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Pharmacokinetic and endocrinological parameters of a slow-release depot preparation of the GnRH analogue ICI 118630 (Zoladex) compared with a subcutaneous bolus and continuous subcutaneous infusion of the same drug in patients with prostatic cancer*

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Summary. Seventeen patients with advanced prostatic cancer were treated with the gonadotrophin-releasing hormone analogue DSer (tBU)6 AzaGly10 GnRH (ICI 118630), either as a constant SC infusion, or in the form of a monthly SC slowrelease depot formulation, in which case patients were randomised to receive one of three doses. Six of these patients also received a 250-μg SC bolus of ICI 118630, for pharmacokinetic studies, before starting the infusion or the depot. Drug levels were measured using a double-antibody radioimmunoassay. In contrast to the SC infusion, which gave a smooth serum 118630 level profile, drug release from the depot preparation was not constant, levels varying in a predictable manner throughout each 28-day period, reaching a peak proportional to the dose of ICI 118630 received, between days 15 and 18 of each cycle. With all methods of administration there was an initial rise in LH, usually followed by a rise in testosterone, after which the SC infusion and the depot were both effective in reducing serum LH to basal levels and testosterone into the castrate range within 1 month.

It is too early to make any assessment of clinical response; however, depot treatment was well tolerated: Four patients experienced an initial flare in bone pain, probably related to the initial rise in testosterone, and twelve patients experienced flushing; one patient with pre-existing hydronephrosis and hydroureter developed renal failure, possibly related to a tumour flare reaction. No patients have experienced cardiovascular side effects or local reaction.

Introduction

It has now been firmly established that long-acting synthetic analogues of gonadotrophin-releasing hormone (GnRH), when given in a high dose at frequent intervals, will cause desensitisation of anterior pituitary lutenising hormone (LH)-releasing hormone receptors, resulting in fall of serum LH a fall of and testosterone to castrate levels [4].

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Much interest has recently been shown in the use of this approach in the treatment of advanced prostatic carcinoma [1–3, 10, 11, 13, 15]. Preliminary reports have been encouraging, with a response rate of the order obtained by conventional hormonal manipulation [1–3, 13, 15], and a recently published multicentre randomised study of 199 patients comparing diethylstilbestrol with the GnRH analogue Leuprolide found equivalent response rates in the two arms [9].

A major drawback of GnRH analogue treatment is that it has, until recently, been necessary to give treatment on a daily basis, either by SC injection [1, 2, 10, 11, 15] or by a nasal spray [3, 13]. Whilst most of the younger patients can be taught to inject themselves, it is more difficult in the older age group, some of whom will require daily attendance by the district nurse or a relative. The nasal spray uses large amounts of drug, and absorption may be unreliable. Compliance with a daily treatment schedule is also a potential problem. To circumvent these problems, a slow-release depot formulation of one GnRH analogue D-Ser (tBU)6 AzaGly10 GnRH (ICI 118630) has recently been developed, in which the analogue is contained within a biodegradable lactide-glycolide co-polymer which theoretically allows release of the drug over a 30-day period.

We have recently described an assay for ICI 118630 [5], and in this report describe the pharmacokinetics of drug release from the depot preparation of ICI 118630 in three doses and compare them with those seen following a continuous SC infusion of the drug in solution form and following a single 250 μg SC bolus. We also describe the endocrine response of patients treated with a SC bolus, the SC infusion, and the depot preparation.

Patients materials and methods

Seventeen patients have entered these studies. All patients had histologically proven prostatic carcinoma. Four of the patients had no evidence of distant metastases but were considered eligible for the study, as they all had extensive locally invasive disease extending through the prostatic capsule and not considered curable by surgery or radiotherapy. No patient had received prior sex hormone or antihormone therapy, and no patient had had an orchidecto-

my or had received radiotherapy for carcinoma of the prostate. Patients with concurrent active malignancy were excluded. All patients gave written informed consent to participate in the studies. Study protocols had been approved by the appropriate hospital ethical committees. All drugs were supplied by ICI Pharmaceuticals plc. The solution preparation contained 250 μg ICI 118630 per ml in a citrate buffer. The depot preparation was supplied in the form of a thin rod preloaded into a syringe-type applicator and was delivered through a 16-gauge needle. It was supplied in three doses, 3.6, 1.8, or 0.9 mg, with a theoretical drug release rate over a 30-day period of 120, 60, and 30 μg per day, respectively.

