and Walker et al. [20], respectively. The Ki67 proliferative index was calculated as the proportion of cells showing intense nucleoplasmic and nucleolar staining patterns [21]. Results are shown as the mean ± SD of six replicates.

164,384. In contrast to the expansion of the cell population that occurs in the presence of the steroid, the pure antioestrogen virtually abolishes the growth of the MCF-7 cells, allowing at best one doubling of the initial cell number with the cells

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