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SHORT COMMUNICATION

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Equivalent single-dose pharmacokinetics of two different dosing methods of prolonged-release fulvestrant ('Faslodex') in postmenopausal women with advanced breast cancer

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Abstract *Purpose*: To compare the pharmacokinetics of two different dosing methods of fulvestrant ('Faslodex'), an estrogen receptor antagonist with no known agonist activity, for the treatment of advanced breast cancer. *Methods*: Postmenopausal women with advanced breast cancer were randomly assigned to receive a single 5-ml intramuscular injection of 250 mg fulvestrant, or two 2.5-ml intramuscular injections with a total of 250 mg fulvestrant. Blood samples were taken for pharmacokinetic analysis up to 28 days after injection. *Results*: Plasma concentrations of fulvestrant were measurable up to 28 days after both dosing methods. The concentration-time profiles were relatively shallow, spanning an approximate threefold range from 3 h after dosing to C_{min} measured on day 28. Peak plasma concentrations (C_{max}) of fulvestrant occurred between 1 and 11 days after dosing, with mean C_{max} values of 6.0 and 6.2 ng/ml following one 5-ml injection and two 2.5-ml injections, respectively. The plasma concentration-time profiles were very similar in terms of duration and concentration, and overall exposure to fulvestrant was similar in both dosing groups (the ratio of the $AUC_{0–28}$ of the single-injection group to that of the double-injection group was 1.01; 95% confidence interval 0.68–1.51). *Conclusion*: This study found no evidence of any pharmacokinetic difference between one 5-ml injection and two 2.5-ml injections. The two methods can be used interchangeably, depending on which is more convenient in any particular clinical setting.

Keywords Advanced breast cancer · Fulvestrant · Estrogen receptor downregulator · Antiestrogen · Pharmacokinetics

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Introduction

Fulvestrant ('Faslodex') is an estrogen receptor (ER) antagonist that has no known agonist activity and results in ER downregulation [1, 2, 3, 4]. Results from two phase III clinical trials have shown fulvestrant to be at least as effective as anastrozole in the treatment of postmenopausal women with advanced hormone receptor-positive breast cancer, who have previously been treated with antiestrogen therapy (mainly tamoxifen) [5, 6]. Fulvestrant is given as a 250-mg dose in a prolonged-release intramuscular (i.m.) formulation. The required injection volume (5 ml) may be considered too large for a single i.m. injection in some clinical settings. As an alternative, the same dose and volume could be administered in two separate injections of 2.5 ml at the same clinic visit. Theoretically, these different modes of administration of fulvestrant could result in different pharmacokinetic profiles of the drug. Therefore, in the present study the pharmacokinetics of a single 5-ml injection and of two separate 2.5-ml injections were compared.

Patients and methods

Patients and trial design

The study, conducted at three UK centers, had an open, randomized, parallel-group design, and included postmenopausal women with breast cancer not considered amenable to curative treatment. Patients were to be suitable candidates for antiestrogen therapy and to have a life expectancy of >3 months; however, they were excluded if they had life-threatening visceral metastases. All patients received 250 mg fulvestrant as a long-acting i.m. formulation in one of two randomly assigned dosing methods: either as a single i.m. injection of 5 ml, or as two separate i.m. injections of 2.5 ml, given at the same visit. Injections were given into the buttock, with patients assigned to the two-dose method receiving one injection in each buttock. The study was conducted in accordance with the Declaration of Helsinki, and was approved by the ethics committee for each participating center before the recruitment of any patients. All patients gave written informed consent to participate.

