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Evaluation of Two Lithium Carbonate Formulations

Thomas S. Foster, Richard E. Crass, James A. Bustrack, Randall B. Smith, and **James W. Munson**

An open, two-way crossover study of Latin-square design was used to compare the bioavailability of a new capsular formulation of lithium carbonate, Pfi-Lithium (Pfipharmecs Division, Pfizer, Inc.), with that of a standard capsular formulation, Eskalith (Smith Kline & French Laboratories).

Eighteen healthy, adult male volunteers received both formulations in a randomly determined order. After administration of each 300-mg dose of lithium carbonate, serial blood specimens were obtained. Data obtained from these specimens were subjected to pharmacokinetic evaluation.

There were no significant differences ($p < 0.05$) in peak plasma concentration, time to peak plasma concentration, and area under the plasma concentration-time curve.

These single-dose data suggested that the two formulations were bioequivalent.

Index terms: Blood levels; Capsules; Drugs, availability; Equivalency, generic; Lithium carbonate; Pharmacokinetics; Psychotherapeutic agents

Lithium salts have been used in medicine for more than 100 years. Their use in the treatment of gout and diabetes mellitus and as a hypnotic long preceded their consideration in the therapy of manic patients. Lithium carbonate is now widely accepted not only for the treatment of mania per se, but also for the prophylaxis of manic-depressive disease. Other salt forms have been found to be effective.[1]

The antimanic action of lithium has generally been associated with serum levels in the range of 0.6 to 1.5 meq/liter. The onset of toxicity is usually seen above 1.8–2.0 meq/liter. Many investigators, both in the United States and abroad, have attempted to monitor fluctuations in serum lithium in relation to dosing. Variations in serum levels in response to different formulations of lithium carbonate, or in response to other lithium salts, have been attributed, at least partially, to differences in the rate of absorption of the various lithium products.[1–4] The rate of gastric emptying has been identified as a factor. The ingestion of food, the presence of diarrhea, or the ingestion of medicines such as propantheline or metoclopramide, which can alter gastric emptying, may influence absorption.[4,5]

Study Objective and Design

We studied the plasma concentration-time profile of a newly formulated capsular dosage form of lithium carbonate (treatment B; Pfi-Lithium,[a] Pfipharmecs Division, Pfizer, Inc.) by comparing it with a marketed standard formulation (treatment A; Eskalith,[b] Smith Kline & French Laboratories). An open, nonblinded study of Latin-square crossover design was used, with 18 subjects receiving both regimens in a randomly determined order. The resulting concentration-time curves for the two treatment groups were compared with respect to the area under the plasma concentration-time curve (AUC), peak plasma concentration (C_p), and time to peak concentration (t_p).

Materials and Methods

Patient Selection. Eighteen (18) normal adult male volunteers between the ages of 18 and 35 years were selected for participation in this investigation. All subjects were selected after successful completion of a thorough history and physical examination, and after demonstration of a clinically normal laboratory battery consisting of a blood chemistry examination, complete blood count, and urinalysis. Potential subjects were excluded from participation if they had a known allergy or intolerance to lithium, had a history of any acute or chronic systemic disease, had donated blood within two months of the start of the study, or had received any medication by any route within 10 days before the study began. Each subject voluntarily provided informed consent, after being presented with full details of the investigation in both written and oral form. The mean age and weight of the subjects at the time of the study were 25.1 ± 4.1 years and 78.1 ± 7.9 kg, respectively.

Treatments. The drug products used for this study were lithium carbonate capsules 300 mg (Pfi-Lithium, Lot

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MD9-59-732) and lithium carbonate capsules 300 mg (Eskalith, Lot 18J07). The administrations of the study drugs on the two study days were separated by a two-week washout period. On each of the study days, subjects arrived at the study facility in a fasting state (minimum of 10 hours of fasting; water was allowed ad lib).

Dosing and Serum Sampling. Before drug administration, a 10-ml blood sample was collected from each subject. The subjects were then assigned to receive one of the two dosage forms in a computer-generated random order. The capsules were given with 240 ml of water. Following drug administration, venous blood samples were obtained from either the left or right antecubital fossa using disposable 20-gauge, 1½-inch needles. The blood specimens were collected in heparinized evacuated tubes. Ten milliliters of blood were drawn at 0.33, 0.67, 1.0, 1.5, 2.0, 4.0, 8.0, 12.0, 24.0, and 36.0 hours after dosing. Following blood withdrawal, samples were centrifuged within 30 minutes of collection at 2200 rpm for 20 minutes, and the plasma was harvested into polypropylene (Falcon) tubes. Immediately after harvest, all samples were frozen and were maintained in the frozen state until analyzed.

