Short Communication

Suppression of plasma 6-keto-prostaglandin F\textsubscript{1a} and 13,14-dihydro-15-keto-prostaglandin F\textsubscript{2a} by aminoglutethimide in advanced breast cancer

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Human breast cancers have been shown to produce prostaglandins PGE\textsubscript{2} and PGF\textsubscript{2a} in vitro (Greaves et al., 1980; Rolland et al., 1980a; Bennett et al., 1980a; Dowsett et al., 1976) and raised levels are found in blood draining the tumours in patients (Stamford et al., 1980). Breast cancer explants in vitro produce osteolysis, partly by a PG-mediated mechanism (Powles et al., 1976; Bennett et al., 1975; Dowsett et al., 1976). Prostaglandins PGE\textsubscript{2}, PGF\textsubscript{2a} and prostacyclin are potent oestogenic agents in vitro (Raisz et al., 1977; Bennett et al., 1980b).

Aminoglutethimide is an effective endocrine therapy in advanced postmenopausal breast cancer producing an increased response rate in bone metastases compared with tamoxifen (Smith et al., 1981). Even patients with progressive bone metastases may have pain relief (Harris et al., 1982). Aminoglutethimide inhibits several cytochrome P450-containing enzymes, including adrenal desmolase and 11-\beta-hydroxylase (Dexter et al., 1967; Faglia et al., 1971) and peripheral aromatase (Santen et al., 1978). Metyrapone inhibits 11-\beta-hydroxylase and also prostaglandin synthetase, which is associated with cytochrome P450 (Maclouf et al., 1977). Because of the marked effects of aminoglutethimide on bone metastases and its similarity to metyrapone, we measured PG levels in patients treated with aminoglutethimide. The stable metabolites of PGF\textsubscript{2a} (13,14-dihydro-15-keto-prostaglandin F\textsubscript{2a}, PGFM) and prostacyclin (6-keto-prostaglandin F\textsubscript{1a}, 6-keto-PGF\textsubscript{1a}) were measured before and during treatment.

Twenty-eight patients with advanced postmenopausal breast cancer were treated with aminoglutethimide 250 mg × 3 daily plus replacement doses of hydrocortisone (20 mg twice daily). After 2 weeks the aminoglutethimide was increased to 250 mg × 4 daily and the hydrocortisone continued. Response was assessed by standard UICC criteria (Hayward et al., 1977), with a duration of 3 months from start of treatment required for complete or partial response and stable disease. There were 2 complete responses, 10 partial responses and 1 disease stabilisation. Fifteen patients had progressive disease. The pretreatment characteristics of the patients are shown in Table I. None of the patients had received anti-inflammatory analgesics in the month before treatment.

| Pretreatment characteristics of 28 patients treated with aminoglutethimide |
|---------------------------|---------------------------|
|                          | Responders | Non-responders |
| Age (years)              | 54 (7)      | 52 (11)        |
|                         | median 54   | 51             |
| Time since last menstrual period (years) | 6.7 (7.7) | 6.2 (6.7) |
|                         | median 5    | 5              |
| Tumour-free interval (months) | 46 (28)     | 36 (48)        |
|                         | median 51   | 24             |
| Weight (kg)              | 68 (10.5)   | 57 (6.3)       |
|                         | median 67   | 56             |
| Sites of recurrence      |             |                |
| Soft tissue/nodes        | 9           | 12             |
| Pleura/lung              | 3           | 5              |
| Bone                     | 5           | 5              |
| Liver                    | 1           | 1              |
| Previous endocrine therapy | 5           | 4              |
| Previous chemotherapy    | 2           | 1              |

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treatment. Ten ml blood samples were taken before treatment and after 1 month, and collected in tubes at 0°C containing 0.1 ml EDTA (70 mg ml⁻¹), 0.1 ml acetylsalicyclic acid (5 mg ml⁻¹ saturated solution). The samples were spun at 1500 g and stored at −20°C until assay in one batch. Samples were collected over a 6-month period, and stored for a maximum of 9 months. The samples were assayed by a new immunoassay that did not require prior extraction or chromatography (Strickland et al., 1982). Eleven patients who had simple mastectomy and involved lymph nodes had blood samples taken 6 weeks after the operation as controls.

