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ORIGINAL ARTICLE

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A phase I study to determine the effect of tamoxifen on the pharmacokinetics of a single 250 mg oral dose of gefitinib (IRESSA) in healthy male volunteers

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Abstract *Objectives*: To determine the effect of tamoxifen on the pharmacokinetics of a single 250 mg oral dose of gefitinib (IRESSA) in healthy volunteers. *Methods*: An open-label, single-center, phase I study in healthy male volunteers. Each volunteer received a single 250 mg oral dose of gefitinib on day 1. On days 11–14, oral loading doses of 60 mg tamoxifen were administered, followed by 20 mg tamoxifen for a further 16 days to maintain steady-state exposure. On day 24, volunteers received a second single 250 mg oral dose of gefitinib. The last dose of tamoxifen was given on day 30. Pharmacokinetic and safety assessments were conducted throughout the trial. *Results*: A total of 18 volunteers were recruited. The presence of tamoxifen did not have a clinically significant effect on the primary variables AUC and C_{max} of gefitinib, nor on the secondary variables $AUC_{(0\text{-}t)}$, t_{max}, $t_{1/2}$, and λ_z. The geometric least square mean values for AUC were 3,407.6 versus 3,397.9 ng.h/ml in the absence and presence of tamoxifen, respectively (90% CL 0.894, 1.112) and for C_{max} were 110.8 versus 103.6 ng/ml, respectively (90% CL 0.786, 1.111). The combination of gefitinib with tamoxifen was generally well tolerated by the volunteers. There were no serious adverse events and no volunteer discontinued the study due to an adverse event. NCI-CTC grade 1/2 drug-related adverse events were observed in seven volunteers, including loose stools and skin events associated with gefitinib, and lethargy and headache, flushing, and dizziness associated with tamoxifen. *Conclusions*: This study suggests that tamoxifen has no significant effect on the pharmacokinetics, tolerability, or safety of a single 250 mg oral dose of gefitinib. Therefore, in clinical investigations of this combination, no dose adjustment of gefitinib is indicated.

Keywords Gefitinib (IRESSA) · Tamoxifen · Pharmacokinetics · Volunteer

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Introduction

Aberrant activation of the epidermal growth factor receptor pathway is a common feature of many solid tumors. New agents that target this pathway include the epidermal growth factor receptor tyrosine kinase inhibitor gefitinib (IRESSA). Phase I monotherapy trial results demonstrated that this agent was generally well tolerated and had promising activity in a range of tumors. Response rates of 12% and 18.4% were reported for gefitinib 250 mg/day monotherapy in two phase II trials in patients with recurrent non-small-cell lung cancer (NSCLC), with disease control (response plus stable disease) in >40% of patients [1, 2]. Consequently, gefitinib 250 mg/day has been approved for the treatment of recurrent NSCLC in many countries. Potential in other tumors is currently under investigation.

The selective estrogen receptor modulator tamoxifen is widely used for the treatment and prevention of breast cancer [3–5]. Due to the different mechanisms of action of gefitinib and tamoxifen, together with preclinical data that suggested possible delays in the development of hormone resistance when gefitinib was added to tamoxifen compared with tamoxifen alone [6], there is interest in clinical evaluation of this combination. However, one area for concern is the possibility of drug–drug interactions. Indeed, tamoxifen may enhance its own clearance following repeated dosing [7].

In humans, tamoxifen is extensively metabolized to several active and inactive products, primarily by

CYP3A4. In vitro evidence shows that tamoxifen markedly induces CYP3A4 in human hepatocytes and suggests that the mechanism of tamoxifen-mediated alteration in drug clearance pathways in humans may involve induction of CYP3A4 by tamoxifen and/or its metabolite [8].

