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Technical Note

Influence of Food on the Bioavailability of Ro 15-0778 in Humans

Alice A. Holazo,[1,2] Evelyn E. Pinili,[1] Francis T. De Grazia,[1] and Indravadan H. Patel[1]

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INTRODUCTION

Ro 15-0778 (1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-[(*E*)-alpha-methylstyryl]naphthalene) is a member of a new class of highly active retinoids called "arotinoids." These compounds are under clinical investigation for a variety of skin disorders. Ro 15-0778 is metabolized to an inactive phenolic metabolite, Ro 14-6113, which is present in plasma following oral administration of Ro 15-0778 to humans. The structures of the parent drug and metabolite are shown in Fig. 1.

Food has been shown to influence the bioavailability of orally administered drugs (1,2). For most drugs, the absorption from the gastrointestinal tract is reduced or delayed by food. However, it is increased for a small number of poorly water-soluble drugs such as griseofulvin (3,4), nitrofurantoin (5,6), and carbamazepine (7). Recently, food intake has also been shown to increase significantly the bioavailability of retinoids such as acitretin, accutane, and etretinate (8–10). Relative bioavailability increased approximately two- to three-fold when these drugs were administered with food. A similar effect may also occur with Ro 15-0778, a structurally related compound. Hence, the present study was conducted to determine the effect, if any, of food on the bioavailability of Ro 15-0778 from Neobee capsules.

MATERIALS AND METHODS

Twelve healthy male subjects, ranging in age from 20 to 31 years (mean, 25 years) and in weight from 65 to 84 kg (mean, 73 kg), participated in this study after giving their written, informed consent. The subjects were in good general health as determined by baseline history, physical examination, hematologic examination, urinalysis, and determination of serum chemistries. Subjects with clinically significant abnormal baseline findings or who had a history of significant disease, subjects with a history of hypersensitivity to Ro 15-0778 or other retinoids, and subjects who required prescription or over-the-counter (OTC) medication prior to and/or during the course of the study were excluded. The protocol was approved by the Institutional Review Board at L.A.B. GmBH and Co., Neu-Ulm/FRG.

Subjects received two drug treatments in a randomized crossover fashion with a 1-week washout period between treatments. The subjects reported to the Research Unit 12 hr prior to the start of each treatment. A light snack was served 10 hr prior to dosing, after which an absolute fast, except for water, was maintained until dosing. The next morning each subject received one of two treatments. Treatment A consisted of a 96-mg dose (3 × 32-mg soft gelatin capsules of Ro 15-0778 in Neobee oil) with 120 ml of water followed by a complete fast, and Treatment B consisted of a 96-mg dose (3 × 32-mg soft gelatin capsules of Ro 15-0778 in Neobee oil) with 120 ml of water halfway through a standard breakfast. The standard breakfast consisted of 2 poached eggs, 1 slice of toast with a pat of margarine, and 8 oz of skimmed milk. Following both treatments a fast was maintained until the 4-hr blood sample was obtained, after which lunch was provided. Dinner was served 10 hr after dosing. The subjects remained ambulatory for at least 2 hr after drug administration.

Ro 15-0778 is subject to photoisomerization, and therefore, all blood samples were collected into foil-wrapped heparinized tubes under yellow light. A 15-ml blood sample was collected prior to drug administration (0 hr) and then 10-ml samples were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 11, 14, 24, 27, 30, 33, 48, 60, 72, 84, and 96 hr after drug administration. All subjects were confined to the study site until the 33-hr blood sample was collected. They returned to the unit at appropriate times for collection of the remaining samples. Plasma concentrations of Ro 15-0778 and Ro 14-6113 were measured by a specific HPLC method. All analytical work was performed at Hoffmann-La Roche, Nutley, N.J. In brief, the assay for both compounds involves the precipitation of the plasma proteins with acetonitrile, followed by extraction of the entire mixture into methyl-t-butyl ether, and subsequent analysis by reversed-phase HPLC. The HPLC system consisted of a Model M6000A reciprocating piston pump (Waters, Milford, Mass.), a Waters Intelligent Sample Processor (WISP) Model 710B, and a Spectroflow Model 757 absorbance detector operated at 280 nm (Kratos, Ramsey, N.J.). The isocratic mobile phase used was a mixture of methanol:acetonitrile:water (90:5:5) at a pressure of

[1] Department of Drug Metabolism, Hoffmann-La Roche, Inc., Nutley, New Jersey 07110.
[2] To whom correspondence should be addressed.

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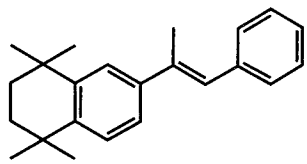
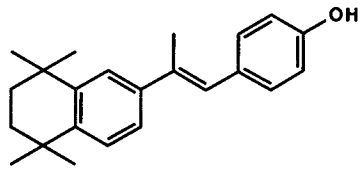


Ro 15-0778



Ro 14-6113

Fig. 1. Structures of Ro 15-0778 and Ro 14-6113.

2000 psi and a constant flow rate of 2 ml/min. The column used was a prepacked 24 cm × 4.6-mm-ID stainless-steel column containing 5-μm Spherical Sepralyte microparticulate C18 bonded silica gel (Analytichem International, Harbor City, Calif.). The retention times of Ro 15-0778 and Ro 14-6113 were 6.9 and 3.3 min, respectively. The sensitivity limit of detection was 0.02 μg/ml for both compounds. The mean coefficients of variation for interassay precision for Ro 15-0778 and Ro 14-6113 were 4.9 and 6.1%, respectively, over a concentration range of 0.02 to 2.0 μg/ml.

