Evaluation of the effect of different kinds of foods on the bioavailability of a sustained-release theophylline tablet

M. N. Gai, A. M. Thielemann and A. Arancibia

Department of Science and Pharmaceutical Technology. Faculty of Chemical and Pharmaceutical Sciences, University of Chile, Santiago, Chile

Abstract. Food-induced changes on the bioavailability of a sustained-release theophylline tablet, which uses acrylic resins Eudragit as sustaining agent, were studied in 12 healthy male volunteers. The tablet was developed in our laboratory using conventional technology. It presented a good bioavailability pattern and maintained plasmatic concentrations within the therapeutic range for 12 hours under conditions of steady-state. The study design was a 4 × 4 latin square involving 12 subjects who received a single dose of the tablet while fasting of with a standarized normal, high fat or high fat/high protein meal. The results showed no differences in AUC, K, t_{max}, ka and MRT. Statistical differences were found in C_{max} comparing the fasting condition with high fat/high protein diet. A delay was also observed in the detection of the drug in plasma when the tablet was administered with high fat and high fat/high protein food, but clinically the changes seem to be irrelevant.

Key words: theophylline – sustained-release – food – bioavailability – acrylic resins

Introduction

Theophylline has been employed for many decades in the treatment of chronic asthma. When administered in conventional preparations, it is necessary to dose it frequently in order to maintain therapeutic levels. This fact, in addition to its wide subject to subject variation in the pharmacokinetic parameters and its narrow therapeutic range, have been its major limitations [Hendeles et al. 1977 and Bolme et al. 1982]. Sustained-release formulations have been developed in order to avoid the fluctuation of plasma concentrations in the steady-state with a 12-hour dosage, which represents a great advantage in the mode of administration of theophylline [Andersen et al. 1983, Weinberger and Hendeles 1983, Hendeles et al. 1984].

A combination of two types of acrylic resins, Eudragit S100 and Eudragit RSPM has allowed the development of a sustained-release tablet obtained by conventional technology which has a good bioavailability pattern [Gai et al. 1989, Pezoa et al. 1992]. Food intake exerts a complex influence on the bioavailability of drugs. It may interfere not only in the tablet disintegration, drug dissolution and drug transit through the gastrointestinal tract, but it may also affect the metabolic transformation of drugs in the gastrointestinal wall and in the liver [Melander 1978].

Food may influence drug absorption as a result of physiological changes in the gastrointestinal tract or physical or chemical interactions between particular food components and drug molecules. Depending on the type and degree of interaction, drug absorption may be reduced, delayed, increased or not affected, by concomitant food intake. Changes in drug absorption could be clinically significant, depending on the type of drug and the extent of the change. For drugs with narrow therapeutic range, such as theophylline, the changes could be very important [Toothaker and Welling 1980].

Some sustained release theophylline products have presented dose-dumping when they are administered together with a fat meal. The exact mechanism which produces the dumping of the drug is yet unclear [Hendeles et al. 1985]. The effect that food exerts on the bioavailability of sustained-release products is a complex and non-predictable situation. For this reason, it is necessary to study each new theophylline

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Reprint requests to Dr. M. N. Gai, Department of Science and Pharmaceutical Technology, Faculty of Chemical and Pharmaceutial Sciences, University of Chile, Casilla 233, RCH-Santiago, Chile.

formulation for the possible changes in the bioavailability pattern when it is administered concomitant with food. The purpose of the present study was to evaluate the possible changes in the bioavailability of the formulation when it was administered with three kind of foods; normal, high fat and high fat/high protein diet. Control situation was the fasting condition, followed by a normal diet.

Subjects, material and methods

Study design

The study was carried out on 12 healthy young, male, non-smoking volunteers. They were informed about the course, risks and aims of the study and they gave their written consent. The study protocol was approved by the Ethics Committee of the Faculty. The experimental design was made in a crossover fashion, using a 4 × 4 latin square sequence. Clinical laboratory tests and physical examination were performed on all the subjects in orden to check their health state. The subjects fasted overnight and they have a diet free of methylxanthines 3 days prior to the study. On the day of the experiment, they swallowed one tablet together with the selected breakfast or with 150 ml of water (control situation). In the latter situation, the fast was maintained for 3 hours and at this time they received a normal breakfast.

