Effect of three different diets on the bioavailability of a sustained release lithium carbonate matrix tablet

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Abstract. Background: Food-induced changes on the bioavailability of a sustained release lithium carbonate matrix tablet, which uses an acrylic matrix of Eudragit RSPM as sustaining agent, have been studied in healthy male volunteers. The tablet was developed in our laboratory using conventional technology. Subjects, materials and methods: The study design was a 4 × 4 Latin square involving 12 subjects who received a single dose of the tablet while fasting or with a standarized normal, high fat or high fat/high protein meal. Results: The results showed no differences in half-lifeβ, renal clearance, Vdβ, AUC, t_{max}, X_u^∞, fraction absorbed and MRT. Higher C_{max} (mg/l) were obtained when the tablet was administered with any kind of meal: 2.09 ± 0.47 (fast), 2.95 ± 1.04 (normal diet), 2.64 ± 0.54 (high fat diet) and 2.87 ± 0.67 (high fat/high protein diet). The analysis of the ratio C_{max}/AUC indicated that changes in C_{max} were more probably due to changes in the rate of absorption. To evaluate if the magnitude of the change could be clinically relevant, C_{max} and C at 12 hours (dosing interval) were treated by the superposition method in order to establish maximum and minumum concentrations at steady-state. For all the experimental conditions both concentrations would remain in the therapeutic range (4.2 – 10 mg/l or 0.6 – 1.4 mEq/l). Conclusion: The behavior of the formulation is appropriate for a sustained release tablet and fasting or non-fasting state seems not to be a major consideration for bioavailability when deciding on the regimen administration.

Introduction

Lithium salts are used in the treatment of mania and for the prevention of recurrent attacks of manic-depressive illness. In the last two decades pharmacokinetic knowledge of the drug has allowed a safe management of the therapy [Amdisen 1977, Amdisen and Carson 1986, Baldessarini 1990, Schou 1988].

Conventional lithium carbonate dosage forms make the drug immediately available for absorption, producing rapid and relatively high blood levels. The goal of sustained release (SR) lithium preparations is to diminish the incidence of side-effects controlling drug liberation during the first hours after the administration, thus preventing high blood levels, because the drug itself has a long half-life [Amdisen and Carson 1986, Schou 1988].

Food may affect drug bioavailability (BA), inducing some physiological changes on the gastrointestinal (GI) tract. Food may accelerate, enhance, delay or decrease drug absorption. Therefore, its influence is so complex that the consequences of the co-administration of drugs and food remains yet unpredictable [Charman et al. 1997, Melander 1978, Toothaker and Welling 1980, Williams et al. 1993].

Changes in drug absorption could be clinically significant depending on the type of drug and the extent of the change. Indeed, they are more relevant for drugs with narrow therapeutic index, such as lithium. In addition, food could alter the in vivo performance of SR products, which have designs that allow the liberation of the drug over several hours; in spite of administration outside of mealtimes, they will necessarily be in contact with food while the system is still liberating drug.

Dumping is another risk factor in SR products. Dose-dumping has been demonstrated for some sustained release theophylline products, also a drug with narrow

therapeutic index. The mechanism to explain dumping remains unclear as yet, but the presence of a fatty food was responsible for the phenomenon, probably due to the interference between some components of the diet and the SR system [Hendeles et al. 1985].

We have been working in our laboratory on the development of a SR tablet of lithium carbonate (Li) using a matrix system and conventional technology [Gai et al. 1992]. The excipient used to control drug liberation is an acrylic resin, Eudragit RSPM, which is insoluble at any pH but swells in contact with water, forming a porous structure through which the drug is released [Eudragit Handbook]. The aim of the present study was to evaluate possible changes in BA of this SR Li tablet when it was concomitantly administered with three different types of food: normal, high fat and high fat/high protein diets. The fasting condition served as control, followed by a normal diet.

Subjects, materials and methods

Subjects

The study was carried out on 12 healthy young, male volunteers. Medical history, laboratory tests and physical examination were made to all the subjects in order to check their health state. They were informed about 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.

