Effect of high-fat diet on the pharmacokinetics and safety of flumatinib in healthy Chinese subjects

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Abstract

Purpose To evaluate the effect of a high-fat diet on the pharmacokinetics and safety of flumatinib mesylate tablets in healthy Chinese subjects.

Methods This study was a randomized, open-label, single-dose, two-period crossover trial in which subjects were randomly assigned to take 400 mg of flumatinib mesylate after a high-fat diet or a fasted state. After a 14-day washout period, the two groups were administered flumatinib mesylate under opposite conditions. Blood samples were collected at baseline 0 and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 48, 72, and 96 h, respectively. Plasma concentrations of flumatinib and its metabolites (M1 and M3) were analyzed using liquid chromatography-mass spectrometry. Pharmacokinetic parameters were calculated using the non-compartmental module of the Phoenix WinNonlin Version 7.0 software. BE module of WinNonLin was used for statistical analysis of AUC 0–t, AUC 0–∞ and Cmax in plasma.

Results Twelve healthy subjects, half male and half female, were enrolled. One subject withdrew due to a treatment-emergent adverse event. Eleven subjects were administered drugs on fasting and 12 were administered drugs after a high-fat diet. On high-fat diet/fasting, the least square geometric mean (LSGM) ratios of flumatinib, M1, M3, and their 90% confidence interval (CI) were as follows: for flumatinib, Cmax, AUC 0–t and AUC 0–∞ were 281.65% (225.80–351.31%), 167.43% (143.92–194.79%), and 166.87% (143.47–194.09%); for M1, Cmax, AUC 0–t, and AUC 0–∞ were 188.59% (145.29–244.79), 163.94% (149.11–180.24%), and 164.48% (150.36–179.94%); for M3, Cmax, AUC 0–t, and AUC 0–∞ were 63.47% (54.02–74.57%), 85.23% (74.72–97.22%), and 96.73% (86.63–108.02%).

Conclusion Among the subjects, oral administration of 400 mg of flumatinib was safe and well tolerated. High-fat diet significantly increases the exposure to flumatinib, therefore, fasting may be recommended.

Clinical trial registration The study was registered at chictr.org Identifier: ChiCTR-IIR-17013179.

Keywords Pharmacokinetics · Flumatinib · High-fat diet · Healthy subject

Background

Chronic myelogenous leukemia (CML) also called chronic granulocytic leukemia, is a slowly progressing blood and bone marrow disease that usually occurs during or after middle age,
and rarely occurs in childhood [1]. A reciprocal chromosome translocation (9 and 22), called the Philadelphia chromosome, causes a constitutive activation of the BCR-ABL tyrosine kinase, leading to CML [2–5]. Current strategies for CML treatment involve the use of tyrosine kinase inhibitors, which can inhibit the BCR-ABL phosphorylation, thereby preventing the proliferation of cancer cells and activating subsequent apoptosis [2, 6–9]. Currently, resistance to the first-line drug imatinib has led to the development of other novel tyrosine kinase inhibitors [10].

Previous pharmacokinetic (PK) data of flumatinib showed that it was safe and well-tolerated, and Cmax and AUC0–t were linearly related to doses in the range of 200–1000 mg [11]. Preclinical pharmacokinetic studies showed that, in rats and beagles, the maximum blood concentration could be reached in about 5 h after oral administration of the drug. Furthermore, flumatinib mesylate was widely distributed in tissues, with tissue drug concentration higher than that in plasma concentration. The parent drug flumatinib was present in plasma, urine, and feces. The primary metabolites in plasma were N-desmethyl flumatinib (M1), which was approximately 10% of that of the parent drug in plasma and has been shown to have similar pharmacological properties as the parent drug. The amide hydrolysis product (M3), which was inactive but approximately 30% of that of the parent drug in plasma [12]. Therefore, plasma concentrations of flumatinib, M1, and M3 were necessary to evaluate their circulating levels in humans.