The first six patients to enter these studies each received a single 250-μg SC bolus of ICI 118630; in four patients this was administered 24 h before the start of treatment with the SC infusion, and in two patients, 5 days before the start of treatment with the depot preparation.

The SC infusion was given in a calculated daily dose of 120 μg per day, delivered from a 5-ml syringe mounted on a Graseby Dynamics portable syringe pump, via a butterfly-type cannula inserted SC into the chest or anterior abdominal wall. The syringe and cannula were changed twice weekly. Blood samples for ICI 118630, LH and testosterone levels were taken 24 h before, and at 0, 2, 4 and 8 h after, the start of treatment, and then at daily intervals for the first 4 days and at weekly intervals thereafter (up to 63 days in one patient).

Two patients responding to the SC infusion were transferred to the depot preparation after 43 and 50 days, respectively. The remaining two patients were withdrawn from the study after 15 and 63 days, respectively. The first patient was withdrawn because acute renal failure had developed. He had been receiving long-term prednisolone therapy for Wegener's granulomatosis and presented with acute urinary retention; the intravenous urogram showed bilateral hydronephrosis and hydroureter. At transurethral resection of the prostate, he was found to have extensive locally invasive prostatic cancer involving the trigone of the bladder. Treatment with ICI 118630 was started 7 days postoperatively, and 14 days later he developed oliguric renal failure, which was probably due to hypotension and hypovaloaemia resulting from a combination of septicaemia secondary to a urinary tract infection, a postprostatectomy salt-losing state, and inadequate steroid replacement; however, these factors may have been compounded by a drug-induced tumour flare reaction, which has been previously described for this group of drugs [6, 14], causing an increase in the pre-existing urnary tract obstruction. The second patient was withdrawn at 2 months, owing to the coexistence of a bronchial carcinoma, which had been overlooked on the initial X-ray as it was obscured behind a rib. It was felt that the second malignancy would complicate future assessment.

The depot preparation was given by SC injection into the abdominal wall under a local anaesthetic at 4-weekly intervals. Patients transferred from the infusion initially received two courses of treatment at the highest dose (3.6 mg). If LH and testosterone levels remained depressed the patients were reallocated to receive the intermediate dose level (1.8 mg) for 2 courses; if the hormone levels still remained depressed they were transferred to the lowest dose (0.9 mg), remaining at this dose whilst endocrine and clinical response was maintained.

The first ten patients entering the depot study directly, including the two who had received the 250-μg SC dose, were randomised to receive one of the three dose levels: 3.6 ($n=3$), 1.8 ($n=4$), 0.9 ($n=3$). Randomisation ceased in September 1984 following reports suggesting that some patients treated with the lowest dose (0.9 mg) took up to 44 days to achieve castrate levels of testosterone [12]. Three patients subsequently entering the study received the 3.6-mg dose, and all patients receiving the lower doses were transferred to the 3.6-mg dose. Blood sampling in depot patients was as described, except that after the first week of treatment samples were taken twice weekly wherever possible. In one patient receiving the 1.8-mg dose a more detailed profile was carried out over the first month of treatment, with daily blood samples taken from day 11 to 22 and samples taken every 30 min between 0900 and 1700 h on day 16.

