PAPERS AND SHORT REPORTS

Advanced carcinoma of the prostate: treatment with a gonadotrophin releasing hormone agonist

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Abstract

Ten patients with advanced progressive adenocarcinoma of the prostate were treated with a long acting analogue of gonadotrophin releasing hormone. Eight of these patients responded to treatment in terms of pain relief and clinical regression of tumour. Serum gonadotrophin and testosterone concentrations were significantly suppressed by the end of the second week of treatment, testosterone concentrations being comparable with those achieved by castration. The two patients who failed to respond had both relapsed previously when receiving conventional treatment, and neither showed any endocrine response to the analogue.

Superagonists of gonadotrophin releasing hormone may be the treatment of choice in adenocarcinoma of the prostate, but further trials are required to establish long term safety and efficacy.

Introduction

Carcinoma of the prostate increases in incidence with age and is the most common cancer in men over 60.[1] Eighty per cent of tumours initially respond to lowering of the serum testosterone concentration, which may be achieved either by bilateral orchidectomy or by administration of oestrogens.[2]

Serum testosterone concentration is controlled by the hypothalamic pituitary axis. The secretion of the decapeptide gonadotrophin releasing hormone from the hypothalamus controls the anterior pituitary release of luteinising hormone and follicle stimulating hormone, which in turn control testicular production of testosterone. Secretion of gonadotrophin releasing hormone is pulsatile, and this is essential to maintain secretion of luteinising hormone and follicle stimulating hormone.[3] Continuous stimulation of gonadotrophes by long-acting agonists of gonadotrophin releasing hormone results in a paradoxical fall in concentrations of luteinising hormone and follicle stimulating hormone[4] and hence in concentrations of testosterone.[5] We evaluated one of these analogues, ICI 118,630, as a possible treatment of advanced progressive carcinoma of the prostate.

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Patients and methods

The study had prior approval of the Royal Postgraduate Medical School and Hammersmith Hospital ethics committee. Ten patients, aged 64-82, gave informed written consent to participate in the study. All had carcinoma of the prostate stage T_3 or T_4 (TNM classification[6]) confirmed histologically, and all had progressive disease. Of the 10 patients, five had relapsed or failed to respond while receiving conventional endocrine treatment. The remaining five had not previously been treated and had poorly differentiated tumours.

The gonadotrophin releasing hormone agonist ICI 118,630 was given by subcutaneous injection. For the first week of treatment the patients were in hospital and received 250 μg twice a day. The dose was then reduced to 250 μg once a day. During their stay in hospital patients were encouraged and taught to administer their own injection. After discharge they were seen weekly for the first month of treatment and fortnightly thereafter.

Response was determined by assessing the effect on each patient's need for analgesia and by the patients' own appraisal of how much the disease interfered with their daily life, determined with a scoring system. Patients were examined by one investigator (GW) before starting treatment and at six weeks and three months of treatment. At each visit they were questioned about side effects of treatment, and in particular any change in sexual activity was noted. Weight and blood pressure and results of urine analysis were recorded at each visit.

Blood was taken at each visit for measurement of full blood count; urea, creatinine, and electrolyte concentrations; and acid phosphatase and tartrate labile acid phosphatase activity; and for biochemical screening including serum calcium and albumin concentrations and

alkaline phosphatase activity. The endocrine response was assessed by measuring serum concentrations of luteinising hormone, follicle stimulating hormone, and testosterone. Two basal samples were taken on consecutive days before the start of treatment. Samples were then taken before the drug was given on the first, third, fifth, and seventh days of treatment. In addition, on the day of the first dose and at the end of the first week of treatment (after the thirteenth dose) blood samples were taken at zero, one, two, and four hours after the dose to assess the acute response of serum luteinising hormone concentrations to the drug. On the day of attendance at the hospital patients were asked to omit their usual dose. Blood samples were then taken immediately before the drug was given and one hour afterwards. Serum concentrations of luteinising hormone and follicle stimulating hormone were measured by radioimmunoassay as described previously[7 8] using Medical Research Council 68/40 and 78/549 respectively as standards. Serum testosterone concentration was measured as described previously.[9]

The data on the eight patients who responded to treatment are given as means and SEM; significance was determined with a paired Student's *t* test.

