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The Effect of Previous Endocrine Therapy on Responses to a Single Dose of an LHRH Analogue

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Summary. Serum concentrations of gonadotropins, testosterone and dehydrotestosterone were determined in patients receiving conventional endocrine therapy for advanced metastatic adenocarcinoma of prostate. The effect over 4 h of a single dose of a long acting analogue of LHRH was determined in these patients and compared to the response in patients receiving the analogues as first choice of treatment. Oestrogen therapy was found to suppress basal and stimulated gonadotropins and testicular androgens. Cyproterone therapy only partially reduced basal hormone concentrations and the response to the LHRH analogue was delayed. Orchidectomy resulted in elevated gonadotropins and an exaggerated response to the analogue. As patients who relapse while failing conventional therapy, may subsequently be treated by further endocrine manipulation, precise determination of their endocrine status should predict any expected benefit. Patients previously treated with stilboestrol are unlikely to respond to orchidectomy or LHRH analogue.

Key words: Adenocarcinoma of prostate, Endocrine therapy, LHRH analogue.

Introduction

Adenocarcinoma of the prostate has been shown to be androgen dependent with 80% of tumours responding to a reduction in circulating testosterone. The recent introduction of superactive analogues of gonadotropin releasing hormone (LHRH) has renewed interest in endocrine manipulation for this malignancy [1, 3, 11, 12]. Substitution of aminoacids at the sixth and tenth positions results in analogues of LHRH with increased potency and duration of action. These analogues are potent agonists of LHRH and the first dose results in a prompt rise in gonadotropins and testoterone [1]. However, regular daily therapy with these long acting analogues results in a paradoxical fall in serum gonadotropins. Serum testosterone has subsequently been shown to be reduced to the castrate range and this has been associated with clinical improvement [1].

Although the acute endocrine response to the analogue has now been well documented in patients not previously treated by conventional endocrine manipulation, no information is available as to the responses of serum gonadotropins or testosterone in patients previously treated by either orchidectomy, oestrogens or antiandrogens. Following relapse, additional conventional therapy or LHRH analogues [9] may be used though with little additional benefit [10]. The purpose of this study was to define the precise endocrine environment in patients treated by conventional means and to determine the effect of previous endocrine therapy on the response to a single dose of an LHRH analogue (ICI 118,30 "Zoladex") over 4 h, providing information on the potential additional benefit of a change in therapy in the management of these patients.

Patients and Methods

The endocrine response to a single dose of LHRH analogue (250 μg of ICI 118,630 "Zoladex") was determined in fourteen patients undergoing conventional endocrine therapy for adenocarcinoma of prostate. Four patients had previously undergone orchidectomy, six patients had received oestrogen therapy (Stilboestrol 3 mg daily) and four patients had been treated with an antiandrogen, cyproterone acetate. Clinically, these patients were stable and had no evidence of progression of the tumour. The responses were compared to those observed over the first 4 h in newly diagnosed patients with adenocarcinoma of the prostate in patients receiving the analogue as first choice of management [1].

Basal blood samples were taken from the patients. They then received 250 μg of LHRH analogue ICI 118,630 "Zoladex" by subcutaneous injection. Further samples were taken after 1 and 4 h.

Serum was separated and analysed for serum luteinising hormone (LH), follicle stimulating hormone (FSH), testosterone and dehydrotesterone (DHT) by specific radioimmunoassay [4, 7].

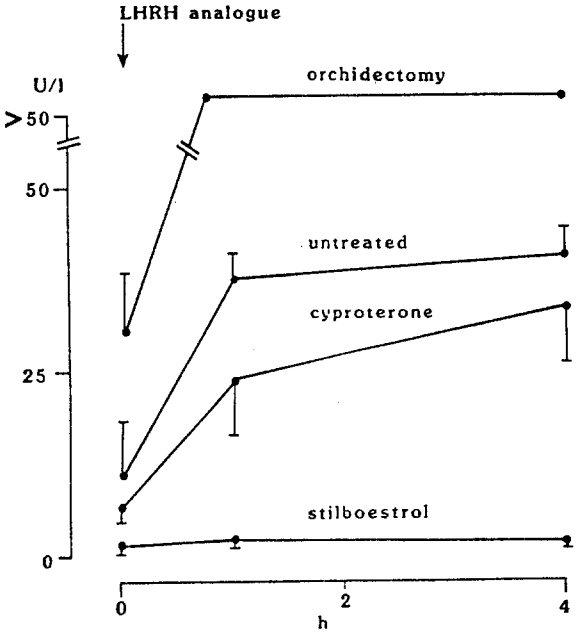

Fig. 1. Response of serum LH to single dose of LHRH agonist (ICI 118,630 "Zoladex") over 4 h, in patients previously untreated compared to patients treated with oestrogens, cyprosterone or orchidectomy. Results represent mean and standard error of the mean (SEM)