Blood sampling and analysis

Blood samples were taken for assay of fulvestrant immediately before, and 3 h and 1, 2, 7, 10, 14, 21 and 28 days after dosing. Plasma samples were spiked with an internal standard ([d6]-fulvestrant). Fulvestrant and the internal standard concentrations were detected by a high-performance liquid chromatography system with an Inertsil YMC-ODS-AQ 3F C18 column, coupled to a Sciex API III$^+$ triple quadrupole mass spectrometer. Fulvestrant was quantified using a 1/x weighted linear least squares regression line generated from spiking standard amounts of fulvestrant over the concentration range 0.25 to 50.0 ng/ml. The limit of quantitation for the assay was 0.25 ng/ml and the coefficient of variation ranged from 10.4% to 11.0% for standards of 45.0 ng/ml and 0.50 ng/ml, respectively.

Pharmacokinetic analysis

Maximum plasma fulvestrant concentration (C_{max}), plasma concentration at 28 days (C_{min}), and time to maximum concentration (t_{max}) were determined from the individual plasma concentration-time profiles. Area under the plasma concentration-time curve in the first 28 days ($AUC_{0–28}$) was calculated using the linear trapezoidal rule up to the last sampling point (±1 day). A first-order, two-compartment pharmacokinetic model was fitted to the data for each dosing method using a naive pooled data approach, i.e. it was assumed that all plasma concentrations had come from the same patient. The data were weighted by the reciprocal of the concentrations (1/y). Analysis was performed using the validated software package WinNonLin (version 1.5; Scientific Consultants).

Tolerability

Patients were followed-up for 8 weeks to record safety data. Patients whose disease had not progressed after 28 days could receive further single injections of 5 ml at 28-day intervals until disease progression. These patients were followed-up for safety assessments every 3 months until evidence of disease progression.

Statistical analysis

Data were analyzed descriptively and, for parameters with a log-normal distribution ($AUC_{0–28}$, C_{max}, and C_{min}), the data were $\log_e$-transformed and summarized as geometric means (Gmeans) with coefficients of variation. The two dosing methods were compared by calculating the ratio of the $AUC_{0–28}$ Gmeans and its 95% confidence interval (CI) and *P* value from a one-way ANOVA on the log-transformed data using the SAS (version 6.1) procedure PROC MIXED.

Results

Of 38 patients recruited, 20 (mean age 71 years, range 52–85 years) received one 5-ml injection and 18 (mean age 62 years, range 33–87 years) received two 2.5-ml injections, and 33 patients, in whom the disease did not progress, continued to second doses of the study medication. Comparison of the Gmean plasma concentration profiles generated for the nominal sample times (Fig. 1a), and the observed individual data points with model-fitted plasma concentration-time profiles (Fig. 1b), demonstrated an almost complete overlap between the two dosing methods.

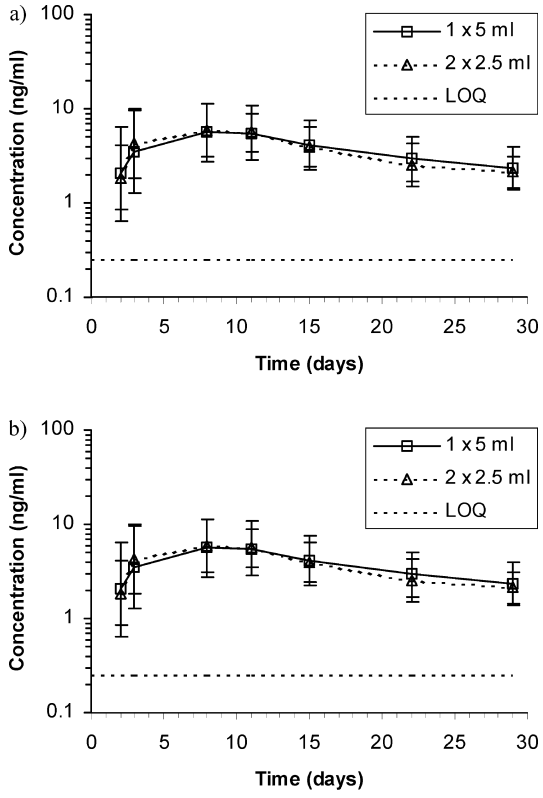

Fig. 1a, b Plasma concentrations of fulvestrant following administration of 250 mg as either a single 5-ml injection or as two 2.5-ml injections. **a** Gmean ± SD (measurements obtained within ±2 days of nominal time); **b** comparison of the observed concentrations and the predicted profiles derived from a fitted model of pooled data (measurements at actual times) (*LOQ* limit of quantitation)

