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A NEW EXTRA LONG ACTING DEPOT PREPARATION OF THE LHRH ANALOGUE ZOLADEX®. FIRST ENDOCRINOLOGICAL AND PHARMACOKINETIC DATA IN PATIENTS WITH ADVANCED PROSTATE CANCER

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Summary—A new depot formulation of the LHRH analogue Zoladex® (goserelin acetate) has been developed which releases the drug over a period of at least 3 months as judged by measurement of drug content in depots at intervals after insertion in male rats and by the suppression of oestrogen secretion and oestrus in female rats. This formulation is based on the lactide/glycolide polymer system used for the standard 1-month Zoladex® depot, but the dose has been increased to 10.8 mg and the characteristics have been modified to enable a longer release of drug to be achieved.

Thirty-eight patients with histologically proven, locally advanced (stage T3 or T4) and/or metastatic prostate cancer were treated with this new longer acting LHRH analogue depot formulation containing 10.8 mg Zoladex®. After initial increase of serum testosterone in the first week of therapy, castration levels were reached in all patients after 4 weeks and this was maintained for more than 14 weeks. At the time of depot exhaustion, when escape from castration levels of androgen occurred, all patients received a single injection of a standard 1-month depot containing 3.6 mg Zoladex® which restored castration levels of androgen thus showing that the pituitary gland was again suppressed. The tolerance and acceptability of the longer-acting depot is high and comparable to the 1-month depot. Taking into account social and psychological factors, patients with advanced prostate carcinoma will soon be able to be treated with a longer acting LHRH depot formulation every 3 months an alternative of the 1-month depot now widely used clinically.

INTRODUCTION

The studies of Huggins and Hodges [1, 2] in 1941 first established the value of castration and oestrogen administration as endrocrine therapy for patients with advanced carcinoma of the prostate. Nowadays, androgen withdrawal by castration is the only well accepted treatment for patients with advanced prostate cancer. Oestrogen therapy is no longer used because of substantial cardiovascular mortality. Furthermore surgery is unacceptable to some patients, is irreversible and is associated with a high incidence of psychological morbidity.

Induction of a potentially-reversible medical castration with luteinizing hormone-releasing hormone (LHRH) analogues has provided a radical new approach to the treatment of hormone-dependent prostrate cancer.

There are two distinct phases in the induction of castration by LHRH analogues. In the initial phase the LHRH analogue stimulates the pituitary–gonadal axis causing a transient rise of serum LH and testosterone during the first two weeks. After this period there is a down-regulation of pituitary LHRH receptors and the pituitary gland becomes refractory and so the serum LH concentration decreases. This causes a reduction in testosterone biosynthesis and serum androgens decrease to castration values.

Pharmacological data show the goserelin acetate (Zoladex®), D-Ser(But)6, Azgly10-LHRH, a synthetic analogue of luteinizing hormone-releasing hormone is a potent LHRH agonist when given parenterally but has low potency when dosed orally. To avoid the need for daily parenteral administration of this peptide analogue a biodegradable, biocompatible depot formulation was developed which

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released the drug continuously over 1 month [3]. The first clinical study of Debruyne *et al.* [4] in patients with advanced prostate cancer showed that this depot induced a fall in serum androgen to castrate values and that these were maintained by 4-weekly depot administration.

Recently, a new longer acting depot formulation of Zoladex has been developed. In order to achieve continuous release over not less than 3 months, injectable depot delivery systems, in the form of cylinders having the dimensions approximately 1.5 mm diameter by 1.8 cm length, containing 10.8 mg Zoladex were prepared. These biodegradable depots were based on a poly(*d*,l-lactide-co-glycolide) polymer having a high lactide content.

For clinical studies the longer-acting depot was presented as a white–cream coloured cylindrical rod in which 10.8 mg Zoladex is dispersed in a matrix of *d*,l,-lactide-glycolide co-polymer having a high lactide content.

