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Do gastrointestinal transit parameters influence the pharmacokinetics of gefitinib?

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ABSTRACT

The selective EGFR tyrosine kinase inhibitor, gefitinib has been shown to be active against certain human carcinomas. It had been noted that a proportion of volunteers consistently had lower gefitinib exposure following oral administration. The shape of the elimination profile in this subset was also different, showing a monophasic elimination pattern rather than the biphasic pattern observed in the majority of subjects. A gamma scintigraphic study was conducted to examine the relationship of gastrointestinal transit and drug absorption in a cohort of rapid clearance subjects ($n = 5$) and normal profile volunteers ($n = 7$). The fasted volunteer panel received a 250 mg gefitinib tablet labelled with [^{111}In]–DTPA together with 240 mL [^{99m}Tc]-labelled water. The rapid clearance cohorts were shown to have a faster mean gastric emptying T90 (37 min vs 74 min) and shorter small intestinal transit time (156 min vs 204 min), resulting in an earlier colonic arrival time (181 min vs 244 min). Mean plasma C_{max} was lower (99.2 ng/mL vs 116 ng/mL) and AUC almost half in the rapid clearance group (2162 ± 81 ngh/mL vs 4996 ± 64 ngh/mL). These data suggest that gastrointestinal transit parameters play a role in the differences in the rapid clearance profile group, also contributing to the biphasic to monophasic switch. However, historical data show, at the recommended dose of 250 mg/day steady-state plasma concentrations adequate for clinical benefit are achieved in patients with non-small cell lung cancer.

1. Introduction

For poorly water-soluble or poorly absorbed drugs, the contact time with the small intestine is a critical determinant of absorption. Early models of the relationship between gastrointestinal (GI) transit and absorption constructed by Ho et al. (1983) attempted to encapsulate this concept in a model of 'intestinal reserve length' derived from an observation of Hoffman et al. (1983) that drugs should be formulated to achieve 95% absorption in a small intestinal length of 180–350 cm. The approach taken was simplistic as it assumed drug absorption to be a simple first order process and transit to be fairly constant and was based on the earlier idea of 'intestinal reserve length' proposed by Borgstrom et al. (1957), who observed that the majority of the nutrients delivered in a liquid meal are absorbed in the first 100 cm of gut. Dressman (1989) suggested that a better way of describing the impact of small intestinal transit time on drug absorption was to calculate the mean residence time which allowed for supply, uptake and removal of the drug. Later modeling approaches utilised data derived from gamma scintigraphy, the formulation being radiolabelled by incorporation of indium-111 or technetium-99m. Using this data, the plasma concentration–time profile can be related to gastric emptying, small intestinal transit time and colonic residence (Wilson et al., 2001).

Gefitinib (Iressa®, AstraZeneca) is a potent inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase. It is a lipophilic dibasic compound (Table 1) that is administered as the free base in Iressa® tablets. The compound exhibits pH-dependent solubility which is higher at low pH, representative of the gastric environment, but drops significantly as the pH increases towards pH 5. Gefitinib has increased solubility in biorelevant media and aspirates of human gastric fluid and intestinal fluid as shown in Table 2; however, the solubility is still likely (or believed) to be low in the intestine. Gefitinib demonstrates high permeability across CACO-2 monolayers and has an absolute bioavailability in humans of 60%, suggesting high or even complete absorption (Swaisland et al., 2005). As defined by the Biopharmaceutical Classification System (Amidon et al., 1995), gefitinib is a Class 2 compound.

Previous healthy volunteer studies with gefitinib have shown the pharmacokinetics to be highly variable (Swaisland et al., 2005). Among the subjects studied there was subgroup (ca. 18% of healthy subjects) that displayed a pharmacokinetic profile following single oral doses of gefitinib that is different to the profile seen in

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Table 1
Summary of physicochemical properties of gefitinib.

Property	
Molecular weight	447 Da
log $D_{7.4}$	3.9
pKa	Dibasic: 5.28, 7.17

Table 2
Mean gefitinib solubility in biorelevant media at 37 °C ($n = 2$).