Study Conditions. After drug administration, all subjects remained at the study facility, where they were monitored for adverse reactions. Subjects were ambulatory but were not permitted to engage in strenuous physical exercise. Two hours after administration of the drug, a light standard breakfast was served. A full lunch was served five hours after dosing. During these meals and throughout the study period, xanthine-containing foods and drinks were prohibited.

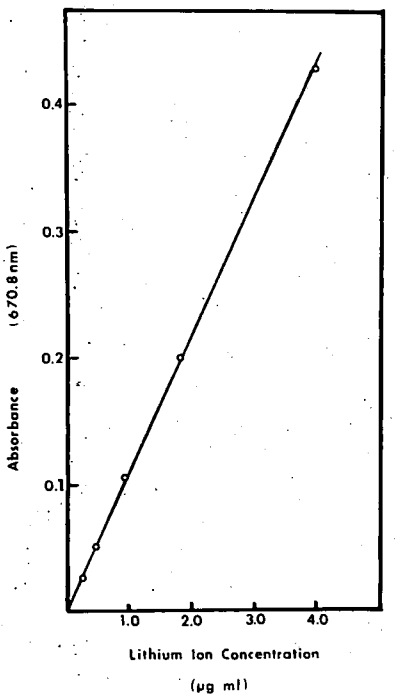
Analysis

Chemical Analysis. An atomic absorption spectrophotometer (Perkin-Elmer Model 460) equipped with a lithium hollow cathode lamp and an air/acetylene flame was used to analyze the plasma samples. Gas flows were set according to the manufacturer's recommendations and lamp alignment, wavelength setting, aspirator speed, and flame alignment were maximized daily before each run. Calibration curves were prepared from a single unit of individual plasma obtained from a local blood bank, and were prepared at the time of analysis to insure that all samples fell within the linear range of the instrument (0–2 μg/ml).

In atomic absorption spectrophotometry, when the lithium hollow cathode lamp and a monochromator setting of 670.8 nm are used, only lithium ions are measured. This was verified in our samples by the lack of measurable response for all zero-time samples. The minimum detectable concentration (signal-to-noise ratio of 2:1) was 0.01 μg/ml.

Excellent linearity was obtained for all standard curves ($r > 0.998$) (see Figure 1). Standards were measured before the analysis of the samples and once again after the analysis. In all cases, the values agreed within 3%. The day-to-day precision was assessed by measuring three spiked samples on each day of the study. The values obtained were 0.75 μg/ml (C. V.=2.7%), 2.05 μg/ml (C.V.=2.4%) and 3.10 μg/ml (C.V.=3.6%) ($n = 9$).

Figure 1. Representative standard curve (absorbance versus lithium ion concentration) demonstrating excellent assay sensitivity.



All results are reported as lithium ion concentrations in units of μg/ml. These values can be converted to meq/ml by dividing by 6.94.

Pharmacokinetic Analysis. The mean plasma concentration-time data for each formulation were fit to a sum of three exponentials, Equation 1,[6] using the SAAM 23 computer program.[7]

$$C = Ne^{k_a t} + Le^{\alpha t} + Me^{-\beta t} \quad (1)$$

Equation 1 is the expected equation after oral administration for a drug whose disposition is described by a two-compartment model, where C is the plasma concentration at time t, k_a is the absorption rate constant, α is the rate constant for distribution, and β is the disposition rate constant.

Area under the plasma concentration-time curve (AUC) was calculated by the trapezoidal rule up to 36 hours after drug administration.

Statistical Analysis. The lithium plasma concentrations at each time point C_i,j and k were submitted to analysis of variance using the following model:

$$C_i,j,k = \mu + S_i + W_j + F_k + e_{ijk} \quad (2)$$

In Equation 2, i, j, and k are the indices for subjects, weeks, and formulations, respectively, and S_i, W_j, and F_k are fixed effects. The e_{ijk} are assumed to be independent and distributed $N(0, \sigma^2)$. Bioavailability variables C_p, t_p, and AUC were also submitted to analysis of variance using the model described in Equation 2.