All the subjects received lunch at 6 hours and an evening meal at 10 hours from the beginning of the experiment, according to the kind of diet selected for each volunteer. Heparinized blood samples were collected through an indwelling catheter in a forearm vein. Plasma was separated by centrifugation and it was stored at −20° C until assayed.

Plasma theophylline assay

Theophylline was determined by a high performance liquid chromatography method, used in previous works in our laboratory [Gai et al. 1989, Pezoa et al. 1992], employing a Merck-Hitachi chromatographer. Samples were added with HCl 0.1 N and 8-chlorotheophylline (internal standard) and they were cleaned-up by solvent extraction with a mixture of isopropanol/chloroform 5/95. The organic phase was separated by mean of Whatman 1 PS filter and was evaporated to dryness in a water bath at 50° C under nitrogen stream. The residue was dissolved in 100 µl of mobile solvent and 20 µl were injected to the HPLC.

The chromatographic conditions were the following:

Mobile solvent:	Monobasic potassium phosphate 0.05 M/methanol 80/20 pH 5.
Column:	Octadecylsilane (ubondapack C 18) 15 cms, 10 µm.
Pre-column:	Octadecylsilane 2.5 cms.
Flow rate:	1.7 ml/minute
Detection:	UV 272 nm.

Calibration curves were prepared with methylxanthine free human plasma added with known theophylline concentrations and were treated in the same way as the samples. The limit of detection was 40 ng and the coefficient of variation was 3.4%.

Formulation

The formulation used in this study was developed in our laboratory and it has the following composition:

Theophylline	300 mg
Avicel PH 101	20 mg
Spray dried lactose	20 mg
Eudragit S 100	20 mg
Eudragit RSPM	60 mg
Magnesium stearate	4,5 mg
Aerosil	0,5 mg

Theophylline was granulated with an ethanolic solution of Eudragit S 100. The granulate was mixed with the other components of the formulation and the tablet was obtained using conventional technology. The tablet is stable from a physical, chemical and biopharmaceutical standpoint and it has a good bioavailability pattern, maintaining plasmatic concentrations within the therapeutic range for 12 hours in condition of steady-state [Pezoa et al. 1992].

Meals

Three kind of diets were employed in the study: normal, high fat and high fat/high protein diet. The control situation was the fasting condition followed by a normal diet. All the diets were adjusted to make them isocaloric.

a) Normal diet: breakfast and evening meal consisted of milk, sugar, bread, butter and marmelade. Lunch consisted of meat, rice, tomato salad, bread, apple and juice. Caloric intake of normal diet is composed of 10.6% of proteins, 25.8% of fats and 63.6% of carbohydrates.
b) High fat diet: breakfast and evening meal consisted of milk, sugar, bread and butter. Lunch consisted of meat, tomato salad, french fried potatoes, bread, apple and juice. Caloric intake

of high fat diet is composed of 10.6% proteins, 42.1% of fats and 47.3% of carbohydrates.

c) High fat-high protein diet: breakfast and evening meal consisted of milk, sugar, bread, butter and fresh cheese made with low-fat milk. Lunch consisted in meat, french fried potatoes, tomato salad, bread, apple and juice. Caloric intake of high fat/high protein diet is composed of 14.9% of proteins 42.9% of fats and 42.2% of carbohydrates.

All the components of each meal were weighed and their quantities modified according to the kind of diet. Total caloric intake on the day of the experiment was 2,200 kcal for all the subjects and all the diets.

Pharmacokinetic analysis

Area under the plasma concentration versus time (AUC), maximum concentration (C_{max}), time at which C_{max} is reached (t_{max}) and K were calculated by the classical pharmacokinetic methods. Wagner and Nelson's method was used to determine the absorption profile and ka; the statistical moment theory was used to calculate the mean residence time (MRT).