Medium	Gefitinib solubility (mg/mL)	Final pH
SGF	>9.590	1.6
HGF	4.980	5.0
Sørensen's phosphate buffer (pH 6.8) at 25 °C	0.002	6.9
HIF	0.085	7.0
FaSSIF (Dressman and Reppas, 2000)	0.085	6.4
FeSSIF (Dressman and Reppas, 2000)	1.950	5.4

Where SGF, simulated gastric fluid (NaCl 2 g/L + 65.75 mL/L 1 M HCl); HGF, human gastric fluid; HIF, human intestinal fluid; FaSSIF, fasted simulated small intestinal fluid; FeSSIF, fed simulated small intestinal fluid

the majority of individuals dosed. This different profile is characterised by a monophasic decline in plasma concentrations with a shorter terminal half-life ($t_{1/2}$) and often a lower C_{max} than most subjects, resulting in lower exposure (AUC). Additionally, this "rapid clearance" profile appeared to be consistent within the individual subject following more than one single dose administration, even where those doses were administered a considerable time apart.

A number of investigations have been conducted in an attempt to identify the sources of variation in gefitinib pharmacokinetics (Swaisland et al., 2006). A consideration of relevant physiological processes and of the biopharmaceutical properties of gefitinib suggests that GI transit time, gastric pH, intestinal solubility or polymorphism in enzyme or transport proteins might influence the pharmacokinetics of gefitinib (Bergman et al., 2007). The study described in this communication was designed to determine whether GI transit parameters influence the shape of the plasma concentration–time profile of gefitinib. Two groups of healthy volunteers were identified on the basis of data from their previous participation in pharmacokinetic studies involving gefitinib to have a 'normal' (biphasic) or a 'rapid clearance' (monophasic) pharmacokinetic profile. A single oral dose of gefitinib 250 mg was administered and the plasma concentration–time pharmacokinetic profile defined. Each dose incorporated a radiolabelled core within the standard clinical trials tablet to enable scintigraphic imaging. This facilitated correlation of plasma concentration–time profiles and individual transit measurements.

2. Materials and methods

2.1. Materials

Gefitinib (Iressa®, AstraZeneca) tablets, formulation number F012653, batch number ADM 83473E01, were sourced from Investigational Products Section at AstraZeneca, Macclesfield, UK. The tablets were the standard film-coated clinical trial tablets. The radiopharmaceuticals, [^{111}In]–diethylene triaminepentaacetic acid, [^{111}In]–DTPA, and technetium-99m labelled diethylene triaminepentaacetic acid, [^{99m}Tc]–DTPA, were provided by the West of Scotland Radionuclide Dispensary, Glasgow, UK. Lactose BP (Thornton & Ross) and bone cement (Palacos® R-40, Schering-Plough Ltd.) were supplied by the Pharmacy Department, Glasgow Royal Infirmary, Glasgow, UK.

2.2. Methods

2.2.1. Radiolabelled tablet manufacture

Lactose was radiolabelled by adding [^{111}In]–DTPA [activity 20 MBq at time of dosing (TOD)] onto 200 mg lactose. The [^{111}In]–DTPA was dried onto the lactose using a hot air drier.

A single hole was drilled into the edge face of the tablet using a bench model drill fitted with a 1.2 mm bit as described by Perkins et al. (2001). Tablets were individually weighed to estimate the content removed. After the hole was filled with [^{111}In]–DTPA labelled lactose (0.5 MBq at TOD), the tablet edge was sealed with bone cement ensuring that the contact faces were not contaminated with sealant. The effect of the procedure on the subsequent release rate was compared with non-drilled samples using a release test currently employed at AstraZeneca. In addition to the usual 15, 30, 45 and 60 min time points, samples were also collected at an 'infinity' time point, i.e. after overnight stirring at 50 rpm.

2.2.2. Clinical scintigraphic study

2.2.2.1. Study design. This was a single-centre, open label, comparative study of the two cohorts. The study was conducted at the Bio-Imaging Centre, Glasgow Royal Infirmary, Glasgow, UK. The study followed the tenets of the Declaration of Helsinki, was approved by the Glasgow Royal Infirmary Research Ethics Committee and the Administration of Radioactive Substance Advisory Committee and was conducted to good clinical practice. The total radiation dosimetry was 0.19 mSv, which is within the normal background limits of exposure in the UK.