The maximum plasma concentration (C_{max}) and its time of occurrence (t_{max}) were read directly from the plasma concentration-time data. The area under the plasma concentration–time curve from time zero to 96-hr postdose (AUC_{0-96}) was calculated by linear trapezoidal summation. The elimination rate constant (β) was estimated for Ro 15-0778 only and was done by fitting the descending plasma concentration–time data to a polyexponential equation using nonlinear least-squares regression analysis (11). The terminal half-life ($t_{1/2}$) was calculated by dividing ln 2 by β.

RESULTS

Ro 15-0778 was well tolerated by all the subjects, and clinically significant adverse events attributable to the drug were not observed.

The mean pharmacokinetic parameters of Ro 15-0778 and Ro 14-6113 in both fasted and fed states are presented in Table I. The corresponding plasma concentration–time profiles are shown in Fig. 2. In the fasted state, plasma concentrations of Ro 15-0778 were nonmeasurable or close to the assay sensitivity limit (0.02 μg/ml) in 8 of 12 subjects. C_{max} ranged from 0.02 to 0.13 μg/ml and occurred 4 to 14 hr after drug administration. When the drug was administered with food, higher plasma concentrations of Ro 15-0778 were observed in all subjects, with C_{max} values ranging from 0.42 to 2.40 μg/ml and occurring at 2 to 8 hr after dosing.

The higher C_{max} and earlier t_{max} values suggest that the rate of absorption of Ro 15-0778 from the Neobee formulation was increased in the presence of food. The extent of absorption from the capsule was also greatly enhanced when the drug was administered with food as shown by the increase in the AUC_{0-96} values from 0.99 to 11.92 μg · hr/ml. Plasma concentrations of Ro 14-6113, the phenolic metabolite, were also shown to increase in the presence of food (Fig. 2), reflecting the enhanced absorption of Ro 15-0778 from the capsule when given with food.

DISCUSSION

The influence of food on the gastrointestinal absorption of Ro 15-0778 from soft gelatin capsules was studied in

Table I. Mean (± %CV) Pharmacokinetic Parameters for Ro 15-0778 and Ro 14-6113 After Administration of a Single 96-mg Oral Dose of Ro 15-0778 in the Presence and Absence of Food

Parameter	Ro 15-0778 Fasted	Ro 15-0778 Fed	Ratio, fed/fasted[a]
C_{max} (μg/ml)	0.07 (43)	1.49 (33)	23.4 (49)
t_{max} (hr)	6.9 (39)	4.8 (44)	0.7 (57)
AUC_{0-96} (μg · hr/ml)	0.99 (82)	11.92 (35)	15.2 (70)
$t_{1/2}$ (hr)	—	24.1[b]	

Parameter	Ro 14-6113 Fasted[c]	Ro 14-6113 Fed	Ratio, fed/fasted[a]
C_{max} (μg/ml)	0.04 (40)	0.26 (38)	6.7 (44)
t_{max} (hr)	12.5 (62)	6.7 (15)	0.7 (47)
AUC_{0-96} (μg · hr/ml)	1.66 (62)	7.24 (17)	5.4 (103)

[a] Mean of individual parameter ratios.
[b] Harmonic mean.
[c] $N = 8$.

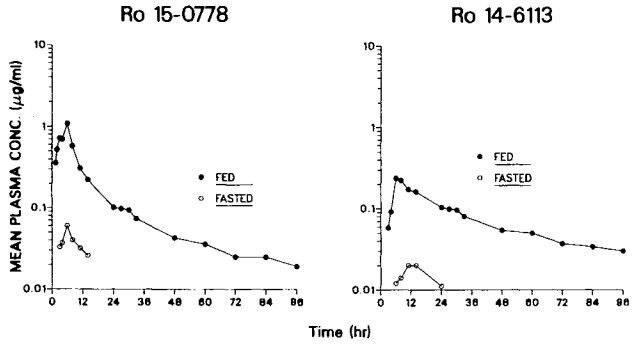


Fig. 2. Mean plasma concentration–time profiles of Ro 15-0778 and Ro 14-6113 following oral administration of 96 mg of Ro 15-0778 under fasted (○) and fed (●) conditions.

healthy subjects by administering a 96-mg dose (3 × 32-mg capsules) of Ro 15-0778 with a standard breakfast and during a complete fast. The results observed in the present study are consistent with the findings in previous studies on the effect of food on the bioavailability of retinoids (8–10), except that the food effect in the present study is more pronounced. Coadministration of food with accutane capsules resulted in a 1.5- to 2-fold increase in bioavailability (9), and administration of a high-fat meal with etretinate resulted in a three- to five-fold increase in plasma concentrations (10). In a recent study (8), the apparent bioavailability of acitretin was increased twofold in the presence of food.

Food has been shown to increase the bioavailability of drugs subject to extensive first-pass metabolism (12,13) and drugs which are poorly water-soluble (3–7). The food effect on drugs subject to extensive first-pass metabolism is explained, at least in part, by the transient elevation of the splanchnic–hepatic blood flow (14,15). The food effect on drugs which are poorly water-soluble is rationalized in terms of delayed gastric emptying and gastrointestinal transit, which allow more complete dissolution and/or prolonged residence at the site of absorption (14). Food may also increase absorption of fat-soluble drugs directly by increasing rate of dissolution or indirectly by increasing the flow of bile, with its solubilizing agents, into the intestinal tract (3,4). As previously suggested (9), the last two possibilities seem to be the most plausible explanation for the increased bioavailability of retinoids when administered with food. Since Ro 15-0778 is structurally related to the retinoids, the increased bioavailability of the drug in the presence of food could also be similarly explained.

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