Samples from all patients were assayed for levels of LH, testosterone, and ICI 118630. Testosterone was measured by radioimmunoassay (RIA) after extraction with diethyl ether; the intra-assay coefficient of variation (CV) was 7% and the interassay CV was 10%. LH was measured by double-antibody RIA using MRC 68/40 as standard, intra- and interassay CVs being 4.1% and 5.8%, respectively. ICI 118630 was measured using a standard double-antibody RIA incorporating ICI 118630 radioiodinated with chloramine T as previously described [5]. The lower limit of detection was between 30 and 50 pg/ml, and intra- and interassay CVs were 5% and 12%, respectively. In addition, blood was taken for haematological and biochemical parameters, including acid phosphatase, prior to the start of treatment and at 4-weekly intervals thereafter.

The median follow-up period is only 4 months, and therefore clinical response data are not described. Nine patients have completed at least three courses of treatment and are thus considered evaluable for biochemical response. All patients with the exception of the one withdrawn at 15 days are evaluable for endocrine response and all are evaluable for toxicity.

Results

Figure 1 shows pharmacokinetic and endocrine data for the three evaluable patients who received the 250-μg SC bolus on day 0 followed 24 h later by the 120-μg/day SC infusion. Within 10 min of the SC bolus there was a sudden rise in serum ICI 118630 levels in all patients, reaching peak levels of 8–10 ng/ml within the first 2 h, after which levels fell in an exponential fashion as previously described [5]. At 24 h, just before the SC infusion was started, ICI 118630 levels were still detectable at 0.2–0.4 ng/ml. Following the start of the SC infusion levels rose sharply over the first 8 h and then more gradually to reach plateau levels (0.9–1.3 ng/ml) by 4 days.

LH levels also rose sharply following administration of the 250-μg SC bolus, reaching a peak within 12 h in all patients. Levels then began to fall, but remained considerably above baseline at 24 h. Within 2 h of starting the infusion there was a further transient rise in LH, or a decrease in the rate of fall, after which levels fell rapidly to below basal levels within 3 weeks in all patients.

There was a minor increase in testosterone levels over the first 4 days of treatment in all patients, after which time there was a rapid fall, castrate levels (<3.5 nmol/l)

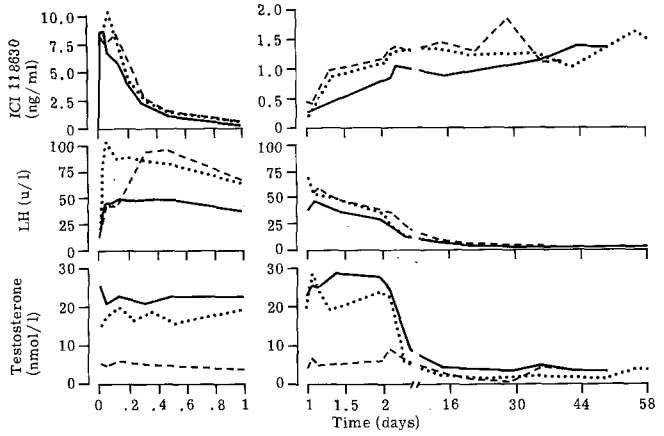

Fig. 1. Serum ICI 118630, lutenising hormone and testosterone levels for 3 patients treated with a 250 μg SC bolus ICI 118630 on day 0, followed by 120 μg per day constant SC infusion starting on day 1. Conversion: SI to traditional units: Testosterone: 1 nmol/l approx. = 0.29 mg/ml