2.2.2.2. Study population. Twelve males (age range 28–60 years) recruited from the AstraZeneca, Alderley Park healthy volunteer panel, who had previously provided well-defined gefitinib plasma concentration–time profiles, were enrolled. The subjects were selected for inclusion into the study on the basis of their previous gefitinib pharmacokinetic profiles and stratified into two groups, which were described as having either the normal biphasic profile with a terminal half-life greater than 20 h (Group A: normal profile) or the monophasic profile with a terminal half-life shorter than 20 h (Group B: rapid clearance profile; lower C_{max} and/or more rapid clearance/lower bioavailability). Group A comprised 7 subjects, mean age 43.7 years [range 35–60 years]. Group B comprised 5 subjects, mean age 35 years [range 28–42 years]. Six subjects were originally recruited in each group; however it was discovered from historical data during the course of the study that one of the subjects recruited into Group B had been incorrectly assigned. This data was therefore transferred into Group A prior to data analysis.

2.2.2.3. Study conduct. Written informed consent was obtained from each subject prior to the start of any study related procedures. Subjects underwent a pre-study medical examination and screening procedure at the AstraZeneca, Alderley Park Clinical Pharmacology Unit during the 28 days prior to dosing. Subjects were resident at the Glasgow study centre from the evening prior to dosing with gefitinib until 48 h after dosing. Subjects fasted from 2200 h the evening before the study day. After discharge from the centre, the subjects were followed up at the Alderley Park Clinical Pharmacology Unit until the end of the study and all subjects underwent a post-study medical assessment.

On the morning of the study, an intravenous cannula was placed into the antecubital vein and a pre-dose blood sample was taken. Anterior and posterior markers containing a small amount of [^{111}In] label were taped to the abdomen of each volunteer, above the hepatic flexure, to allow accurate alignment of sequential images in subsequent analysis. Subjects took a single [^{111}In]-labelled tablet with 240 mL water containing 1 MBq technetium-99m labelled diethylene triaminepentaacetic acid while standing.

Subjects were imaged in a standing position. Paired anterior and posterior static scintigraphic images of 30 s duration were taken immediately following administration, then every 5 min until 20 min post-dose, then every 30 min until 6 h post-dose, and then hourly until 12 h post-dose. A final image was taken at 24 h post-dose. Subjects received lunch (approx. 2000 kJ) at 4 h post-dose, a snack (approx. 1000 kJ) at 7 h post-dose, an evening meal (approx. 4600 kJ) at 10 h post-dose and a snack (approx. 1000 kJ) at 12 h post-dose.

2.2.2.4. Data analysis. Regions of interest were constructed for the stomach and colon using summed frames at the appropriate time periods to identify the organs. From the scintigraphic analysis, the time of gastric emptying and the arrival at the ileocaecal junction and entry into the colon were recorded. The time of dispersion of the inner core, reflected in the spreading of the indium-111 in the GI tract contents, was determined by examination of the scintiscans.

2.2.2.5. Determination of plasma concentrations and derived pharmacokinetic parameters for gefitinib. Following dosing, samples were taken at 15, 30 min and 1 h post-dose then hourly until 10 h post-dose, then at 12, 24, 48, 72, 96, 120, 144, and 168 h post-dose. Blood samples were centrifuged within 30 min of collection at $1500 \times g$ for 10 min. Plasma samples were stored at −20 °C prior to analysis. Plasma concentrations of gefitinib were determined using liquid–liquid extraction after basification followed by high performance liquid chromatography (HPLC) with tandem mass spectrometric detection (Jones et al., 2002).

Pharmacokinetic parameters were determined using non-compartmental methods (WinNonlin version 3.1). The C_{max} and t_{max} for each volunteer were determined directly from their plasma concentration–time profiles. The rate constant of the slowest disposition phase (λz) was calculated by log-linear regression of the terminal portion of the concentration–time profiles. The $t_{1/2}$ was calculated from the equation 0.693/λz. The area under the plasma concentration time curve up to the time of the last quantifiable plasma concentration, AUC_{0-t}, was calculated by the linear trapezoidal rule and extrapolated to infinity (AUC) using the terminal rate constant.

3. Results

3.1. In vitro dissolution testing

The results of the *in vitro* dissolution testing are shown in Table 3. The dissolution was unaffected by the drilling of the interior core and replacement of the material with [^{111}In]-labelled lactose. Previous *in vitro* studies confirm that the dispersion of the central core and release into solution corresponds with complete disintegration of the core thus validating the scintigraphic methodology (data on file, AstraZeneca).

Table 3
Mean results from *in vitro* dissolution testing of radiolabelled tablets.