Results and Discussion

Mean plasma concentrations and standard deviations achieved following oral administration of Eskalith (treatment A) and Pfi-Lithium (treatment B) are shown in Table 1. The comparisons of the observed mean concentrations and the simulated plasma concentration-time profiles for treatments A and B, using the best estimates of k_a, α, and β, are shown in Figures 2 and 3. The best estimate of β determined from the fit of each formulation was 0.035 $hr,^{-1}$ corresponding to a half-life ($t_{1/2}$=19.8 hr) that is consistent with plasma half-lives previously reported for slow to normal excretors ($t_{1/2}$=20 hr).[8]

The means for observed time to peak concentration (t_p), peak plasma concentration (C_p), and calculated AUC after administration of each treatment are shown in Table 2. There were no significant differences among subjects, weeks, or formulations for these parameters, as demonstrated in Table 3.

Analysis of lithium plasma concentrations at each time point demonstrates no significant differences between formulations or weeks at any time (Table 4). There were,

Table 1. Mean Lithium Plasma Concentrations after Oral Administration of Lithium Carbonate

Time (hr)	Plasma Concentration (μg/ml) Treatment A[a]	Treatment B[b]
0.00	0.00 ± 0.01	0.01 ± 0.01
0.33	0.46 ± 0.58	0.45 ± 0.43
0.67	1.55 ± 0.69	1.71 ± 0.73
1.0	1.85 ± 0.49	2.07 ± 0.66
1.5	1.85 ± 0.28	1.97 ± 0.45
2.0	1.62 ± 0.29	1.72 ± 0.32
4.0	1.14 ± 0.23	1.13 ± 0.20
8.0	0.71 ± 0.12	0.77 ± 0.21
12.0	0.54 ± 0.13	0.56 ± 0.14
24.0	0.39 ± 0.12	0.41 ± 0.12
36.0	0.23 ± 0.09	0.25 ± 0.11

[a] Treatment A = Eskalith (Smith Kline & French Laboratories).
[b] Treatment B = Pfi-Lithium (Pfipharmecs Division, Pfizer, Inc.).

Table 2. Mean (± S.D.) Observed Time to Peak (t_p), Peak Plasma Concentration (C_p), and Area Under the Curve (AUC) after Oral Administration of Lithium Carbonate

	t_p (hr)	C_p (μg/ml)	AUC* $\int_0^{36hr}$ (μg·hr/ml)
Treatment A	1.235 ± 0.460	2.13 ± 0.27	20.50 ± 2.87
Treatment B	1.275 ± 0.797	2.29 ± 0.50	21.86 ± 4.65

Table 3. Results of Analysis of Variance for C_p, t_p, and AUC after Oral Administration of Lithium Carbonate

Dependent Variable	F Value[a] Subjects	Weeks	Formulations
C_p	1.27	0.14	1.55
t_p	1.14	1.19	0.03
AUC	1.93	0.05	1.50

[a] Degrees of freedom: error, 15; subjects, 16; weeks, 1; formulations, 1. None of the F values is significant ($p < 0.05$).

Figure 2. Mean plasma lithium concentrations after administration of a single 300-mg Eskalith capsule. One standard deviation is charted above and below each mean. The line through the data is a computer-fitted curve generated from study-group data.

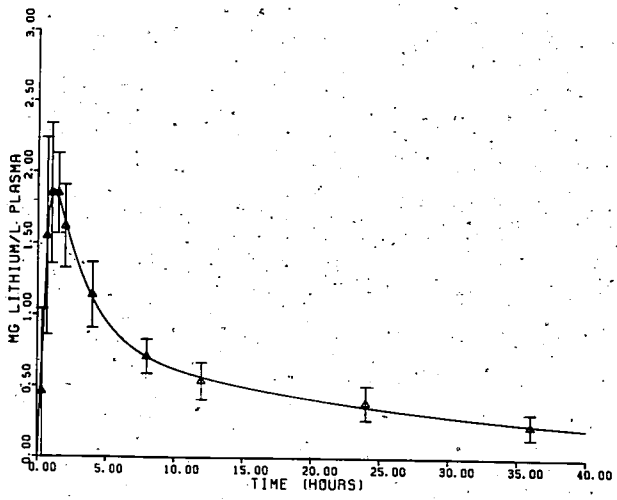


Figure 3. Mean plasma lithium concentrations after administration of a single 300-mg Pfi-Lithium capsule. One standard deviation is charted above and below each mean. The line through the data is a computer-fitted curve generated from study-group data.