Some studies have shown that tamoxifen may alter drug elimination pathways, resulting in reduced plasma levels of co-administered compounds. In a study to determine the impact of tamoxifen on the pharmacokinetics of the aromatase inhibitor letrozole in post-menopausal women with breast cancer, letrozole area under the plasma concentration-time curve from 0 to infinity (AUC) values were reduced when combined with tamoxifen (mean AUC reduction of 37.6% in the combination periods) [9]. This could have been due to an induction of letrozole-metabolizing enzymes (possibly CYP3A4) by tamoxifen. Similarly, in a study to evaluate the pharmacokinetics of the aromatase inhibitor anastrozole and tamoxifen alone or in combination as adjuvant endocrine therapy for early breast cancer in post-menopausal women, the presence of tamoxifen reduced anastrozole minimum/trough plasma concentration after repeated dosing (C_{min}) by 27% [10]. This reduction in plasma levels of anastrozole may also be due to CYP3A4 induction, although this remains to be established.

With regard to studies using tamoxifen in combination with gefitinib, since CYP3A4 is believed to be the major CYP450 enzyme involved in the metabolism of gefitinib, any effect of tamoxifen on the pharmacokinetics of gefitinib should be identified. Conversely, preclinical studies in rat and dog showed that gefitinib has no enzyme-inducing potential and so would not be expected to have an effect on the pharmacokinetics of tamoxifen (AstraZeneca data on file). The aim of the study was to determine the potential effect of induction of CYP3A4 by tamoxifen on the pharmacokinetics of gefitinib.

Methods

Study design

This was an open-label, single-center, phase I study conducted on healthy volunteers, who were involved in the study for approximately 6 weeks. Each volunteer received a single 250 mg oral dose of gefitinib on day 1 (the dose approved in the USA and other countries for the treatment of patients with advanced NSCLC). On days 11–14, a loading oral dose of 60 mg tamoxifen was administered (in order to more rapidly achieve predicted steady-state concentrations equivalent to a daily 20 mg dose of tamoxifen), followed by 20 mg tamoxifen for a further 16 days to maintain steady-state exposure. Once tamoxifen steady state was estimated to have been maintained for 10 days (the duration of dosing required to achieve maximal CYP3A4 induction by rifampicin), volunteers received a second single 250 mg dose of gefitinib on day 24. The last dose of tamoxifen was given on day 30 (Fig. 1).

Objectives

The primary objective of the study was to determine the potential effect of induction of CYP3A4 by tamoxifen on the pharmacokinetics of gefitinib by assessment of AUC and maximum plasma concentration after single-dose administration (C_{max}). Secondary objectives were to further characterize and compare the pharmacokinetic profile of gefitinib with and without tamoxifen, and to assess the safety and tolerability of the combination.

Statistics

The primary end points of AUC and C_{max} were statistically analyzed. These end points conform to a log-normal distribution and were, therefore, logarithmically transformed prior to analysis. For AUC and C_{max}, the effect of tamoxifen on gefitinib was presented in terms of the geometric least square (gls) means for each group (with and without tamoxifen), the treatment effect (i.e. the ratio of the gls means for gefitinib plus tamoxifen:gefitinib alone), and the 95% confidence interval.

Previous studies of healthy individuals were used to provide an estimate of the within-subject variability of AUC (standard deviation [SD] 0.239 on the log scale) and C_{max} (SD 0.284 on the log scale) after an oral dose of gefitinib (AstraZeneca data on file). The sample size of this study was based on the width of the confidence