The aims of the study were to define the release profile and duration of action of this new 10.8 mg Zoladex depot in suppressing serum testosterone to surgically castrate levels and to assess its safety, tolerance and acceptability.

When serum testosterone had risen to twice castration values (on two consecutive occasions) following exhaustion of the depot, it was important to establish that the pituitary gland was still capable of being suppressed and so all patients received a single injection of a standard 28 day depot containing 3.6 mg Zoladex at the time to evaluate the response.

PATIENTS AND METHODS

A consecutive group of 38 patients entered this open study. Approval for the study was obtained from the Ethical Committees of the participating hospitals. At entry, all patients had untreated, histologically-proven, advanced carcinoma of the prostate (stage T3, T4 Nx MO or TO to T4 Nx M1) with a life expectancy of more than 3 months. All patients gave informed consent.

The drug was administered as a subcutaneous injection into the abdominal wall from a preloaded syrige with a 14 gauge needle. Local anaesthetic was not used.

The study was in two parts:

(a) Patients received a single injection of the new longer-acting depot formulation of 10.8 mg Zoladex. After castrate levels of serum testosterone were reached, the patients were followed until on two consecutive occasions serum testosterone values were at least twice the upper limit of the surgically-castrate range (2 nmol/l).

(b) When serum testosterone values were at least twice the upper limit of the surgically-castrate range, patients received a single injection of a standard one month depot of 3.6 mg Zoladex and were followed for a further 29 days to confirm that the pituitary–gonadal axis was again suppressed.

Blood samples were taken from every patient for monitoring the endocrinological response and pharmacokinetics of the drug, pretreatment, after day 3, at week 1 and every week thereafter until serum testosterone values reached twice the surgically-castrate level.

Haematological and biochemical parameters, including blood counts and liver and kidney function were monitored one day 1, week 12 and at withdrawal. Any possible adverse events were documented.

RESULTS

All patients satisfied the selection criteria. The average age was 72.5 yr (range 51–90 yr).

Eight patients were withdrawn from the study. Five due to progression two due to death from cardiac arrest and one patient refused further follow-up.

Endocrine response

After an initial increase in serum LH and testosterone during the first week after Zoladex depot administration, there was a decrease in serum testosterone and castration levels were obtained within 28 days in all patients.

Mean serum testosterone and LH levels at initiation of therapy were 13.1 nmol/l (range 8.0–25.2) and 5.4 μg/l (range 1.8–18.9) respectively.

Serum testosterone values for all patients are shown in Fig. 1.

The first increase in serum testosterone to twice surgical-castration values, indicating exhaustion of the 3-month depot, was seen after 14 weeks.

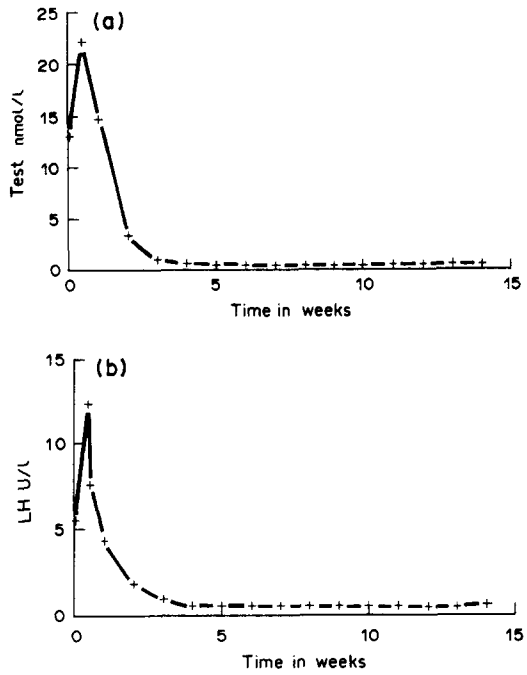

Fig. 1. Serum testosterone (a) and serum LH (b) concentrations following a single sc injection of the new longer-acting 10.8 mg Zoladex depot to patients with advanced prostate cancer. The values for all 38 patients are shown.