Time (min)	% gefitinib released	
	Uncorrected for tablet weight	Corrected for tablet weight
15	46	47
30	78	80
45	87	88
60	90	91
1080 (infinity)	100	102

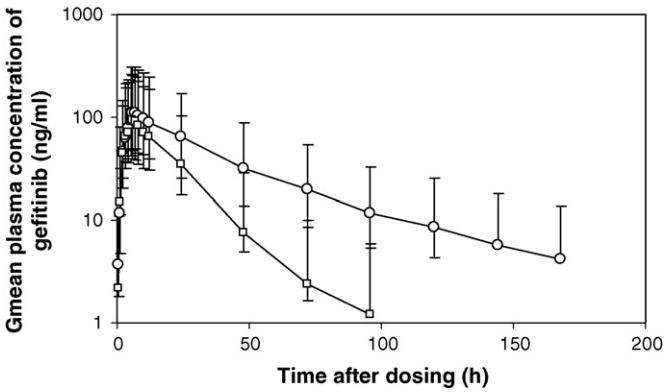

Fig. 1. Pharmacokinetics of gefitinib in normal and rapid clearance groups where ○, normal group profile ($n = 7$); □, altered group profile ($n = 5$).

The results are comparable to those typically observed for gefitinib 250 mg tablets and meet specification (both with and without correction for tablet weight). In addition, 100% release of drug was observed at 'infinity'.

3.2. Clinical study

All clinical laboratory indices were normal on entry to and exit from the trial and all subjects enrolled completed the study. The pharmacokinetic data is summarised in Table 4 and Fig. 1. As mentioned previously, subjects were recruited based on their $t_{1/2}$ determined following various single oral doses of gefitinib in previous Clinical Pharmacology studies. A comparison of historical and current $t_{1/2}$ data shows them to be very similar.

3.3. Pharmacokinetics

The plasma concentration–time profiles for subjects in the Group A (normal profiles) had half-lives ranging from 35.2 to 87.4 h which declined biphasically post C_{max}, with plasma con-

Table 4
Derived pharmacokinetic parameters for gefitinib.

Parameter	Statistic	Volunteer group	
		Normal profile (Group A) ($n = 7$)	Altered profile (Group B) ($n = 5$)
C_{max} (ng/mL)	Gmean (CV)	116 (64)	99.2 (62)
	Range	46.0–241	50.7–244
t_{max} (h)	Median	6.0	5.0
	Range	5.0–7.0	3.0–6.0
AUC_{0-t} (ngh/mL)	Gmean (CV)	4639 (60)	2142 (82)
	Range	1740–9730	952–6760
AUC (ngh/mL)	Gmean (CV)	4996 (64)	2162 (81)
	Range	1800–11700	969–6820
Terminal half-life (h)	Arithmetic mean (SD)	50.0 (18.0)	15.1 (6.75)
	Range	35.2–87.4	10.1–26.2

Where Gmean, geometric mean; CV, coefficient of variation (%); SD, standard deviation; *n*, number of volunteers.

Table 5
Gamma-scintigraphy derived gastrointestinal transit parameters.

Transit parameter (min) mean (range)	*Volunteergroup*	
	Normal profile (Group A) ($n = 7$)	Altered profile (Group B) ($n = 5$)
Time of onset of tablet dispersion	20 (10–40)	27 (16–40)
Time of completion of tablet dispersion	29 (10–61)	32 (16–50)
Gastric emptying T50	41 (13–76)	26 (2–56)
Gastric emptying T90	74 (25–166)	37 (2–76)
Small Intestinal Transit time	204 (170–245)	156 (105–270)
Colonic arrival T90	244 (180–270)	181 (121–270)

Where *n*, number of volunteers.

centrations still clearly detectable at the last time point sampled (168 h). The plasma concentration–time profiles for 4 of the 5 subjects in Group B with half-lives ranging from 10.1 to 16.7 h declined monophasically post C_{max}, with plasma concentrations undetectable at 96–144 h post-dose. For the remaining subject in this rapid clearance PK group, the half-life determined after dosing in this study was longer than that observed in the dataset upon which he was recruited (26.2 h vs 18.8 h) with a clearly detectable plasma concentration (1.62 ng/mL) at 168 h post-dose.

The 12 subjects included in this study provided a range of primary pharmacokinetic parameters that reasonably reflect those previously seen in healthy subjects following a single oral dose of gefitinib 250 mg alone and in the fasted state:

- $t_{1/2}$ ranging from 10.1 to 87.4 h
- C_{max} ranging from 46.0 to 244 ng/mL
- AUC ranging from 969 to 11700 ngh/mL.