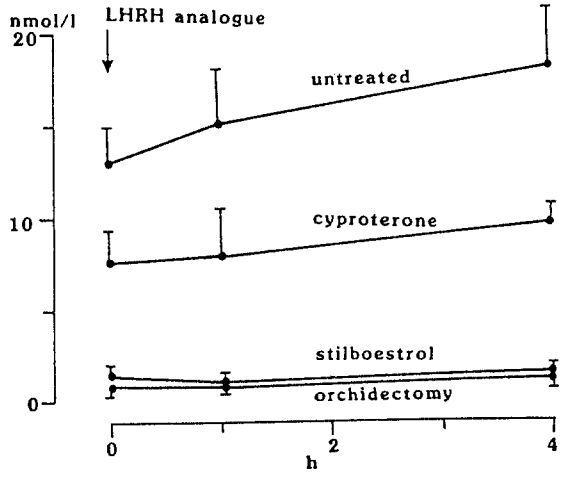

Fig. 2. Response of serum testosterone to single dose of LHRH agonist in the 4 groups of patients

Results

a) Basal Concentrations of Serum Gonadotropins

In the previously untreated patients, serum concentrations of LH were 10.4 ± 2.1 U/l and FSH concentrations were 10.1 ± 2.7 U/l. Similar concentrations were found in patients previously treated with cyproterone acetate (serum LH 7.0 ± 1.3 U/l; FSH 6.9 ± 2.8 U/l). In contrast, gonadotropin concentrations were very low in the patients previously treated with oestrogens (serum LH 1.4 ± 0.2 U/l; FSH < 1 U/1) and were elevated in patients who had previously undergone orchidectomy (serum LH 29.9 ± 6.8 U/l; FSH > 25 U/1).

b) Basal Concentrations of Testosterone

Normal testosterone and DHT concentrations were observed in the previously untreated group of patients (testosterone 13.0 ± 2.6 nmol/l; DHT 2.3 + 0.5 nmol/l). In those patients receiving antiandrogen therapy (cyproterone acetate) concentrations of testosterone were half those of the previously untreated group of patients (7.5 ± 3.0 nmol/l) whereas DHT concentrations were normal (3.0 ± 0.5 nmol/l). Testosterone concentrations were close to the detection limit of the assay in both remaining groups of patients (orchidectomy and oestrogen treated groups).

c) Response to LHRH Analogue

After a single dose of LHRH analogue the serum LH and FSH rose promptly in the patients not previously treated by endocrine manipulation. Over the first hour, concentrations of LH rose fourfold and remained elevated over the four hour test period (Fig. 1). In contrast, the response of gonadotropins was blunted and delayed in the patients previously treated with the antiandrogen, cyproterone acetate. One hour after the dose of the analogue, serum LH concentrations were 23.8 + 6.1 U/l (Fig. 1) and concentrations continued to rise over the 4 h of the test.

In the patients who had previously undergone orchidectomy, the LH response to the analogue was augmented. Oestrogen therapy completely abolished the normal rise in serum LH (Fig. 2).

Over the 4 h test period, there were no significant changes in serum testosterone and DHT in any of the groups studied.

Discussion

Analogues of LHRH or additional conventional therapy may be used in treatment of patients who relapse while receiving endocrine therapy. It is therefore important to determine the precise effect on the endocrine profile of these various forms of therapy as further endocrine manipulation will only be effective if the hormonal environment is significantly altered. This study has documented in detail the effect of endocrine therapy on serum gonadotropins and testicular androgen both basally and in response to a single dose of a superactive agonist of LHRH. The normal response was determined in a group of patients receiving the analogue as first choice treatment for advanced adenocarcinoma of prostate. The concentrations of serum gonadotropins

and testicular androgens in this group were used to compare those in patients receiving conventional endocrine therapy.

This study has demonstrated complete suppression of the pituitary-gonadal axis by treatment of patients with oestrogens. Basal concentrations of testosterone and DHT were in the "orchidectomy" range. Concentrations of gonadotropins were very low in these patients in the basal state. No rise was observed in serum LH concentrations after single dose of the LHRH analogue, in marked contrast to the untreated group where a fourfold, sustained rise in serum LH was observed. This study, therefore, predicts that patients who relapse while taking oestrogen therapy are unlikely to benefit by the addition of LHRH therapy or other similar endocrine therapy as no significant additional endocrine suppression could be achieved.

This has recently been confirmed by a detailed clinical study [9]. As the adrenal production of androgens is independent of this axis, benefits may be obtained by the addition of drugs which interfere with androgen synthesis [2].

Orchidectomy resulted in the expected elevation of both basal and stimulated gonadotropins. Serum concentrations of testicular androgens were low and showed no rise after a single dose of the LHRH analogue. Long term use of LHRH analogues would be effective in suppressing the pituitary release of gonadotropins and thus would provide additional theoretical advantages in these patients. However, the role of gonadotropins as trophic factors to adenocarcinoma of the prostate remains controversial. Only testicular production of androgens is controlled by pituitary gonadotropins; adrenal synthesis of androgens remains unaffected. Thus, unless either LH or FSH have direct actions of themselves on prostate tissue, additional use of LHRH analogues remains questionable. The combination of orchidectomy with stilboestrol therapy has been considered to be optimal treatment for metastatic prostate cancer [5].

Cyproterone therapy was found to reduce circulating testosterone, thus confirming previous reports [7]. However, in this present study, the concentration of the active metabolite of testosterone, DHT, was unaffected by treatment with cyproterone. Serum concentrations of LH were found to be reduced in these patients and the response to a single dose of the LHRH analogue resulted in a delayed and blunted rise in LH concentrations, thus providing further evidence that cyproterone at least in part has an inhibitory effect on LH release [6, 8]. In these patients, further suppression of the pituitary gonadal axis could be achieved by the addition of an LHRH analogue or stilboestrol.

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