Study design

The experimental design was a cross-over fashion, using a 4 × 4 Latin square sequence and a 3-week washout period. Twelve subjects were randomized to treatment sequences in blocks of 3 subjects.

The volunteers fasted overnight. On the day of the study, they swallowed two tablets with the selected breakfast or with 150 ml of tap water (control). In the latter situation, the fasting was maintained for 3 hours and at this time they received a normal breakfast. Lunch was served after 6 hours and an evening meal after 10 hours from the beginning of the experiment, according to the class of diet selected for each group. The volunteers remained for 14 hours in the place where the experiment was performed. They were under medical supervision and were instructed to inform the investigators of any adverse reaction. They were ambulatory but were not permitted to engage in strenuous physical exercise.

Meals

Three types 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 with a normal sodium intake. 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 2200 kcal for all the subjects and all the diets.

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.

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% of proteins, 42.1% of fats and 47.3% of carbohydrates.

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 of 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.

Collection of blood and urine samples

Venous blood samples (10 ml) were collected for 72 hours through an indwelling

catheter from a forearm vein. Serum was separated by centrifugation and was stored at –20° C until assayed. Urine was collected at appropriate intervals during 72 hours. Urine volume was measured for each sample and an aliquot was frozen (-20° C) until its analysis.

Serum and urine lithium assay

Calibration curves were prepared with human serum or urine, added to known lithium concentrations in order to work according to the instrumental conditions and to treat in the same way as the samples. Quantitation of lithium was made by atomic absorption spectrophotometry, diluting the samples in order to work according to the following instrumental conditions: working range, 0 – 4 ppm; wavelength, 670.8 nm; and an oxidizing air/acetylene flame.

Formulation

The formulation used in this study was developed in our laboratory and its composition is indicated in Table 1. Li was granulated with an ethanolic solution of Eudragit S100 (12.5%). The granulate was obtained passing through an 18-mesh screen and dried at 40° C for 2 hours. The dried granulate was mixed with the other components of the formulation and the tablets were compressed on a single punch press, to flat tablets of 11 mm in diameter and a hardness of 6 kg.

Pharmacokinetic analysis

Area under the plasma concentration versus time (AUC), maximum concentration (C_{max}), time at which C_{max} is reached (t_{max}), half-lifeβ, renal clearance and Vdβ were calculated by the classical pharmacokinetic methods. The statistical moment theory was used to calculate the mean residence time (MRT). Pharmacokinetic parameters were calculated using the AUCRPP program [Ritschel 1986]. The total amount of drug excreted in the urine X_u^{∞} was obtained using the equation [Wagner 1980]:

$$[Xu]_t = Xu^{\infty} - \frac{1}{1-e^{-\beta\Delta t}}[(Xu)_{t+1} - (Xu)_t$$

As lithium is almost completely excreted in the urine and considering that the subjets were instructed to abstain from strenuous physical exercise, the fraction absorbed F was calculated from the total amount excreted in the urine divided by the amount administered.

Principle of superposition was used to assess C_{max} and C_{min} at the steady-state [Westlake 1971, Wagner 1974].

Table 1. Composition of formulation used in this study.

Lithium carbonate	300 mg
Avicel PH 101	20 mg
Lactose spray dried	20 mg
Eudragit S100	18.6 mg
Eudragit RSPM	60 mg
Magnesium stearate	2 mg
Aerosil	0.5 mg

Statistical analysis

A multiway analysis of variance (ANOVA) and least significance difference (LSD) test were employed to assess the differences among the elimination half-lives, MRT, and the relation C_{max}/AUC ($p < 0.05$). A non-parametric test was used for the statistical analysis of t_{max} ($p < 0.05$). Bioequivalence of the formulation given under fed and fasted conditions was established when the 90% confidence interval for the log-transformed AUC, C_{max}, X_u^{∞} and F fell within the interval 0.80 to 1.25.

Results

Figure 1 shows the mean profiles of serum concentration versus time in 12 subjects after the administration of the SR Li tablet with the different diets. The pharmacokinetic behavior fitted a two-compartment model, in accordance with previous studies of our group and other authors [Amdisen and Carson 1986, Arancibia et al. 1986, Gai et al. 1992, Mason et al. 1978]. The presence of any kind of food produced a higher C_{max} than the fasting state.