3.4. Gastrointestinal transit parameters

Gastrointestinal transit parameters, derived from scintigraphic images, are summarised in Table 5 and Fig. 2a and b.

Comparison of the two treatment groups showed that for the small number of subjects included in this study, there was an apparent difference in gastric residence time. In general, the tablets were observed to break up in the stomach with complete dispersion of the core and removal of the radiolabelled material from the stomach taking 26 min (range 2–56 min; $n = 5$) in Group B (gastric emptying T50). Although disintegration generally occurred in the stomach, for one subject in Group B the tablet emptied intact from the stomach before the first images after dosing were collected. For Group A subjects gastric emptying (T50) took 41 min (range 13–76 min; $n = 7$). Onset of colonic arrival was generally earlier in those in Group B compared with the normal profile (Group A) subjects as illustrated in representative scintiscans (Figs. 3–5).

In both groups of subjects, increases in plasma concentrations of gefitinib corresponded with the movement of the radiolabelled

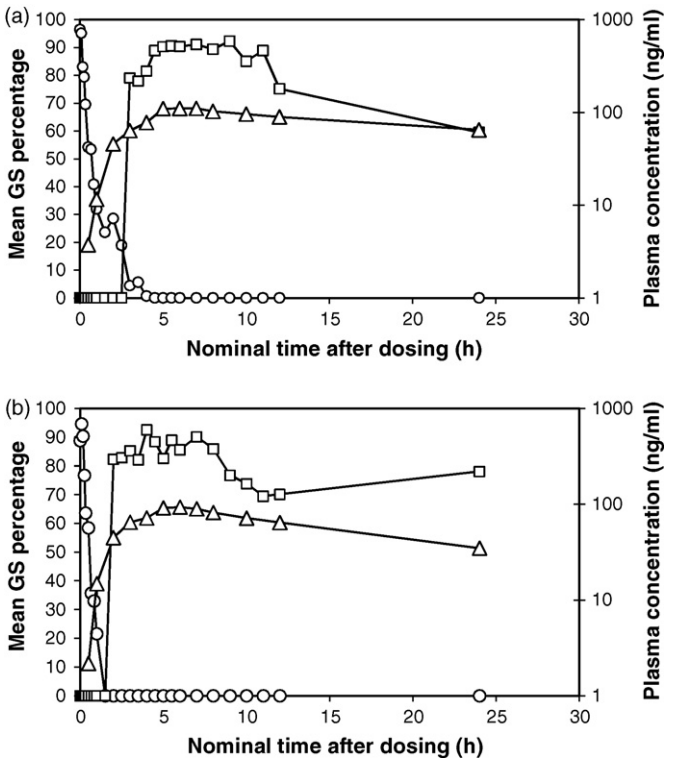

Fig. 2. (a) Gastrointestinal transit parameters for normal group where ○, mean % gastric emptying; □, mean % colonic arrival; △, plasma concentration. (b) Gastrointestinal transit parameters for rapid clearance group Where ○, mean % gastric emptying; □, mean % colonic arrival; △, plasma concentration.

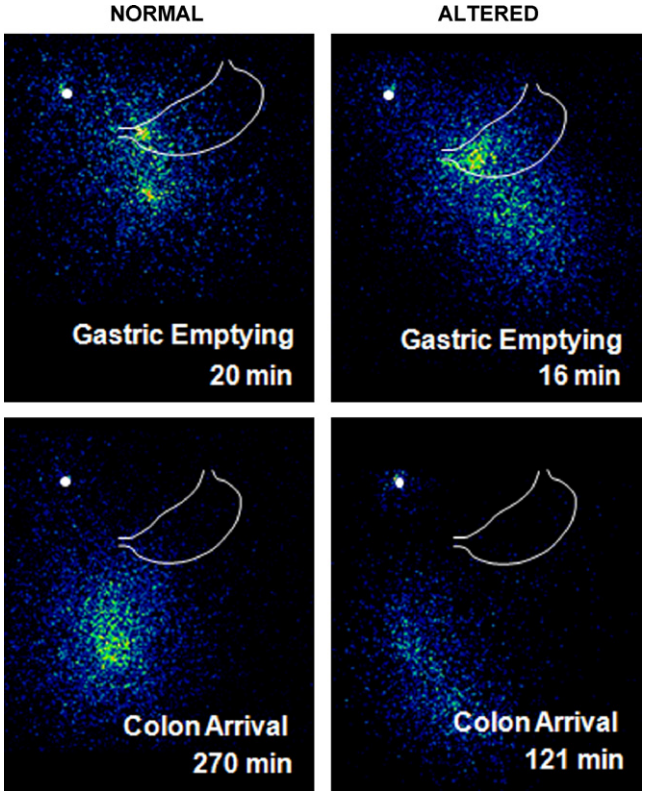

Fig. 3. Example scintigraphic images showing gastric emptying and colonic arrival in normal and rapid clearance subject groups. External marker indicated by white circle.