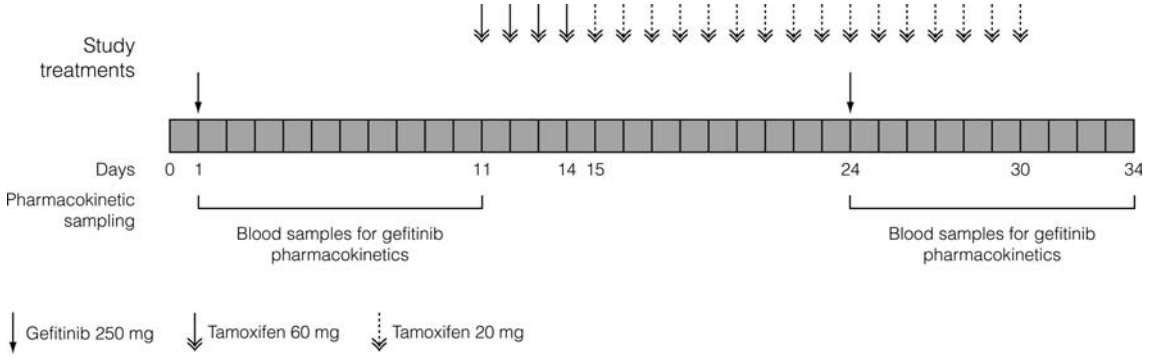

Fig. 1 Schedule of drug administration and gefitinib pharmacokinetic assessments

interval in order to provide an adequate estimate of any treatment difference. These calculations showed that in a study including 12 individuals, there would be at least a 90% chance of showing a significant reduction at the 5% level if the real difference was a 33% decrease. Therefore, it was concluded that 12 individuals completing would give adequate information on the size of any interaction. To ensure that 12 evaluable volunteers completed the study, 18 were entered.

Study population

Volunteers had to fulfill the following criteria: male; aged 18 years or over; normal clinical examination including medical history and resting electrocardiogram; negative screens for serum hepatitis B surface antigen, hepatitis C antibody, and normal ferritin if not done within the past 12 months; body mass index between 18 kg/m^2 and 30 kg/m^2 ; veins suitable for cannulation and repeated venesection.

Key exclusion criteria included: any regular medication or therapy; receipt of another new chemical entity within 4 months prior to this study; participation in a study for a new formulation of a marketed drug within 3 months or in a method development study within 1 month prior to this study; any acute illness within 2 weeks before the start of this study; any clinically significant abnormalities in clinical chemistry, hematology, or urinalysis results; receipt within the previous 3 months of drugs with known significant CYP3A4 inducer/inhibitory effects; receipt of any treatment that modifies gastric pH in the 4 weeks before the first dose of gefitinib; previous medical history of thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism, transient ischemic attack).

Volunteers provided written, informed consent. The trial was conducted in accordance with the Declaration of Helsinki and the principles of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice, and with the approval of appropriate ethics committees.

Assessments

Pharmacokinetic measurements

Venous blood samples (4.9 ml) were taken (via a cannula) throughout the study for the measurement of plasma drug concentrations (Fig. 1). Within 30 min of collection, samples were centrifuged at 4°C and 1,000 g for 10 min to provide plasma samples, which were stored at −20°C until analysis. Samples were analyzed for gefitinib, tamoxifen, and *N*-desmethyl-tamoxifen using high-performance liquid chromatography with tandem mass spectrometric detection methods. Induction of CYP3A4 was not measured directly.

The primary variables were AUC and C_{max} of gefitinib when administered in the presence and absence of tamoxifen. Secondary variables were AUC from 0 to the time of the last measurable concentration ($AUC_{(0\text{-}t)}$), time to reach maximum plasma concentration (t_{max}), terminal half-life ($t_{1/2}$), slowest disposition rate constant (λ_z) of gefitinib when administered in the presence and absence of tamoxifen, and C_{min} for tamoxifen and *N*-desmethyl-tamoxifen throughout the tamoxifen dosing period.

Safety assessments

Clinical chemistry and hematology assessments and urinalysis were carried out at enrollment and throughout the study. All adverse events (AEs) were reported (including onset, resolution, and evaluation of causality) and graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. A post-study medical examination was performed within 14 days of the last blood sample being taken for gefitinib pharmacokinetics, when the plasma concentration of gefitinib should have declined to negligible levels.

Results

Study population

The demographic characteristics of the 18 volunteers who were included in the study are shown in Table 1.