When the serum testosterone had risen to twice the surgical castration value, an injection of a standard 3.6 mg Zoladex depot gave an immediate decrease in serum testosterone to castration values in all patients.

The mean value for the medical castration levels is shown in Fig. 2 for all patients.

Pharmacokinetics

The concentrations of Zoladex in serum samples were determined by radioimmunoassay [5]. Peak concentrations were seen after 7 days with a continuous, but declining, release of the drug to very low or undetectable serum concentrations over the remainder of the study.

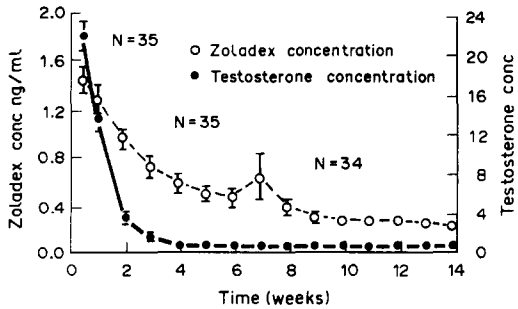

Fig. 2. Mean serum testosterone and Zoladex values ± SD for all 38 patients with advanced prostate cancer given a single depot of the new longer-acting depot containing 10.8 mg Zoladex.

Serum Zoladex concentrations are shown in Fig. 2. It is remarkable that a concentration of Zoladex in serum as low as 0.05 ng/ml manages to maintain castrate serum testosterone concentrations. Serum testosterone only increases above castrate values when serum Zoladex concentrations fall to below the detection limit (0.05 ng/ml) of the assay.

Tolerance and acceptability

The depot was well tolerated systemically in all patients. No local intolerance was observed at the injection site in any patient.

Pharmacological effects related to the reduction of serum testosterone, such as loss of libido and impotence, were present in most of the patients: breast tenderness was seen in one patient. Hot flushes were noticed in 10 patients and transient worsening of symptoms in four patients. No haematological or biochemical toxicity was observed. One patient had papillomatous exanthema on both legs which disappeared spontaneously and was considered to be unrelated to treatment; one patient had thrombosis of one leg, 2 weeks after a TUR.

DISCUSSION

The new extra long acting depot formulation of 10.8 mg Zoladex dispersed in a biodegradable biocompatible matrix of lactide-glycolide copolymer seems to be very effective at suppressing serum testosterone to surgically castrate values in patients with advanced prostate cancer. The duration of action appears to be at least 14 weeks making 3 monthly administration feasible.

After an initial increase of serum LH and serum testosterone in the first week after initiation of therapy, a decrease of serum testosterone to surgically castrate values occurs within 4 weeks and there is no variability in serum testosterone thereafter up to 14 weeks.

Medical castration levels are induced by serum drug concentrations at the limit of detection of the assay (0.05 ng/ml). Increase of serum testosterone is only seen when serum Zoladex concentrations fall below this value.

A second s.c. injection of the standard one-month 3.6 mg Zoladex depot, given at the time when serum testosterone had reached twice surgical castration levels, caused an immediate resuppression of serum testosterone into the castrate range, confirms that the pituitary gland is still capable of being suppressed.

Tolerance and patient acceptibility are very high and the 3-month depot may be preferable to a 1-month depot for some patients for social and psychological reasons. Local anaesthetic was given since experience with the 1-month depot showed this to be unnecessary; the acceptability of this was confirmed in this study.

In summary, we conclude that, like the experience with the standard 1-month depot, the longer acting (3-monthly) 10.8 mg Zoladex depot is well tolerated both locally and systemically. Serum testosterone levels remain at castrate values in all patients for at least 14 weeks. When the depot becomes exhausted of drug and the serum testosterone concentrations begin to increase again, the pituitary gland remains responsive and can be suppressed again after as second depot injection.

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