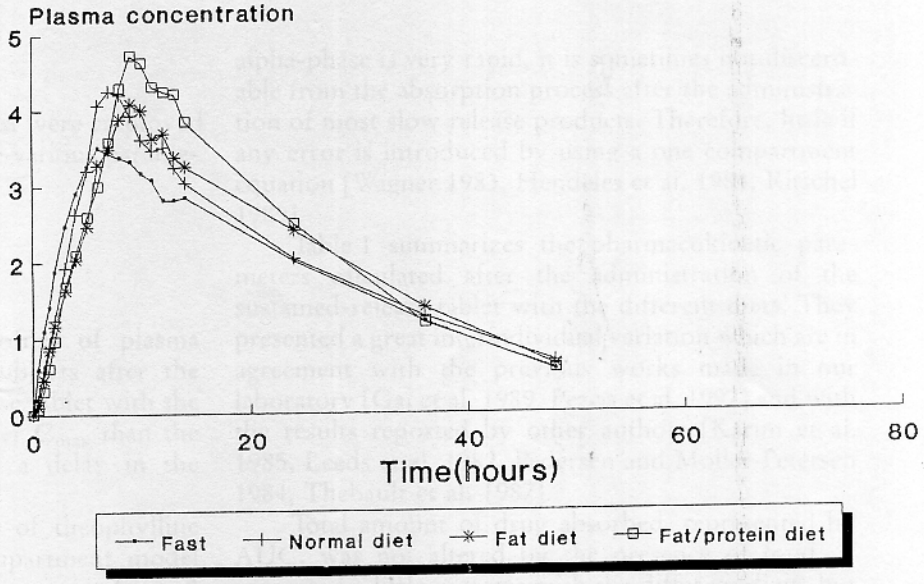

Fig. 2 Semilogarithmic profile of mean concentration versus time obtained after the administration of the tablet in fasting condition and with the different diets

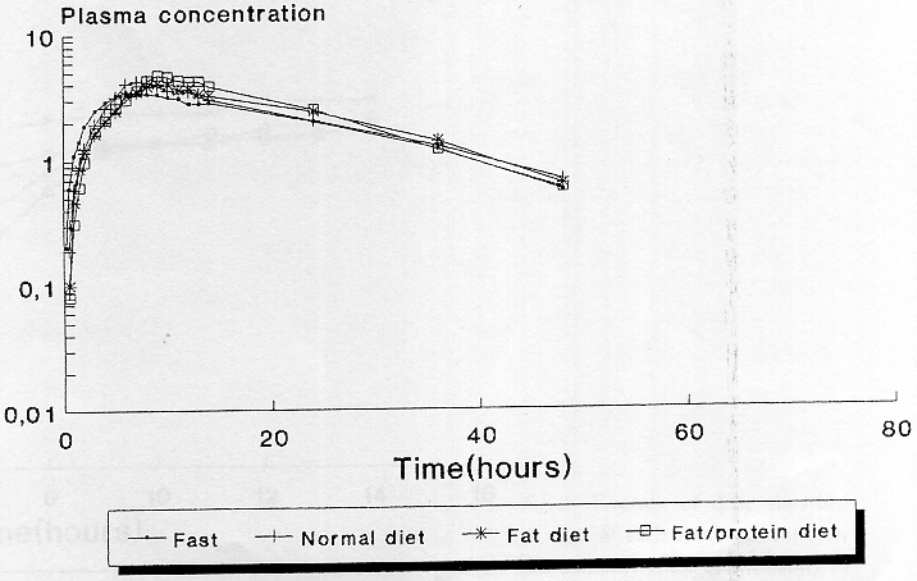

Fig. 1 Mean concentration versus time profiles obtained after the administration of the tablet in fasting condition and with the different diets

Table 1 Pharmacokinetic parameters obtained after the administration of the sustained-release theophylline tablet with the various diets