Several studies have shown that gastrointestinal reactions, including abdominal pain, diarrhea, bloating, are the most common adverse reactions to tyrosine kinase inhibitors [13–16]. Therefore, tyrosine kinase inhibitors are often recommended to be administered with food. However, food may affect gastric pH, emptying, and movement in the stomach, subsequently affecting drug absorption. In addition, since flumatinib is a lipophilic drug, and thus a high-fat diet may increase its solubility and (relative) bioavailability [17, 18]. Results from the Phase Ia clinical trials showed that the flumatinib absorption increased when administrated orally with food. However, as there are many influencing factors in patients with Phase Ia, it is important to evaluate the effect of food on the pharmacokinetics and safety of flumatinib mesylate in healthy subjects [19].

This study aimed to determine the effect of a high-fat, high-calorie diet on the pharmacokinetics of flumatinib in healthy subjects. The subjects were randomized 24 h in advance in one of the two following groups. Group A: at least 10 h after fasting, oral flumatinib administration of 400 mg (2 tablets, day 1, first dose); the washout period was 14 days, half an hour after high-fat diet (timed from the start of diet) oral flumatinib administration of 400 mg (2 tablets, day 15, second dose). Subjects in group B followed the opposite administration sequence from those in group A. In groups A and B, the high-fat diet contained 800–1000Kcal (about 50% from fat) (meal composition is detailed Table 1).

Study design

This study was a single-center, randomized, open-label, two-period, crossover design to evaluate the effects of a high-fat diet on the pharmacokinetics of flumatinib in healthy subjects. The subjects were randomized 24 h in advance in one of the two following groups. Group A: at least 10 h after fasting, oral flumatinib administration of 400 mg (2 tablets, day 1, first dose); the washout period was 14 days, half an hour after high-fat diet (timed from the start of diet) oral flumatinib administration of 400 mg (2 tablets, day 15, second dose). Subjects in group B followed the opposite administration sequence from those in group A. In groups A and B, the high-fat diet contained 800–1000Kcal (about 50% from fat) (meal composition is detailed Table 1).

Pharmacokinetic evaluations

Blood samples for pharmacokinetic (PK) evaluation were collected at 0 h before the initiation of dosing (pre-dose), and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 48, 72, and 96 h after dosing. Blood samples were centrifuged at 2000g for 10 min at 4 °C. Centrifugation was completed within 60 min after sample collection. The plasma was stored at −70 °C for further analysis. Plasma concentrations of flumatinib and its main metabolites (M1 and M3) were determined using liquid chromatography-mass spectrometry (LC–MS/MS) [20].

Subjects

Healthy Chinese subjects were screened for eligibility about 1 week before drug administration. Eligibility criteria included healthy Chinese adults, aged 18–45 years, body mass index (BMI) of 19–24 kg/m², and a minimum weight of 50 kg. The subjects had no history of cardiovascular, endocrine, metabolic, neurological, gastrointestinal, hepatic, pulmonary, infectious, immunological, or psychiatric diseases. We excluded subjects with a history of alcohol abuse, cigarette or drug dependence, or under concomitant treatments defined as using any drug that inhibits/induces hepatic metabolizing enzymes, within 30 days, or having undergone a surgery in the last 4 weeks. In addition, female subjects who were pregnant, planning on conceiving, using oral contraception, or in the menstrual cycle were excluded from this study.

The study was approved by the Medical Ethics Committee of the Third Xiangya Hospital of Central South University (an independent data safety monitoring committee, certified by the Association for the Accreditation of Human Research Protection Program). All participants provided written informed consent prior to any study-related procedure.

Methods
Safety evaluations

All subjects who participated in the study were included in the safety analysis. Safety was evaluated by vital signs, physical examination, ECG, laboratory examination, adverse events (AEs), and combined medication. All adverse events that occurred during the trial were classified into mild, moderate, and severe levels based on NCI CTCAE v4.03.