In all but one non-responding patient with progressing liver secondaries, both 6-keto-PGF₁α and PGFM fell on treatment (Figure 1). On treatment, levels were significantly lower than in post mastectomy controls (P < 0.001). The pretreatment levels of PGs did not differ significantly from controls (Table II). The percentage suppression of 6-keto-PGF₁α was greater in both responders and non-responders than that of PGFM (Table II). The levels of PGs in patients with bone secondaries did not differ from those without clinical and radiological evidence of bone secondaries (Table II). Two other patients received flurbiprofen 200 mg 3 × daily alone and their PGFM and 6-keto-PGF₁α levels fell into the lower range of those treated with aminoglutethimide.

Table II Prostaglandin suppression in patients receiving aminoglutethimide

|       | (n) | 6KF₁α mean ± s.d. (P) | PGFM mean ± s.d. (P) |
|-------|-----|------------------------|----------------------|
| Responders (13) |   | 6K₁α: 50 ± 21 (<0.001) | PGFM: 76 ± 18 (<0.001) |
| Non-responders (15) |   | 6K₁α: 49 ± 36 (<0.001) | PGFM: 67 ± 20 (<0.001) |
| Bone secondaries (10) |   | PGFM: 134 ± 39 | PGFM: 190 ± 29 |
| No bone secondaries (18) |   | PGFM: 147 ± 52 | PGFM: 205 ± 44 |
| Controls (11) |   | PGFM: 126 ± 56 | PGFM: 198 ± 48 |

PGFM, 13,14-dihydro-15-keto-prostaglandin F₂α. P value is paired t-test comparing pre-treatment values with post treatment values of PGFM or 6KF₁α.

Aminoglutethimide and hydrocortisone produce a suppression of 6-keto-PGF₁α to 50% of basal levels. Oestrone is suppressed to the same degree by aminoglutethimide and is supposed to be the main mode of action of the drug.

All the patients were receiving a replacement dose of hydrocortisone but is is unlikely that this
caused the PG suppression. We have already shown that this dose of hydrocortisone does not change cortisol levels in patients (Harris et al., 1983) and hydrocortisone is not a potent anti-inflammatory steroid. The anti-PG effect of steroids is mediated by stimulating the release of the phospholipase A\textsubscript{2} inhibitor macrocortin/lipomodulin. \textit{In vitro}, this requires higher cortisol levels for its increased production than occurred in the patients (Blackwell et al., 1980; Hirata et al., 1980).

Tamoxifen has a direct effect on prostaglandin synthesis by human breast cancer \textit{in vitro} (Ritchie, 1980), but the concentration required to inhibit PGE production by 47\% (5 \times 10^{-5}M) was 100 times greater than the levels in plasma from patients (5 \times 10^{-7}M, Wilkinson et al., 1980). In contrast to tamoxifen, aminoglutethimide has never been reported to produce a hypercalcaemic “flare”, suggesting that the anti-PG effects of tamoxifen \textit{in vitro} may not be relevant clinically.

In many animal reproductive systems, oestrogens can stimulate PG production by the target organ, although progesterone is also required (Barcikowski et al., 1974; Robinson et al., 1976; Fenwick et al., 1977; Caldwell et al., 1972). It is possible therefore that oestrogen suppression could have produced a secondary indirect fall in PGs. If breast cancer tissue was the main source of PGs, this is an unlikely mechanism because the fall of PG levels was the same in responders and non-responders to aminoglutethimide. Other endocrine responsive organs (uterus, ovaries) are unlikely to be a major source of PGs in postmenopausal women with low basal oestrogen levels. A direct effect is most likely, similar to that produced by flurbiprofen.

Although 6-keto-PGF\textsubscript{1a} may be a useful marker in gynaecological tumours (Alam et al., 1982) and PGFM fell in bronchial carcinoma patients after surgery (Fiedler et al., 1980), these PGs are not useful markers of hormone response in breast cancer patients. The levels probably fell as the result of inhibition of prostaglandin synthesis in a wide range of tissues, including tumour. Flurbiprofen alone can relieve bone pain and reduce serum calcium and urine hydroxyproline excretion (Powles et al., 1980). The marked subjective and objective effects of aminoglutethimide with a replacement dose of hydrocortisone on bone secondaries may be due to a dual mode of action in lowering oestrone and inhibiting PG production. Aminoglutethimide with hydrocortisone appears as potent as flurbiprofen in lowering PGFM and 6-keto-PGF\textsubscript{1a} levels. Because of evidence that human breast tumours with elevated PG production may have high metastatic potential (Bennett et al., 1980a; Rolland et al., 1980b), the use of aminoglutethimide as an adjuvant endocrine therapy may be particularly useful.

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