Tables 2, 3, and 4 summarize all the pharmacokinetic parameters obtained in this study. They showed high interindividual vari-

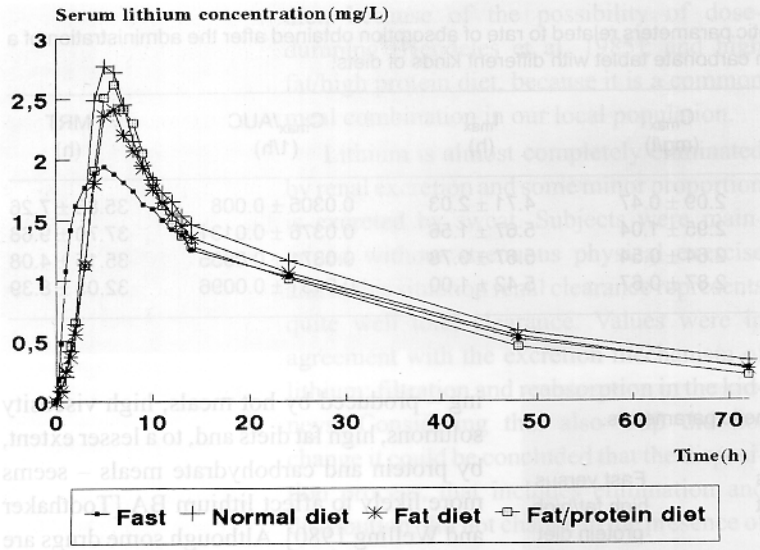

Figure 1. Mean serum concentration of lithium obtained after the administration of the tablet in fasting and fed conditions.

Table 2. Disposition pharmacokinetic parameters obtained after the administration of a sustained release lithium carbonate tablet with different kinds of diets.

Diet	Half-lifeβ (h)	Renal clearance (l/h/kg)	Vdβ (l/kg)
Fast	25.08 ± 4.98	0.0182 ± 0.005	0.643 ± 0.145
Normal	26.21 ± 6.26	0.0173 ± 0.007	0.607 ± 0.191
High fat	24.18 ± 3.77	0.0203 ± 0.006	0.694 ± 0.205
High fat/high protein	21.84 ± 6.97	0.0215 ± 0.007	0.640 ± 0.176

Table 3. Pharmacokinetic parameters related to amount absorbed obtained after the administration of a sustained release lithium carbonate tablet with different kinds of diets.

Diet	AUC (mg/l)	Xu_{∞} (mg)	Fraction absorbed (%)
Fast	71.64 ± 20.83	83.97 ± 20.21	74.44 ± 17.92
Normal	82.72 ± 25.01	87.20 ± 11.42	77.30 ± 10.12
High fat	72.02 ± 15.63	92.55 ± 15.86	82.05 ± 14.06
High fat/high protein	67.54 ± 14.55	92.01 ± 12.40	81.57 ± 10.99

ation, characteristic for this drug. Table 2 contains parameters related to disposition. Statistical analysis of pharmacokinetic parameters are shown in Table 5. Half-lifeβ was quite long and did not show statistical differences among the different diets. Calculated values for renal clearance and Vdβ demonstrated that lithium did not change its elimination or its distribution when the SR tablet was administered with the different meals.

Table 3 contains the parameters related to the amount absorbed. Mean values show some differences but they were not statistically different, demonstrating that the amount absorbed was not affected by the presence and/or the class of meal (Table 5).

Table 4 summarizes the pharmacokinetic parameters more closely related to the rate of absorption. When the tablet was administered with any class of meal, C_{max} was significantly higher than the fasting situation was found. T_{max} was delayed by food but the difference was not significant. MRT was practically unaltered in presence of food; values are in agree with those of SR formulations and for drugs with a long half-life as lithium and, as a measure of the amount of 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 (Table 5).