Statistical analysis

Phoenix WinNonlin Version 7.0 (Pharsight Corporation, Sunnyvale, CA, USA) software was used to calculate the pharmacokinetic parameters ($T_{\text{max}}$, $C_{\text{max}}$, AUC$_{0-t}$, AUC$_{0-\infty}$, $t_{1/2}$, V/F, CL/F) of flumatinib and its main metabolites using a non-compartmental method (NCA module). Linear Up Log Down trapezoidal method was used for AUC calculation. The BE module of WinNonLin was used to analyze AUC$_{0-t}$, AUC$_{0-\infty}$, and $C_{\text{max}}$ of flumatinib in fed and fasting states after logarithmic conversion. The treatment group (fasting, high-fat diet), the treatment sequence (A, B), and treatment phase were fixed effects in the model, and the subjects nested in the sequence were random effects. The adjusted mean difference (fasting/high-fat diet) and its 90% confidence interval estimated by the model, were taken as the negative number to obtain the corresponding PK parameter geometric mean ratio (postprandial/fasting), to estimate its 90% confidence interval, and to evaluate the effect of a high-fat diet on the pharmacokinetics of flumatinib.

Results

Subjects

This study was conducted between May 8, 2017 and June 10, 2017. Thirty-six eligible patients were invited to participate in the study; a total of 12 patients agreed to be enrolled and were randomly assigned to group A or group B ($n=6$ each). One subject in group B withdrew due to adverse events before the second period (Fig. 1). Half of the subjects were male and half were female. Age, height, weight, and BMI of the subjects were $23.5\pm 4.72$ years, $165.0\pm 7.20$ cm, $59.2\pm 5.10$ kg, and $21.8\pm 1.92$ kg/m$^2$, respectively. The demographic and baseline characteristics of all subjects are presented in Table 2. Twelve subjects were involved in pharmacokinetics evaluations of high-fat diet and safety analysis, 11 subjects were included pharmacokinetics evaluations of fasting and the food effect on flumatinib pharmacokinetics.

Pharmacokinetic evaluations

The mean plasma concentration versus time profiles of flumatinib, M1 and M3 in healthy Chinese subjects receiving a single oral dose of flumatinib mesylate tablet (400 mg) are shown in Fig. 2. The $C_{\text{max}}$, AUC$_{0-t}$, AUC$_{0-\infty}$, and the secondary pharmacokinetic endpoints ($T_{\text{max}}$, $t_{1/2}$, V/F, CL/F and MRT) of flumatinib, M1 and M3 are shown in Table 3.

Table 1

| Nutrients | Chinese oil sticks (100 g) | Egg (100 g) | Mixed oil (30 g) | Terunusu milk (250 ml) | Total (g) | Calories (KCal) | Percentage of calories (%) |
|-----------|---------------------------|-------------|-----------------|------------------------|-----------|-----------------|---------------------------|
| Protein (g) | 6.90                      | 13.3        | 0               | 9.00                   | 29.2      | 117             | 11.9                      |
| Carbohydrates (g) | 50.1                     | 2.80        | 0               | 12.5                   | 65.4      | 261             | 26.5                      |
| Fat (g)     | 17.6                      | 8.80        | 30.0            | 11.0                   | 67.4      | 607             | 61.6                      |
| Total       | 74.6                      | 24.9        | 30.0            | 32.5                   | 162       | 985             | 100                       |

*1 g protein was calculated by 4 kcal calories, 1 g carbohydrate by 4 kcal calories, and 1 g fat by 9 kcal calories. The Chinese oil sticks were calculated according to the finished products, and the eggs and mixed oil were calculated by raw food weight. Only the breakfast on the first day of each cycle was different. Other meals were totally the same for all the subjects in this trial.
increased 1.6-fold. Except for the 90%CI of M3 AUC \(_{0-\infty}\) which was within 80.00–125.00%, the other parameters of flumatinib and metabolites M1 and M3 had 90% CI outside 80.00–125.00%. This indicated that a high-fat diet had a significant effect on pharmacokinetic of flumatinib, M1, and M3. And a high-fat diet can increase the peak concentration and systemic exposure of flumatinib and M1.