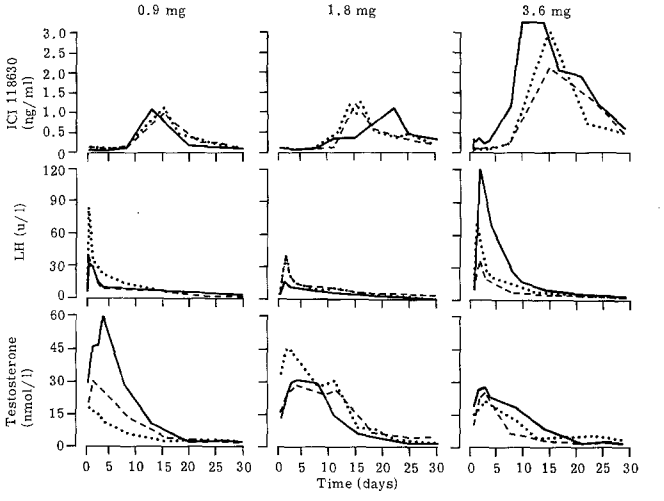

Fig. 2. Serum ICI 118630, lutenising hormone and testosterone levels for the first treatment cycle of the 0.9, 1.8 and 3.6 mg depot doses. Data from three patients for whom complete data were available are shown in each column. Conversion: SI to traditional units: Testosterone: 1 nmol/l approx. = 0.29 mg/ml

bieng reached within 14 days in two patients and within 28 days in the third.

Figure 2 shows pharmacokinetic and endocrine data from the initial cycle of treatment with the depot preparation. It is divided into three columns by dose level, each column showing graphs for 3 patients for whom complete data sets were available. In contrast to the SC infusion, ICI 118630 was not released at a constant rate from the depot preparation but showed a characteristic pattern, with an early small peak in levels at 2 h after the first depot, followed by a decrease in levels by day 2; levels of this early peak increased with the depot dose (Table 1), but there was wide individual variation. Levels began to rise again between days 8 and 11, to reach a second peak between days 15 and 18. No association was seen between depot dose and the time after administration when peak drug levels were observed. Peak and trough serum ICI 118630 levels varied in proportion with dose administered, as shown in Table 1. With the 1.8- and 3.6-mg doses drug levels continued to fall for up to 7 days after injection of the next depot.

LH levels rose sharply within 2 h of the first depot injection in all patients, regardless of dose, reaching peak values within 24 h, after which they fell rapidly, reaching basal levels (< 4 units/l) by day 28 in all patients. There was no association seen between peak levels of LH and depot dose.

Testosterone levels rose in all patients but one after administration of the first depot. Peak levels occurred between days 2 and 4, after which they fell rapidly, reaching castrate levels by the end of the first month in all patients but one (treated with the 1.8 mg-dose of depot), whose testosterone reached castrate levels by day 33. No association was seen in this study between dose of deport and the time to castrate levels of testosterone, or between the dose of depot and the peak level of testosterone, or the day on which that peak occurred.

Figure 3 shows pharmacokinetic and endocrine data for the two patients transferred from the SC infusion to the depot preparation, and shows the serum ICI 118630 levels with each cycle of treatment. In conjunction with Fig. 2, it demonstrates that drug release patterns are reproducible not only between but also within patients, and further, the variation in drug levels with dose of depot. It can also be clearly seen that LH and testosterone levels remained sup-

Table 1. Mean (±SEM) of peak and trough ICI 118630 levels and day for each dose of depot

Depot dose (mg)	Mean initial peak (ng/ml) (±SEM)	Mean peak level (ng/ml) (±SEM)	Mean peak (day) (±SEM)	Mean trough level (ng/ml) (±SEM)	Mean trough (day) (±SEM)
0.9	0.145 (0.058) $n=3$	0.929 (0.081) $n=15$	15 (0.3) $n=15$	0.074 (0.006) $n=16$	30.2 (0.6) $n=16$
1.8	0.175 (0.019) $n=4$	1.717 (0.193) $n=16$	17.4 (0.5) $n=16$	0.236 (0.036) $n=13$	35 (1) $n=13$
3.6	0.231 (0.039) $n=6$	2.848 (0.199) $n=27$	15.6 (0.334) $n=27$	0.403 (0.034) $n=13$	34.8 (0.9) $n=13$