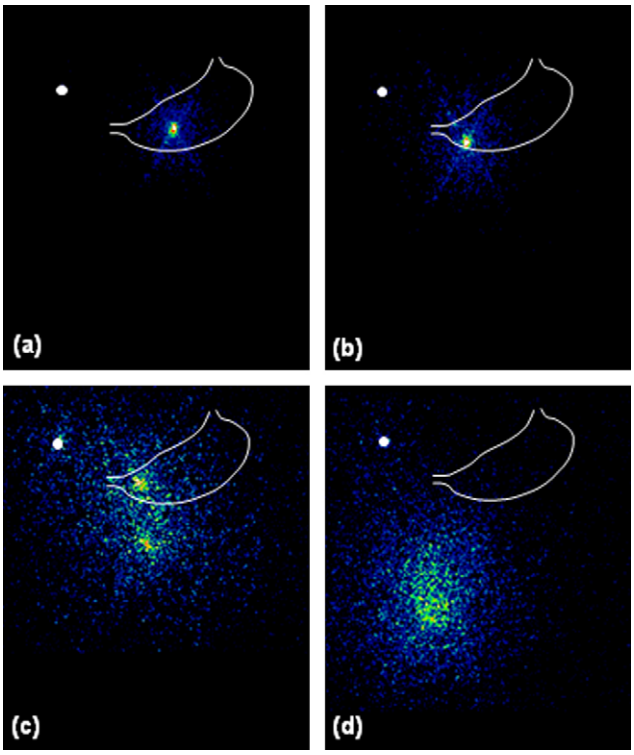

Fig. 4. Scintigraphic images from Subject 001 (normal Group) (a) tablet image (^{111}In) immediately after dosing, (b) onset of tablet dispersion at 16 min (c) completion of tablet dispersion at 20 min. Colonic arrival of tablet marker occurs at image (d; 270 min). External marker indicated by white circle.

material from the stomach to the small intestine, while colonic arrival coincided with the plateau or decrease in the gefitinib plasma concentration curve as demonstrated in Fig. 2a and b.

4. Discussion

Drug absorption is a complex process dependent upon drug properties such as solubility and permeability, formulation factors, and physiological variables including gastric acid secretion, gastric emptying time, GI blood flow, and surface area (Martinez and Amidon, 2002) along with phenotypic differences in drug transporter function, luminal conditions, and overall drug transit through the GI tract (Dietrich et al., 2003; Pang, 2003).

Variability within a population of the plasma concentration–time profiles after oral dosing is anticipated as a function of either (i) genetic, and therefore metabolic, differences in individuals or (ii) those differences relating to physiological variables. Both these factors result in observable differences in the rate and extent of drug absorption expressed as C_{max}, t_{max} and AUC. Sometimes, a difference in shape of the curve which is complex and defies simple descriptors results from an interaction of physicochemical and physiological processes; for example, solubility changes seen as a formulation traverses stomach to intestine and experiences huge differences in luminal pH.

The 12 healthy male subjects enrolled in this study had previously received at least 1 dose of gefitinib with sufficient follow-up of pharmacokinetic sampling to identify the profile as being either bi- or monophasic. The pharmacokinetic data generated by this study are highly consistent with those originally reported for these subjects in studies conducted up to six years earlier.

Given the multifactorial nature of drug absorption, it is not realistic to believe that it would be possible in one study to fully elucidate all of the factors responsible for the pharmacokinetic profile differences, and several more studies would therefore need to be conducted. Nevertheless, the data from this study does indicate that differences in drug transit through the GI tract may be, in part, responsible for the differences in the pharmacokinetic profiles between the 2 healthy volunteer groups. In particular, the results from imaging show that the residence time in the stomach and small intestine were generally shorter for the monophasic profile subjects compared to those with the normal biphasic profile. Furthermore, the increase in plasma concentration of gefitinib corresponded in both treatment groups with gastric emptying, while the plateau (t_{max}) of the plasma concentration–time curve corresponded with colonic arrival. Collectively, these data suggest that there is a slowing down in the absorption of gefitinib as the material arrives in the colon.