Pharmacokinetic results

For each of the primary variables of this study, AUC and C_{max} of gefitinib, the estimate of the treatment ratio, i.e. the ratio of gefitinib plus tamoxifen to gefitinib alone, was close to 1 (Table 2). The 90% confidence limits indicate that there is no evidence to support the hypothesis that either variable was 33% lower when gefitinib was given in the presence of steady-state levels of tamoxifen compared with when it was given alone. The lower and upper 90% confidence limits of AUC fell

Table 1 Demographic characteristics

Number of volunteers	18
Age (years)	
Mean (SD)	43.3 (7.3)
Range	33–57
Weight (kg)	
Mean (SD)	82.4 (10.4)
Range	68–105
Height (cm)	
Mean (SD)	177.0 (6.5)
Range	165–189
Race (n)	
Caucasian	18

Table 2 Analysis of AUC and C_{max} for gefitinib in the presence and absence of tamoxifen

	Gefitinib 250 mg alone		Gefitinib 250 mg + tamoxifen		Estimate of treatment ratio[a]	Lower 90% CL	Upper 90% CL
	n	Gls mean	*n*	Gls mean			
AUC (ng· h/ml)	18	3,407.6	18	3,397.9	0.997	0.894	1.112
C_{max} (ng/ml)	18	110.8	18	103.6	0.935	0.786	1.111

CL confidence limit
[a] Treatment ratio = ratio of gefitinib + tamoxifen:gefitinib alone

within the accepted range for bioequivalence studies (confidence interval 0.8–1.25), indicative of no significant effect [11].

The largest individual treatment ratio observed was 72% higher for AUC and 127% higher for C_{max} in the presence of tamoxifen, which falls within the previously defined (Study 1839IL/0208) intra-subject ratio range of up to twofold for AUC and up to threefold for C_{max} (AstraZeneca data on file). The geometric mean plasma concentrations of a single oral dose of gefitinib 250 mg in the presence or absence of steady-state levels of tamoxifen are shown in Fig. 2.

The mean/median values of the derived secondary pharmacokinetic parameters were similar following gefitinib 250 mg with and without the presence of tamoxifen (Table 3). There was no evidence to suggest that the presence of tamoxifen affected the $t_{1/2}$ of gefitinib. In the absence of tamoxifen, $t_{1/2}$ ranged from 15.8–62 h, compared with 14.1–58.2 h in the presence of tamoxifen. The mean $t_{1/2}$ ratio for gefitinib between treatments (with tamoxifen [day 24]/without tamoxifen [day 1]) was 0.97.

In general, tamoxifen steady-state trough levels (C_{min}) were achieved after four loading doses of 60 mg (day 15) and were maintained during the 20 mg/day dosing period for 16 days thereafter. One volunteer reached steady state between days 15 and 20. For *N*-desmethyl-tamoxifen, plasma concentrations reached steady state by day 27 (Fig. 3).

Safety results

All 18 volunteers received two separate 250 mg oral doses of gefitinib, plus tamoxifen in the form of 4 separate 60 mg and 16 separate 20 mg oral doses. There were no serious AEs and no volunteer was discontinued from the study as a result of AEs. There were no clinically significant electrocardiogram, vital sign, hematology, clinical chemistry, or urinalysis findings.

Of the 18 volunteers, 17 experienced at least 1 AE. Of the 55 AEs, 41 were NCI-CTC grade 1, 12 were grade 2, and 2 (non-drug-related headache and abdominal pain) were grade 3. The majority of AEs (51 out of 55) resolved, with the exception of 4 that were ongoing at the post-study medical examination (NCI-CTC grade 1 venepuncture site bruise, paresthesia, and rash, and grade 2 cannula site reaction), which subsequently