Parameter	Diet Fast	Normal	High fat	High fat/high protein
AUC ($\mu g \cdot h \cdot ml^{-1}$)	105.80 ± 33.19	115.01 ± 33.73	115.01 ± 31.89	116.65 ± 37.75
$t_{1/2}$ (h)	13.67 ± 5.99	14.12 ± 5.65	12.23 ± 4.02	10.03 ± 2.25
C_{max} ($\mu g \cdot ml^{-1}$)	3.85 ± 1.35	4.53 ± 1.32	4.50 ± 1.20	5.37 ± 1.48
T_{max} (h)	7.50 ± 2.84	7.92 ± 1.62	8.83 ± 1.80	9.08 ± 2.23
MRT (h)	23.92 ± 8.19	24.07 ± 8.75	24.00 ± 4.68	21.11 ± 3.93
t* (h)	0.313 ± 0.216	0.604 ± 0.310	0.688 ± 0,285	1.146 ± 0.569
ka (h^{-1})	0.3043 ± 0.220	0.2622 ± 0.103	0.2119 ± 0.090	0.1601 ± 0.044

t* Time at which theophylline is detected by the first time in plasma

Statistical analysis

A multiway Anova and LSD test were employed to assess the differences between the various parameters calculated.

Results

Figure 1 shows the mean profiles of plasma concentration versus time in 12 subjects after the administration of the sustained-release tablet with the different diets. Food produced higher C_{max} than the fasting state and it also produced a delay in the detection of theophylline in plasma.

The pharmacokinetic behavior of theophylline fits better to an apparent one compartment model (Figure 2). Theophylline fits more accurately a 2 compartment model after an intravenous dose. As alpha-phase is very rapid, it is sometimes not discernable from the absorption process after the administration of most slow release products. Therefore, little if any error is introduced by using a one compartment equation [Wagner 1983, Hendeles et al. 1984, Ritschel 1989].

Table 1 summarizes the pharmacokinetic parameters calculated after the administration of the sustained-release tablet with the different diets. They presented a great interindividual variation which are in agreement with the previous works made in our laboratory [Gai et al. 1989, Pezoa et al. 1992] and with the results reported by other authors [Karim et al. 1985, Leeds et al. 1982, Pedersen and Moller-Petersen 1984, Thebault et al. 1987].

Total amount of drug absorbed, represented by AUC, was not altered by the presence of food. It presented a little increase with the different diets, but it was not significant. It is important to note that this

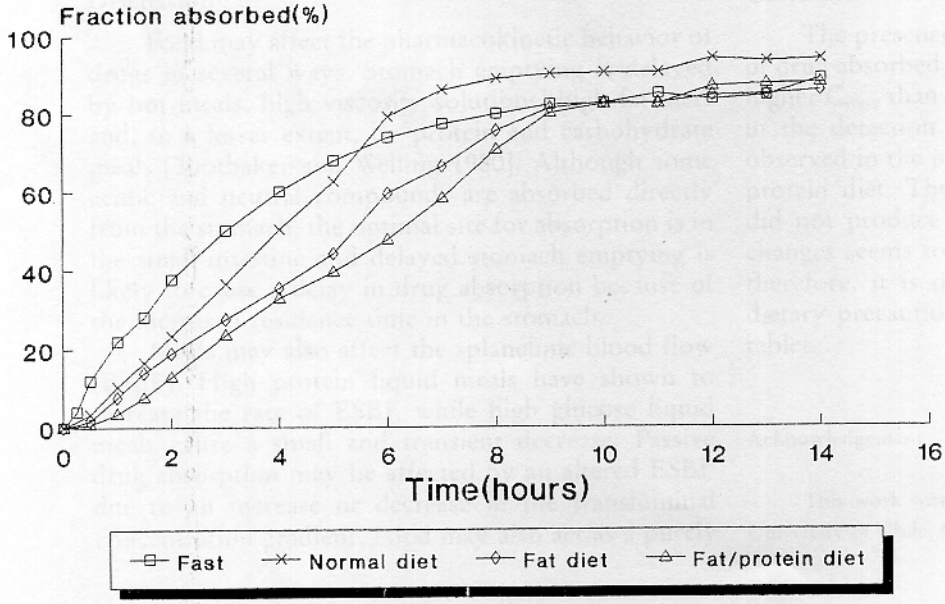

Fig. 3 Fraction of dose absorbed at time of each measurement after the administration of the tablet in fasting condition and with the different diets

parameter presented the lesser variation among the different conditions, indicating that the extent of the absorption was the parameter less affected by food. Elimination half-lives were in agreement with the values reported by other authors. They presented an important variability and fluctuated around the dosification frequency proposed for this formulation (12 hours). They did not show any statistical difference among the different diets.