**Safety evaluations**

Safety evaluations were performed in all subjects (\(n = 12\)). In the fasting group, there were nine cases of...
treatment-emergent adverse event (TEAE) (81.8%) and eight (72.7%) were related to the study drug. (Table 5). In the high-fat diet group, there were ten cases of TEAE (83.3%) and seven (58.3%) were related to the study drug. Except for one case of moderate acute gastroenteritis (withdrawal), the other TEAEs were mild. Acute gastroenteritis was completely relieved after treatments, including anti-infection, spasmolysis, antiemesis and acid suppression. Other mild adverse events disappeared without any treatment. The TEAE related to the drug included mild gastrointestinal symptoms (abdominal pain, diarrhea, and abdominal distension) and mild laboratory abnormalities (alanine aminotransferase, blood magnesium, and uric acid slightly increase).

Discussion

The results of the Phase Ia clinical trial showed that there were significant differences in AUC and Cmax of flumatinib and M1 between fasting and high-fat diet (p < 0.05), implying the oral absorption of flumatinib could be promoted by postprandial administration. These are similar to the results of our study in healthy people. This is consistent with a report on a similar drug (ivosidenib), in which a 98% increase in Cmax was observed in healthy subjects who were given the drug after a high-fat diet, as compared to the fasting [21]. The increase in bioavailability of lapatinib after low-fat and high-fat diet were 167% and 325%, respectively [22]. The reasons for our results are as follows, First, a high-fat diet increases the secretion of bile acid (BA), especially secondary BA, such as deoxycholic acid and lithocholic acid, which slows gastric emptying and weakens intestinal peristalsis, resulting in prolonged retention time of flumatinib in the gastrointestinal tract, thereby increasing absorption [23]. Second, flumatinib is a lipophilic drug, thus, a high-fat diet can increase the solubility of flumatinib, thereby promoting drug absorption and increasing its (relative) bioavailability.

### Table 3 Pharmacokinetics Parameters of Fasting and High-fat Diet

| Parameters | Flumatinib | M1 | M3 |
|------------|------------|----|----|
|            | Fasting (N=11) | High-fat diet (N=12) | Fasting (N=11) | High-fat diet (N=12) | Fasting (N=11) | High-fat diet (N=12) |
| T_{max} (h) | 2.50 (1.50–5.00) | 3.00 (1.50–5.02) | 2.00 (0.50–4.00) | 2.25 (1.50–5.02) | 2.50 (1.50–4.00) | 4.00 (2.00–10.00) |
| C_{max} (ng/mL) | 50.7 ± 32.5 | 132 ± 54.5 | 27.2 ± 7.14 | 54.7 ± 25.5 | 7.95 ± 2.07 | 5.17 ± 2.21 |
| AUC_{0-1} (ng.h/mL) | 832 ± 566 | 1260 ± 582 | 231 ± 101 | 368 ± 176.6 | 68.6 ± 20.4 | 56.6 ± 21.9 |
| AUC_{0-∞} (ng.h/mL) | 847 ± 572 | 1277 ± 586 | 243 ± 108 | 390 ± 191 | 74.1 ± 19.5 | 66.1 ± 25.5 |
| t_{1/2} (h) | 13.3 ± 2.52 | 15.5 ± 4.67 | 22.8 ± 6.96 | 24.4 ± 5.80 | 8.34 ± 1.91 | 8.52 ± 2.40 |
| CL/F (L/h) | 661 ± 380 | 399 ± 229 | / | / | / | / |
| V/F (L) | 11,700 ± 5130 | 8470 ± 4130 | / | / | / | / |
| MRT (h) | 19.2 ± 3.37 | 17.2 ± 3.66 | 24.3 ± 4.37 | 23.5 ± 4.20 | 11.5 ± 2.52 | 14.0 ± 3.69 |

All data are given as the mean ± standard deviation.