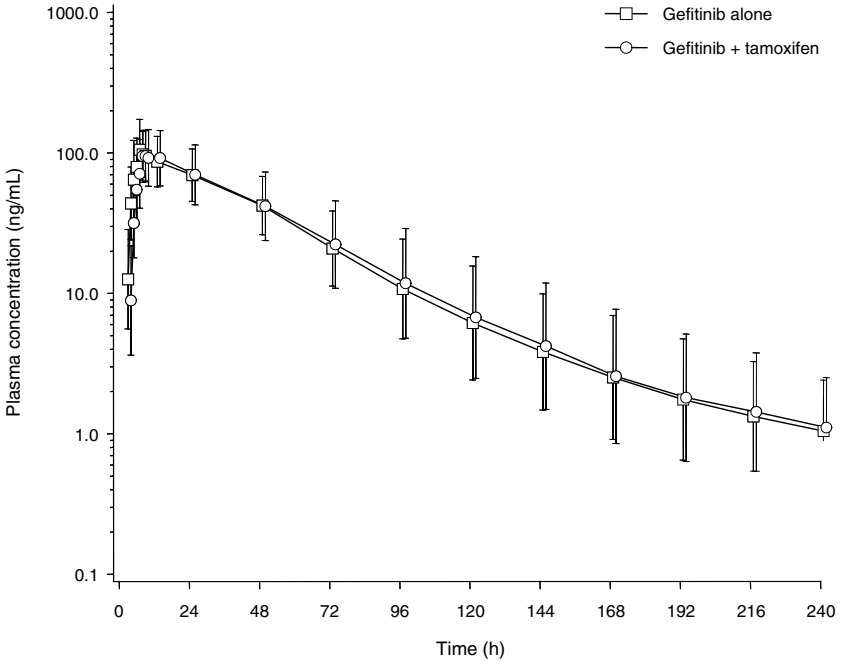

Fig. 2 Plasma concentration-time profile of gefitinib following a single 250 mg oral dose in the presence and absence of steady-state levels of tamoxifen

Table 3 Summary of plasma pharmacokinetic parameters for gefitinib (secondary variables)

		Gefitinib 250 mg alone ($n = 18$)	Gefitinib 250 mg + tamoxifen 20 mg ($n = 18$)
$AUC_{(0\text{-}t)}$, (ng· h/ml)	Geometric mean (CV%)	3,344 (52.39)	3,338 (67.48)
λ_z (h^{-1})	Arithmetic mean (SD)	0.020 (0.009)	0.021 (0.010)
t_{max} (h)	Median (range)	5 (5–7)	6 (4–8)
$t_{1/2}$ (h)	Arithmetic mean (SD)	39.05 (12.65)	37.90 (12.61)

CV coefficient of variation

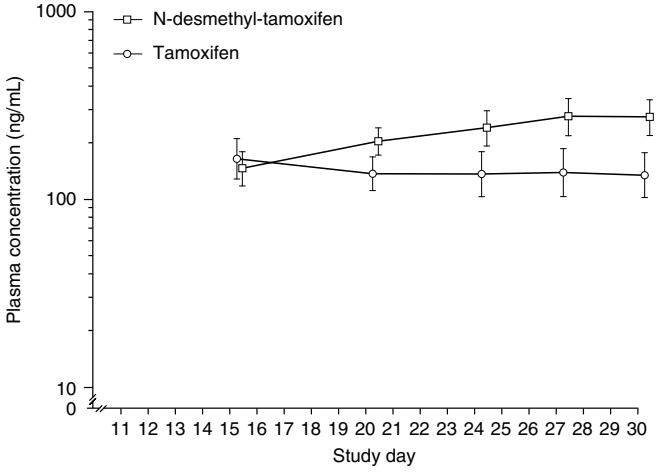

Fig. 3 Geometric mean trough plasma concentrations of tamoxifen and *N*-desmethyl-tamoxifen

resolved. The most commonly reported AEs were headache (in six volunteers) and cannula site reaction (in seven volunteers). Seven of the 18 volunteers had at least 1 AE considered by the investigator to be related to gefitinib and/or tamoxifen, all of which were NCI-CTC grade 1/2 (Table 4). All of the drug-related AEs for gefitinib given either alone or in combination with tamoxifen were mild (NCI-CTC grade 1).

A single 250 mg oral dose of gefitinib was generally well tolerated and in combination with tamoxifen did not appear to increase the incidence of AEs compared with tamoxifen alone.

Discussion

CYP3A4 is believed to be the major CYP450 enzyme involved in the metabolism of gefitinib and in vitro studies suggest that tamoxifen markedly induces CYP3A4 in human hepatocytes [8]. Therefore, this study was conducted to determine if tamoxifen had any effect on the drug clearance pathway of gefitinib.