In order to distinguish if the higher C_{max} were more attributable to changes in amount absorbed or to the rate of absorption, the ratio C_{max}/AUC was evaluated (Table 3). The statistical analysis showed differences among the different diets and the fasting condition (Table 5), indicating that changes in C_{max} are more probably due to changes in the rate of absorption.

To evaluate if changes in C_{max} will be clinically relevant, and if the formulation would provide serum concentrations in the therapeutic range during dosing interval, C_{max} and C_{min} at the steady-state were obtained by the superposition method. For all the experimental conditions both concentrations remain between 4.2 – 10 mg/l or 0.6 – 1.4 mEq/l (Table 6).

Discussion

There are few studies concerning the influence of food on the BA of lithium and specially for SR lithium formulations. A report of dumping in a SR formulation was explained by the fact that the formulation had a pH-dependent dissolution [Jeppson and Sjögren 1975].

Table 4. Pharmacokinetic parameters related to rate of absorption obtained after the administration of a sustained release lithium carbonate tablet with different kinds of diets.

Diet	C_{max} (mg/l)	t_{max} (h)	C_{max}/AUC (1/h)	MRT (h)
Fast	2.09 ± 0.47	4.71 ± 2.03	0.0305 ± 0.008	35.88 ± 7.26
Normal	2.95 ± 1.04	5.67 ± 1.56	0.0376 ± 0.0131	37.70 ± 9.68
High fat	2.64 ± 0.54	5.67 ± 0.78	0.0371 ± 0.0055	35.15 ± 4.08
High fat/ high protein	2.87 ± 0.67	5.42 ± 1.00	0.0431 ± 0.0096	32.03 ± 8.39

Table 5. Statistical relations among the pharmacokinetic parameters.

Parameter	Fast versus normal diet	Fast versus high fat diet	Fast versus high fat/high protein diet
$t_{1/2}$	NS	NS	NS
Vdβ	NS	NS	NS
Cl	NS	NS	NS
AUC	BE	BE	BE
C_{max}	NBE	NBE	NBE
t_{max}	NS	NS	NS
Xu_{∞}	BE	BE	BE
C_{max}/AUC	S	S	S
F	BE	BE	BE
MRT	NS	NS	NS

S = significant, NS = non-significant BE = bioequivalent, NBE = non-bioequivalent

The influence of food on the absorption of drugs is so complex that it is imposible to predict its influence on a special drug and the problem becomes more difficult when the drug is administered in a controlled release system.

Some of the physiological changes induced by food could affect the liberation of lithium from the controlled release tablet and its absorption. Among the different changes produced by food, the delay in gastric emptying – produced by hot meals, high viscosity solutions, high fat diets and, to a lesser extent, by protein and carbohydrate meals – seems more likely to affect lithium BA [Toothaker and Welling 1980]. Although some drugs are absorbed directly from the stomach, the optimal place for absorption is the small intestine and delayed stomach emptying is probable to cause a delay in drug absorption because of the increased residence time in the stomach. Other factors could be the changes in the splanchnic blood flow (SBF). High protein liquid meals have shown to increase the rate of SBF, while high glucose liquid meals cause a small and transient decrease [Welling 1977]. Lithium absorption may be affected by an altered SBF due to changes 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, affecting the absorption process. Thus, ingestion of food may influence drug absorption in a variable extent by one or more mechanisms [Melander 1978, Toothaker and Welling 1980].

The selection of the different diets was based on the following considerations: normal diet, because this is the type of meal most frequently used to take the tablet; high fat

Table 6. Projection of C_{max} and C_{min} at the steady-state using the superposition method; 600 mg dose and 12-hour dose interval.

Diet	C_{max} at steady-state mg/l	mEq/l	C_{min} at steady-state mg/l	mEq/l
Fast	5.99 ± 1.30	0.86 ± 0.19	5.01 ± 1.08	0.72 ± 0.15
Normal	7.94 ± 2.80	1.14 ± 0.40	5.86 ± 1.90	0.84 ± 0.27
High fat	6.81 ± 1.40	0.98 ± 0.20	5.22 ± 1.02	0.75 ± 0.14
High fat/high protein	6.38 ± 1.39	0.92 ± 0.21	4.55 ± 1.04	0.66 ± 0.15

diet, because of the possibility of dose-dumping [Hendeles et al. 1985]; and high fat/high protein diet, because it is a common meal combination in our local population.