Results

All 10 patients underwent six weeks of treatment with the agonist. Five patients not previously treated completed three months of treatment and subsequently continued taking the analogue. Of the five patients who previously had failed to respond or had relapsed while receiving treatment, three responded to treatment with the agonist. Two patients showed neither subjective nor objective clinical response to treatment with the agonist and continued to suffer progressive disease.

Subjective assessment—Two patients sustained no benefit. Eight patients (those who responded biochemically) were able to withdraw from narcotic analgesia, which previously had been essential to subdue pain. These patients reported an improvement in the quality of life as assessed on a scoring system. The improvement was noted over five to six weeks.

Objective assessment—The size of the primary tumours decreased during the six weeks of treatment in eight patients—that is, excluding the two non-responders. An obstructed ureter with hydronephrosis

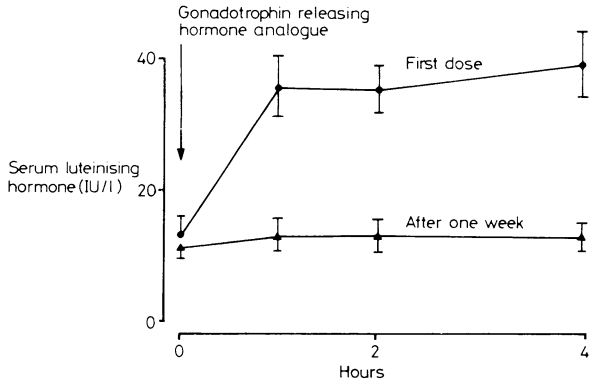

FIG 1—Acute response over four hours of serum luteinising hormone concentration to single doses of gonadotrophin releasing hormone. Top: response to first dose; bottom: response after one week of treatment (n=8).

in one patient was relieved after administration of the analogue and the previously dilated collecting system became normal as assessed by ultrasonography.

Tumour markers—Two patients (responders) had acid phosphatase and tartrate labile acid phosphatase activities within the normal range before starting treatment. All eight patients who responded, however, showed a significant decrease in serum acid phosphatase activity six weeks after starting treatment. In six of these patients the values then fell to within the normal range.

Endocrine response—The first dose of the agonist resulted in a prompt sustained rise in serum concentrations of luteinising hormone (fig 1) and follicle stimulating hormone in all but two of the patients; these two failed to respond clinically to the agonist. This acute response in serum luteinising hormone concentration was almost completely abolished after the thirteenth dose—that is, after the first week of treatment. The rise in serum luteinising hormone concentration peaked at 25·2±3·4 IU/l on the third day of treatment. Serum luteinising hormone concentrations before injection returned to initial, pretreatment values after the first week of treatment, were significantly suppressed below basal values after two weeks, and remained low (2·7±0·4 IU/l) thereafter (fig 2). Over this time the serum testosterone concentration followed the serum luteinising hormone concentration, rising in the first week of treatment and being effectively suppressed to values seen after orchidectomy by the third week of treatment. There was no overall change in serum prolactin concentration over the six weeks of treatment.

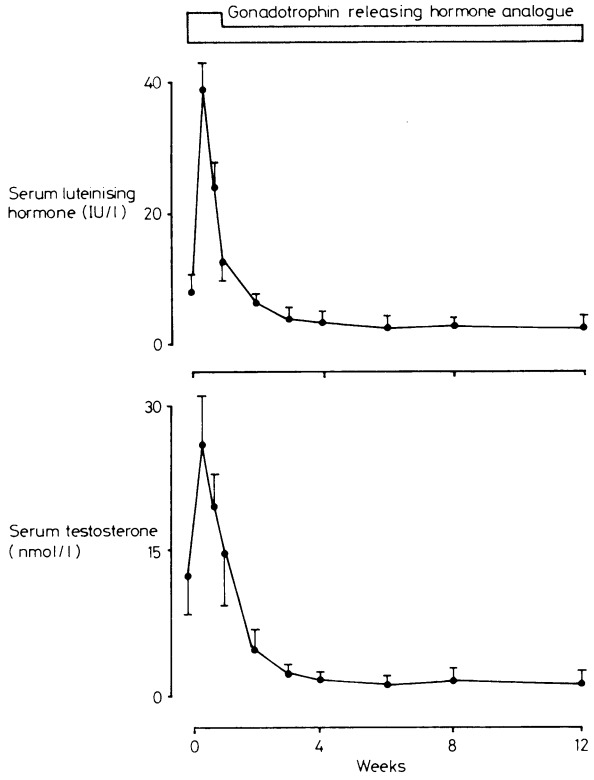

FIG 2—Effects of long term treatment with analogue of gonadotrophin releasing hormone on serum concentrations of luteinising hormone and testosterone over three months.