The volunteers in this study were male, as in all previous gefitinib healthy volunteer studies. Tamoxifen is an endometrial carcinogen, thus precluding its administration to healthy female volunteers. Previous studies have suggested that there are no major differences in the pharmacokinetics of tamoxifen between healthy male volunteers and female patients with breast cancer [7], and there are no significant differences in the pharmacokinetics of gefitinib between male and female patients treated with gefitinib (AstraZeneca data on file). The volunteer population was considered to be appropriate for this phase I clinical pharmacologic study as male patients receive tamoxifen for conditions such as male breast cancer [12] and Peyronie's disease [13]. Tamoxifen has also been administered to male patients

Table 4 Drug-related AEs occurring in seven volunteers

Volunteer	Treatment	AE (MedDRA term)	Causality[a]	Maximum NCI-CTC grade	Outcome at post-study medical examination
1	T alone	Lethargy	T	2	No longer present
2	T alone	Headache	T	2	No longer present
	T alone	Flushing	T	2	No longer present
	T alone	Dizziness	T	2	No longer present
	T alone	Headache	T	1	No longer present
	T alone	Flushing	T	2	No longer present
	T alone	Dizziness	T	2	No longer present
3	G alone	Loose stools	G	1	No longer present
4	G alone	Rash NOS	G	1	No longer present
	T alone	Rash NOS	G	1	No longer present
	G + T	Rash NOS	G	1	No longer present
5	G + T	Rash NOS	G	1	Still present
6	G + T	Fatigue	T	1	No longer present
7	G + T	Dry skin	G	1	No longer present
	G + T	Lethargy	T	1	No longer present

G gefitinib; *T* tamoxifen; *NOS* not otherwise specified
[a] In the opinion of the investigator, there was a reasonable possibility that the AE was caused by the drug

in clinical studies investigating its protective effect on advanced atherosclerosis [14].

Drug interaction studies typically have a randomized, crossover design. However, with such a design, the long half-lives of tamoxifen (7 days) and its main metabolite *N*-desmethyl-tamoxifen (12 days) would require a washout period of at least 2 months (five half-lives of *N*-desmethyl-tamoxifen) after completion of the multiple dosing arm with tamoxifen to avoid administering gefitinib in the presence of tamoxifen-induced enzymes. Therefore, in order to reduce this duration and increase the likelihood that volunteers would complete the study, a non-randomized design was used. Due to the long half-life of tamoxifen, 20 mg daily dosing for 4 weeks would normally be required to reach steady state. Hence, previous clinical studies have used loading doses of tamoxifen to achieve steady state more rapidly [15]. The actual loading dose schedule selected for this study was based on pharmacokinetic modeling of previous healthy male volunteer data. The loading dose approach reduced the time taken to reach steady state, so reducing both the study duration and the total exposure to tamoxifen.

Results from the present study showed that there was little difference in the primary end points of AUC, C_{max}, and other derived pharmacokinetic parameters for gefitinib when given in the presence of steady-state levels of tamoxifen, compared with when given alone. A single 250 mg oral dose of gefitinib was generally well tolerated by healthy male volunteers in the presence and absence of steady-state levels of tamoxifen, the tolerability profile being as expected with these two agents. There were no discontinuations due to AEs. The most commonly reported AEs of headache and cannula site reaction are frequently reported in healthy volunteer studies [16].

As gefitinib is predominantly metabolized by CYP3A4, the absence of any significant effect of steady-state tamoxifen administration on the pharmacokinetics of gefitinib could be interpreted in two ways: either tamoxifen does not significantly induce CYP3A4 in humans, or the 4 days of loading-dose tamoxifen and then maintenance of steady state for 9 days prior to gefitinib dosing was not sufficiently long to achieve full enzyme induction. As rifampicin, a potent inducer of CYP3A4, achieves full induction within 8–10 days, the first explanation appears to be more credible.

This study suggests that tamoxifen has no significant effect on the pharmacokinetics and safety of a single oral dose of gefitinib. Therefore, in clinical investigations of this combination, no dose adjustment of gefitinib is indicated.

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