### Table 4 Effect of high-fat diet on the pharmacokinetics of flumatinib, M1, and M3

| Pharmacokinetics parameters | Flumatinib | M1 | M3 |
|----------------------------|------------|----|----|
|                            | Fasting (N=11) | High-fat diet (N=11) | LSGM ratio high-fat diet/ fasting (%) (90% CI) | Fasting (N=11) | High-fat diet (N=11) | LSGM ratio high-fat diet/ fasting (%) (90% CI) | Fasting (N=11) | High-fat diet (N=11) | LSGM ratio high-fat diet/ fasting (%) (90% CI) |
| C_{max} (ng/mL) | 43.7 | 123 | 282 (226, 351) | 26.3 | 49.6 | 189 (145, 245) | 7.69 | 4.88 | 63.5 (54.0, 74.6) |
| AUC_{0-1} (ng.h/mL) | 696 | 1170 | 167 (144, 195) | 212 | 347 | 164 (149, 180) | 65.5 | 55.9 | 85.2 (74.7, 97.2) |
| AUC_{0-∞} (ng.h/mL) | 710 | 1180 | 167 (143, 194) | 223 | 367 | 164 (150, 180) | 68.7 | 66.5 | 96.7 (86.6, 108) |

AUC_{0-1} area under the concentration–time curve from zero to the final measurable concentration, AUC_{0-∞} area under the concentration–time curve from time zero to infinity, C_{max} maximum concentration, t_{1/2} elimination half-life, MRT mean residence time.
Table 5  Summary of adverse events

| Index | Fasting | High-fat diet |
|-------|---------|---------------|
|       | The first period (N=6) | The second period (N=5) | Total (N=11) | The first period (N=6) | The second period (N=6) | Total (N=12) |
|       | Time | Number | Incidence rate | Time | Number | Incidence rate | Time | Number | Incidence rate | Time | Number | Incidence rate |
| TEAE14 | 14 | 6 | 100.0 | 5 | 3 | 60.0 | 19 | 9 | 81.8 | 18 | 6 | 100.0 |
| SAE related to the study drug | 11 | 5 | 83.3 | 4 | 3 | 60.0 | 15 | 8 | 72.7 | 6 | 3 | 50.0 |
| TEAE related to death | 0 | 0 | 0.0 | 0 | 0 | 0.0 | 0 | 0 | 0.0 | 0 | 0 | 0.0 |
| TEAE related to withdrawal | 0 | 0 | 0.0 | 0 | 0 | 0.0 | 1 | 1 | 16.7 | 0 | 0 | 0.0 |

*TEAE* treatment-emergent adverse event, *SAE* severity adverse even
The combination of a high-fat diet with flumatinib increased the bioavailability of flumatinib and M1. So taking it with food (which may increase its bioavailability) may have clinical implications, such as toxic reactions and increased accumulation. In this study, there was no significant increase in adverse reactions after a high-fat diet as compared with fasting. Combined with the clinical data of Phase II and III, the exposure and bioavailability of flumatinib after a high-fat diet was increased, so postprandial administration may have potential risks. The exposure and bioavailability of nilotinib, which is a BCR-ABL tyrosinase inhibitor, increased significantly after administration with food compared with fasting. In healthy subjects, $C_{\text{max}}$ and AUC were reported to be 112% and 82% higher when taken with food than fasting [26]. Therefore, the marketing instructions for nilotinib indicate that it should be taken on an empty stomach. Therefore, in terms of the selection of the drug administration recommended in the later stage of clinical practice, flumatinib may only be taken on an empty stomach without food.

**Conclusion**

Oral administration of flumatinib at a single dose of 400 mg was safe and well tolerated in healthy subjects on fasting or a high-fat diet. However, considering the significant increase (67%) in the exposure to flumatinib when taken with food, flumatinib may be recommended to be taken in the fasted state.

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**Author contributions**

All authors contributed to the study conception and design. Jie Huang, Qing-nan He designed and supervised the research. Material preparation, data collection and analysis were performed by YK, H-lS, G-pY, QP, X-yY, LY, SY, H-tW, CG performed research. The first draft of the manuscript was written by YK and all authors commented on previous versions of the manuscript. YK, JH and Q-nH reviewed and modified the manuscript. All authors read and approved the final manuscript.

**Compliance with ethical standards**

**Conflict of interest**

There are no competing interests to declare.

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