Conversion: SI to traditional units—Testosterone: 1 nmol/l ≈ 0·29 mg/ml.

Side effects—Two patients reported increased libido. Of these, one had chronic renal failure. One patient reported a considerable reduction in sexual activity after starting treatment with the agonist. No other side effects were noted.

Discussion

Adenocarcinoma of the prostate is amenable to endocrine manipulation as it is often responsive to circulating androgens. Conventional management of this common malignancy is, however, beset by problems. Bilateral orchidectomy, for example, has unpleasant psychological consequences, and treatment with oestrogens, though effective in suppressing serum testosterone concentration and tumour growth, results in increased mortality from cardiovascular disease.[10] Although reducing the dose of oestrogens lessens this risk, the testosterone concentration and tumour growth are then not as effectively suppressed. The development of gonadotrophin releasing hormone agonists provides an alternative means of suppressing serum testosterone concentration. The values obtained in these patients were very low, below that achieved by oestrogen treatment and comparable with those seen after castration.

In this preliminary study eight of the 10 patients responded

to treatment. The two patients who failed to respond clinically to the agonist were subsequently found to have low serum concentrations of luteinising hormone, follicle stimulating hormone, and testosterone and showed no endocrine response. This suggests either absent gonadotrophes or deficient receptors of gonadotrophin releasing hormone. Of these two patients, one was found by computed axial tomography to have a partially empty pituitary fossa, which may possibly explain the lack of endocrine response and absence of clinical improvement.

All five patients in whom the agonist was the primary treatment responded. Interestingly, three patients who had previously relapsed while receiving endocrine treatment responded to the agonist, suggesting that it might have an additional effect other than its lowering action on testosterone concentration, and possibly reflecting its additional considerable suppression of serum gonadotrophin concentration.

The results observed in this study compare favourably with preliminary reports from other centres using other analogues of gonadotrophin releasing hormone.[11 12] Use of these superactive agonists might well provide a safe and more effective treatment for adenocarcinoma of the prostate than any hitherto available. Longer term trials are clearly needed.

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Bulimia nervosa, binge eating, and psychogenic vomiting: a controlled treatment study and long term outcome

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Abstract

An "epidemic" prevalence of binge eating and vomiting (bulimia nervosa) has been reported, and treatment has been claimed to be difficult. This paper describes a short term outpatient treatment programme of eclectic orientation capable of being conducted by non-specialist staff, under medical supervision, in local centres. The treatment programme was evaluated in a controlled trial and in long term follow up. In 30 women with severe bulimia the treatment programme significantly reduced their incidence of dietary manipulation without producing weight gain, weight disorder, or neurotic illness. After treatment all the women had fewer symptoms; 24 stopped binge eating and vomiting at the end of treatment, and a further four stopped shortly afterwards. During formal follow up 20 showed no dietary abuse and a further eight reduced their attacks to an average of three episodes a year: all judged treatment to be a success.

Pretreatment indicators of poorer prognosis include alcohol abuse and a history of anorexia nervosa. Married patients experienced marital difficulties or illness in the spouse.

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Introduction

Bulimia nervosa[1] or the bulimic syndrome is a recently described disorder characterised by powerful and intractable urges to overeat, particularly carbohydrate foods. The fatness, ordinarily the result of such binge eating, is thwarted by psychogenic vomiting, purgation, or intermittent periods of starvation, so that the patient (normally a woman) remains within her normal range for weight.[2] The bulimic episodes are associated with great distress and marked by feelings of loss of control, self disgust, anger, and depression.[3 4] Diagnostic criteria have been established by Russell[1] and by the American Psychiatric Association.[5]

The syndrome is heterogeneous, for although many patients give a history of having had anorexia nervosa[1 6] most of the patients of normal weight have not.[7]

Bulimia nervosa occurs overwhelmingly in women. Its prevalence in general populations is unknown, but symptoms associated with it are common.[6 8-10] Reports from clinics[3 7] and surveys of groups at risk[10 11] suggest that the condition is reaching epidemic proportions. Certainly treatment centres are overwhelmed with referrals, and the letters suggest that there are many patients, previously undetected, who are judged by both their general practitioner and themselves to be ill and who have no locally available treatment.