Table 1 Pharmacokinetic parameters for patients receiving one 5-ml injection and those receiving two 2.5-ml injections of fulvestrant. Values are Gmeans (CV%), except t_{max} median (range) (*n.c.* not calculated)

	One 5-ml injection ($n=20$)	Two 2.5-ml injections	Ratio	95% CI
$AUC_{0–28}$ (ng·day/ml)	106.8 (69.7%)	105.5 (59.3%)[a]	1.01	0.68–1.51
C_{max} (ng/ml)	6.01 (83.2%)	6.17 (67.3%)[b]	0.97	n.c.
C_{min} (ng/ml)	2.32 (57.6%)	2.13 (41.0%)[a]	1.09	n.c.
t_{max} (days)	7.00 (1.2–11.0)	6.98 (3.0–9.1)[b]	1.00	n.c.

[a] $n=17$
[b] $n=18$

All four pharmacokinetic parameters were very similar for the two methods (Table 1). The ratio of the $AUC_{0–28}$ Gmeans was 1.01 ($P=0.95$). Also the C_{max} Gmeans (6.01 vs 6.17 ng/ml) and C_{min} Gmeans (2.32 vs 2.13 ng/ml) were comparable between the one 5-ml injection and the two 2.5-ml injection methods, respectively. The relatively wide range of t_{max} observed was partly a function of the blood sampling schedule, which did not allow a precise estimation of t_{max} (blood samples were not taken every day), and partly because the prolonged-release characteristics of the formulation of

fulvestrant resulted in relatively flat concentration-time profiles, thus making t_{max} somewhat arbitrary.

Both dosing methods were well tolerated with only one drug-related adverse event in each group (headache in the single-injection group; nausea in the double-injection group), with no withdrawals from the trial due to adverse events.

Discussion

Fulvestrant is administered as a 250-mg dose in a prolonged-release i.m. formulation for the treatment of breast cancer. This study compared the pharmacokinetics of a single 5-ml injection with two separate injections of 2.5 ml. Both methods can be used depending on the clinical setting. As the pharmacokinetics of fulvestrant are controlled by the release rate from the injection site, theoretically, the two modes of administration could result in different drug release rates and, hence, pharmacokinetic profiles of the drug.

Following a single i.m. dose of the fulvestrant prolonged-release formulation, absorption into the blood was over an extended period, with similar plasma concentrations detected in all patients at the end of the dosing interval (C_{min}, day 28). This indicates that splitting the dose and using two separate injection sites would have a minimal impact on accumulation and, therefore, efficacy during a repeated monthly administration regimen. No evidence of any pharmacokinetic difference between the two methods was found, although in both dose groups there was a substantial degree of intersubject variation in parameters, with coefficients of variation typically $> 50\%$. However, while not powered as a formal bioequivalence study—due to the practical constraints of recruiting breast cancer patients requiring continuing treatment (and also, therefore, generating partial AUC data)—the ratio of the AUC_{0-28} Gmeans of the two groups was 1.01 (95% CI 0.68–1.51), thereby suggesting that there were no clinically important differences in the overall exposure profiles.

Both methods were well tolerated. There was only one drug-related adverse event in each group and no patients withdrew from the trial due to adverse events, demonstrating that one 5-ml injection and two 2.5-ml injections of fulvestrant have a similar tolerability profile. Based on these findings, the dosing method employed with fulvestrant would not be expected to have an impact on the clinical outcome, indicating that the 250-mg dose of fulvestrant may be administered as either a single 5-ml injection or as two 2.5-ml injections.

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