C_{max} showed lower values in the fasting situation, but the differences resulted statistically significant ($p < 0.05$) only when it was compared to the fasting condition and the high fat/high protein diet. T_{max} showed a trend to increase and ka, a trend to diminish in the presence of food but the differences were not statistically significant. MRT was practically unaltered in the presence of food. The values are in agreement with those of sustained-release formulations and, as a measure of the amount of the time required for the intact drug molecule to move through the body. It can be concluded that this time is the same in fasting and non-fasting conditions.

The time at which theophylline was detected for the first time in plasma was also measured. For practically all the subjects excepting one, the drug was detected in the first plasma sample in the fasting situation (0.25 h). A significant delay ($p < 0.05$) was observed when the tablet was administered with high fat and high fat/high protein diet, reaching up to 3 hours in one subject with the latter diet. Figure 3 shows the absorption profile determined by the Wagner and Nelson method. Fraction absorbed was higher for the fasting situation than for non-fasting one up to 8 hours. At 12 hours the fraction absorbed was practically the same for all, fasting and non-fasting.

Discussion

Food may affect the pharmacokinetic behavior of drugs in several ways. Stomach emptying is delayed by hot meals, high viscosity solutions, high fat diets and, to a lesser extent, by protein and carbohydrate meals [Toothaker and Welling 1980]. Although some acidic and neutral compounds are absorbed directly from the stomach, the optimal site for absorption is in the small intestine and delayed stomach emptying is likely to cause a delay in drug absorption because of the increased residence time in the stomach.

Meals may also affect the splanchnic blood flow (ESBF). High protein liquid meals have shown to increase the rate of ESBF, while high glucose liquid meals cause a small and transient decrease. Passive drug absorption may be affected by an altered ESBF due to an increase or decrease in the transluminal concentration gradient. Food may also act as a purely physical barrier, preventing drug access to the mucosal surface of the gastrointestinal tract thus affecting the absorption process. The ingestion of food may also influence drug absorption by one or more mechanism and may influence drug absorption to a variable extent [Melander 1978, Toothaker and Welling 1980].

Many papers have been published about the influence of food on the bioavailability of sustained-release theophylline formulations and their results are contradictory. Intents have been made in order to relate pH characteristic of the matrix used in the formulation with the pharmacokinetic changes observed in the presence of food, but the relationship has not been found. Food increases both the rate and extent of absorption [Hendeles et al. 1984, Karim et al. 1985], decreases the rate of absorption [Leeds et al. 1982] or its extent [Pedersen and Moller-Pedersen 1984], produces erratic changes [Pedersen and Moller-Pedersen 1984], the changes do not have clinical implications [Thebault et al. 1987] or produces dose-dumping [Hendeles et al. 1985].

The formulation used in this study has Eudragit S 100 and Eudragit RSPM among its components. The former is used in ethanolic solution as granulating agent, is insoluble at acidid pH and becomes soluble at pH higher than 7. The latter is insoluble in water and digestive fluids, but is capable of swelling. It is permeable and forms the matrix when the drug diffuses. Probably the presence of solid food causes a delay in gastric emptying, explaining the delay in the absorption process, since at acidic pH, the Eudragit S 100 does not dissolve, but once the tablet reaches the small intestine, it dissolves and theophylline diffuses through the matrix and the formulation delivers gradually all the dose.

Conclusion

The presence of food does not affect the amount of drug absorbed. High fat/high protein diet produces higher C_{max} than fasting condition. A significant delay in the detection of the theophylline in plasma was observed in the presence of high fat and high fat/high protein diet. The other pharmacokinetic parameters did not produce any change. The magnitude of the changes seems to be without clinical significance and therefore, it is not necessary to recommend special dietary precautions to prescribe the sustained-release tablet.

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