n, number of cycles of treatment used to calculate mean

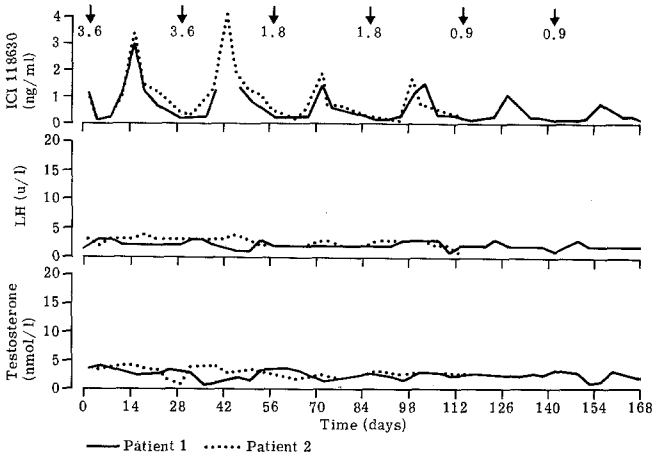

Fig. 3. Serum ICI 118630, lutenising hormone and testosterone levels for two patients transferred from constant SC infusion to the depot preparation of ICI 118630. Depot doses are as indicated. Patient 2 was withdrawn after four cycles. Day 15 sample for second treatment cycle for patient 1 is missing. Conversion: SI to traditional units: Testosterone,1 nmol/l approx. =0.29 mg/ml

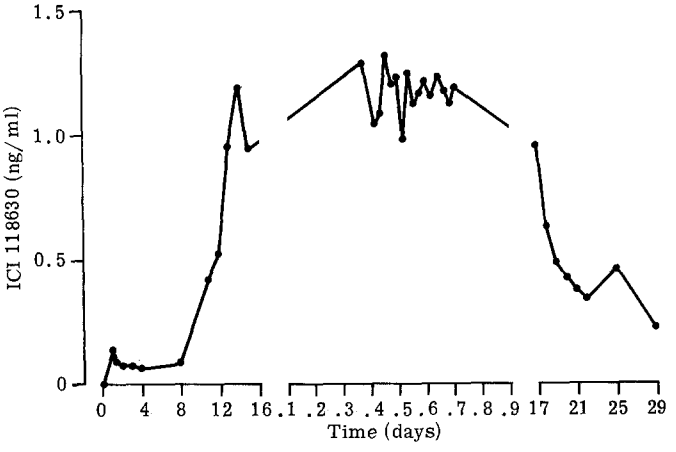

Fig. 4. Detailed profile of serum ICI 118630 levels for the first cycle of treatment in one patient treated with the 1.8 mg depot dose. Samples taken at 30-min intervals between 0900 and 1700 h on day 16

pressed throughout treatment despite the characteristic rise and fall in drug levels. No patient has shown a significant rise in either LH or testosterone once castrate levels had been achieved.

Figure 4 shows a detailed profile of serum ICI 118630 levels over the first month of treatment in one patient treated with the 1.8-mg dose. Daily sampling between days 10 and 16 shows that the rise in drug levels during this period was approximately linear, with a rate of rise of around 5.26 pg ml^{-1} h^{-1}. Sampling every 30 min on day 16 revealed minor fluctuations in serum ICI 118630 levels (0.98–1.32 ng/ml), though in general these were remarkably constant over the 8-h period.

Seven of the nine patients evaluable for endocrine response had an initially elevated acid phosphatase. In four of these seven patients the acid phosphatase either returned to normal or showed a greater than 80% reduction with treatment. Four of nine patients had an initially elevated alkaline phosphatase, and in all four of these there was a significant further rise at the end of the first month of treatment. Three of these four patients did eventually have a significant reduction in levels, which returned to normal in one patient.

Toxicity has been mild. Thirteen patients had skeletal metastases, four of these having an initial flare in bone pain; no patient without skeletal metastases had such a flare. The flare occurred within the first 48 h of treatment and was easily controlled with nonsteroidal anti-inflammatory drugs. Flushing occurred in 12/17 patients. There have been no cases of local reaction or of cardiovascular complications.

Discussion

Development of slow release depot formulations of GnRH analogues is essential if this class of drugs is to succeed in replacing oestrogens and orchidectomy as first-line therapy for advanced prostatic carcinoma. One approach, illustrated in this paper, has been to incorporate the drug into a 50:50 lactide-glycolide co-polymer, which is a substance similar to absorbable suture material. When placed SC it biodegrades totally to lactic and glycolic acids slowly releasing the drug.