The rapid GI transit could be due to either early gastric emptying or to fast intestinal transit. The former would reduce the time for dissolution in the stomach and, due to the much lower solubility in the intestine, lead to an overall reduction in dissolution extent and therefore absorption; the latter would decrease the time for both dissolution and/or permeation. Higher gastric pH, as seen in profound hypochlorhydria would also reduce drug dissolution in the stomach and may have a similar impact to rapid gastric emptying.

It is possible that the lower exposure in the subjects with the rapid clearance profile could be exaggerated because of the reduced amount of gefitinib absorbed and a change in the shape of the profile resulting from the more rapid cessation of absorption. These two factors could combine to result in plasma concentrations that, relative to the limit of quantification of the assay, would present as a monophasic decline coupled with an apparently reduced AUC.

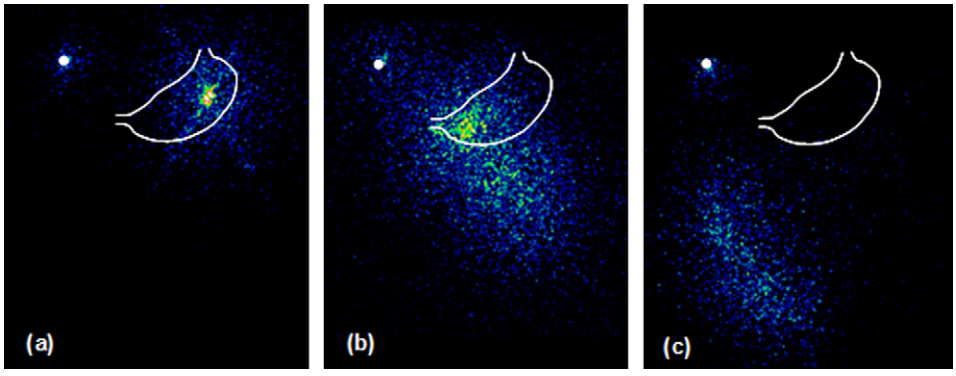

Fig. 5. Scintigraphic images from Subject 011 (altered Group) (a) tablet image (^{111}In) immediately after dosing, (b) onset and completion of tablet dispersion at 16 min. Colonic arrival of tablet marker occurs at image (c; 121 min). External marker indicated by white circle.

Bergman and colleagues have recently described data from intubation techniques (Loc-I-Gut) obtained following direct gastric administration and jejunal sampling of a single oral dispersion of 250 mg gefitinib in 50 mL water containing [^{14}C]-PEG 4000. The objective of the study was to quantify the absorption profile and to examine whether precipitation of the dose occurs in the intestinal lumen. The pharmacokinetic parameters obtained were compared with a separate experiment in which a tablet (250 mg) was administered to non-intubated volunteers with a similar water load (Bergman et al., 2007). Within the Bergman study population, as here, the subjects were stratified into normal (68 subjects) and rapid clearance (24 subjects) and a clear difference in half-life and AUC was seen between the groups consistent with earlier findings. The subsets that were intubated (7 normal, 6 rapid clearance) showed a significant difference in half-life but not the AUC. The samples were examined to determine the crystal habit using Raman microscopy. No differences in the amount of solid recovered or the crystal form were evident.

The purpose of this study was to explore mechanisms that might explain the pharmacokinetic variability observed with gefitinib. Although the results appear to confirm a link between gastrointestinal transit and gefitinib absorption the findings have limitations in respect of predicting clinical efficacy. In previous studies of gefitinib in patients with cancer a clear relationship of dose or plasma concentrations with target inhibition or clinical benefit has not been established (AstraZeneca data on file). Nevertheless, at the recommended dose of gefitinib (250 mg/day), plasma concentrations of gefitinib above the *in vitro* IC_{50} for target inhibition were maintained in most patients in two Phase 2 studies in patients with non-small cell lung cancer. Furthermore, in these studies some patients showing a clinical response had plasma concentrations below the *in vitro* IC_{50}, suggesting that even with the pharmacokinetic variability plasma concentrations of gefitinib following 250 mg/day are adequate for clinical benefit (AstraZeneca data on file).

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