Lithium is almost completely eliminated by renal excretion and some minor proportion is excreted by sweat. Subjects were maintained without strenuous physical exercise and in this situation renal clearance represents quite well total clearance. Values were in agreement with the excretion mechanism of lithium: filtration and reabsorption in the kidneys. Considering that also Vdβ did not change it could be concluded that the disposition process, that includes elimination and distribution, did not change in the presence of food.

AUC is an adequate pharmacokinetic parameter to indirectly measure the amount of drug absorbed, regarding that the disposition does not change. Since this is the situation (Tables 2 and 5), it could be concluded that the amount absorbed remains the same with different kinds of meals. However, for lithium it is possible to measure directly the amount absorbed, because the drug is almost completely excreted by the urine [Amdisen 1977, Amdisen and Carson 1986]. Therefore, collecting all the drug excreted by the urine it is possible to measure the fraction absorbed (F). As lithium has a long half-life it is very difficult to collect urine until no more drug is detected (7 or more days). Wagner developed an expresion to calculate Xu_∞ regarding that the collecting intervals are the same (see equation in "Materials and methods"); this expression was used to calculate finally the fraction absorbed [Wagner 1980]. The statistical analysis for F indicated that the amount absorbed was not modified by meals (Table 5).

C_{max} was the only parameter evidencing changes from the control situation (Tables 4 and 5). Indeed, for a drug with narrow therapeutic index such as lithium, the increase of C_{max} could be a potential risk. When the formulation used in this study was developed, it was compared with a fast release tablet. Analyzing these data, the difference between maximun urinary rate excretion of the fast release tablet was 2.5 times that of the SR tablet, and the amount absorbed was the same [Gai et al. 1992]. In the present study the highest difference in C_{max} was between the normal diet and the fast situation reaching a relation of 1.4. There is undoubtely a change but the tablet still remains as an SR one.

Some authors use the ratio C_{max}/AUC as an attempt to make C_{max} independent of the amount absorbed and as a clearer, more unambiguous measure of the absorption rate than C_{max} [Bois et al. 1994, Endrenyi et al. 1991]. The statistical analysis showed differences among the fasted state and any fed state (Table 5), indicating that changes in C_{max} are due to changes in the rate of absorption.

Another important behavior to evaluate in controlled release formulations is the risk of dumping. It is characterized by the rupture of the system that controls the release of drug, promoting the sudden liberation of all the dose. No evidence of dose-dumping was observed in any particular subject with any class of meal.

Probably the presence of food caused a delay in gastric emptying, allowing a longer residence of the tablet in the stomach. As lithium carbonate is readily soluble in acidic medium, it could be dissolved faster than if the tablet were quickly emptied to the small intestine. As the stomach is not physiologically the best place for drug absorption, when the dissolved drug reached the gut, it was in a higher quantity compared with the fast condition, explaining the higher C_{max}. Additionally, if the SBF increases due to the presence of food, the combination of the higher transluminal concentration difference with a higher SBF could be reponsible for higher C_{max}.

Analysis of C_{max} and C_{min} at steady-state could provide a better indicator about the safety of the formulation when is administered in the fed state (Table 6). Values inside the therapeutic range obtained for both concentrations in the fed and fasted condition, suggest that the tablets are safe enough and the drug could be taken either before or after a meal, although in long-term treatment patients should be encouraged to follow one dose regimen.

Conclusion

The presence of food does not affect the amount of lithium absorbed. All kinds of meals produce higher C_{max} than fasting condition. The other pharmacokinetic parameters did not evidence any change. The formulation

acts as an SR tablet also in presence of food. The magnitude of the change in C_{max} seems not to be clinically relevant, considering that calculated C_{max} and C_{min} at the steady-state would be in the therapeutic range. Therefore, it would not be necessary to recommend special dietary precautions to prescribe the sustained release tablet.

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