Experience with the daily SC injection regimen has shown that a daily dose of 250 μg ICI 118630 is necessary to completely suppress LH and testosterone levels [11]. We have shown in this paper that full suppression of LH and testosterone can be achieved with SC infusion at a dose of 120 μg per day and with all three doses of the depot preparation tested. Thus, it appears that a continuous release system is more potent than a daily SC injection, in that the same effect can be achieved with a smaller total daily dose.

Kerle et al. [7] have recently reported data from 15 patients treated for more than 6 months with a daily SC bolus of 250 μg ICI 118630. Ten patients studied at 6 months all showed a rise in LH levels within 2 h of their daily injection. Five of these patients were also studied at 12 months, when the LH rise was found to be greater than at 6 months. Three of ten patients also showed an associated rise in testosterone levels at 6 months. We have demonstrated that immediately after a 250-μg SC bolus there is a very rapid increase in serum drug levels, which rise to an extremely high peak (8–10 ng/ml) within 120 min. At 24 h (when the next injection would be due) levels have fallen to a low trough (0.17–0.42 ng/ml). It is possible that the very rapid rate of change in drug levels, from low trough to high peak, over the first hour following the 250-μg SC injection (Fig. 1), is sufficient to partially overcome the anterior pituitary desensitisation, resulting in a rise of LH and testosterone levels. This mechanism may also explain the reduced clinical and endocrine response reported in patients treated with less than 250 μg ICI 118630 SC per day [11]. Our data show that 24 h after a single 250-μg SC bolus, drug levels have fallen to a level which is somewhere between the mean trough levels seen with the 1.8- and the 3.6-mg depot doses (Table 1); with daily doses of less than 250 μg per day the 24-h levels of ICI 118630 are likely to be still lower, and may well be too low to provide continuous anterior pituitary suppression, particularly in the presence of the extremely rapid rise in ICI 118630 levels immediately following each SC injection.

As we have shown in Fig. 2–4, the depot preparation of the drug, in contrast to the SC infusion, did not provide

a smooth drug level profile throughout each 28-day period; there is a characteristic release pattern, drug levels starting to rise around day 11 and peaking between days 15 and 18 of each cycle. Despite this release pattern, in contrast to the daily SC bolus regimen [7] there is no further rise in LH or testosterone once suppression has occurred. The explanation may be that the hourly rate of change in drug levels during this period (approx. 5.26 pg ml^{-1} h^{-1}; Fig. 4) is minimal compared with that seen in the first 2 h after a 250-μg SC bolus (approx. 4.5 ng ml^{-1} h^{-1}; Fig. 1).

In this study all doses of the depot were equally effective in suppressing LH and testosterone levels; however, information from another dose ranging study with ICI 118630 suggests that the time to achievement of castrate levels of testosterone is longer with the lower dose levels [12]. For this reason, all patients entering this study after 01. 10. 84 were treated with the 3.6-mg dose, and all patients who had received the lower doses so far were transferred to the 3.6-mg dose at their next visit.

All methods of administration caused a rise in LH and testosterone shortly after the initiation of treatment, and this is likely to be the cause of the "flare reaction" reported with this group of drugs [6, 14]. In this study, four patients with skeletal metastases experienced a flare in bone pain within 48 h of starting treatment, and one patient with pre-existing ureteric obstruction developed renal failure; this, however, was an extremely complicated case, as described above, and it is not clear to what extent a tumour flare contributed to the development of renal failure. Toxicity was otherwise minimal.

It may be possible to prevent the flare reaction, either by blocking the tissue effects of the rise in testosterone by initial simultaneous administration of a pure antiandrogen [8], or by preventing the rise in LH and testosterone altogether by combining the GnRH analogue with an oestrogen for a few days at the start of treatment; this approach is being investigated.

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