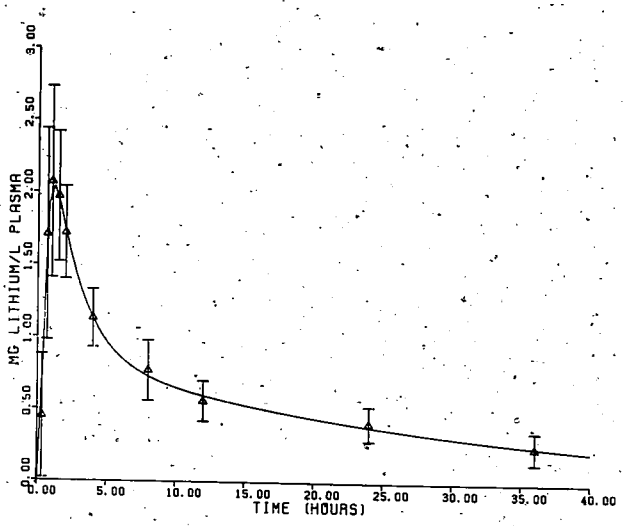


Table 4. Analysis of Variance of Lithium Plasma Concentration at Each Time Point after Administration of Lithium Carbonate

Time (hr)	F Value[a] Subjects	Weeks	Formulation
0.33	1.74	0.41	0.01
0.67	2.40 (p <.05)[b]	1.96	0.71
1.0	1.00	3.69	1.38
1.5	0.97	0.04	0.82
2.0	1.75	4.16	1.40
4.0	3.57 (p <0.01)	1.73	0.01
8.0	3.85 (p <0.01)	0.39	2.36
12.0	4.81 (p <0.01)	0.00	0.90
24.0	5.01 (p <0.01)	1.75	0.33
36.0	13.40 (p <0.01)	1.95	1.41

[a] Degrees of freedom: error, 15; subject, 16; weeks, 1; formulation, 1.
[b] ( ) = Significance level.

however, significant differences between subjects at times greater than two hours. This result was not unexpected because of the previously reported intersubject variability in lithium elimination.[8]

Conclusions

The results of this study clearly demonstrated that there was no difference in extent of absorption of the new lithium carbonate formulation (Pfi-Lithium) when compared with a reference product (Eskalith). Statistical analysis of the data indicated no differences in the rate of absorption as measured by time to peak, peak plasma concentration, and k_a determined by fitting the mean lithium plasma concentration-time data for each formulation. Although the absorptive variables of these two formulations are not significantly different, a point-by-point analysis of plasma concentrations showed significant differences between subjects at times greater than two hours. This fluctuation in serum levels in the disposition phase is probably of little clinical significance.

[a] Manufactured by Pfizer, Inc., 235 E. 42nd St., New York, NY 10017.
[b] Manufactured by Smith Kline & French Laboratories, 1500 Spring Garden St., Philadelphia, PA 19101.

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Drug Waste in Long-term Care Facilities: Impact of Drug Distribution System

Keith A. Parrott

The incidence and cost of drug waste in a long-term care facility (LTCF) were compared for a unit dose and a traditional (30-day card) distribution system.

Drug records for 74 LTCF patients were reviewed retrospectively to determine the number of drugs ordered and doses dispensed during a four-month period via a unit dose distribution system. Based on the same drug orders, the number of doses that would have been dispensed with a 30-day card system was projected. The drug costs and wastage costs for the two distribution systems were compared.

The mean number of drugs ordered per patient was 5.86. Differences between the two systems, mean number of doses dispensed per order, and their average cost per drug order were not statistically significant ($p > 0.05$). Of the total number of doses that would have been dispensed via the 30-day card system, 12.98% would have been wasted, representing 13.07% of the total drug costs.

Because the unit dose system eliminates the drug wastage associated with a 30-day card system, it has a positive impact on LTCF drug costs.

Index terms: Costs; Drug distribution systems; Drugs; Long-term care facilities

The problem of drug waste in long-term care facilities (LTCF) was first alluded to in 1971 by Mathieson and Rawlings.[1] Since that time, several authors have published in this area and have established that a significant problem exists.[2–5] Drug waste is defined, for purposes of this study, as medication that has been dispensed and paid for but not consumed by a particular LTCF patient. Waste would occur, for example, if a 10-day supply of drug were ordered, dispensed and charged, but the patient failed to consume the entire amount because of discharge, an adverse reaction, drug ineffectiveness, remission of symptoms for which the drug was prescribed, or perhaps death. While a mechanism to allow credit for the unconsumed medication would eliminate drug waste as previously defined, this mechanism generally does not exist for third-party payers, including Medicaid.[3,4]

Drug waste also depends on the type of drug distribution system employed.[6] A unit dose drug distribution system is characterized by the delivery of medications to patient care areas in single unit packages just prior to the time of administration. Drug doses are generally as ready for administration to the patient as possible.[6] With a unit dose system, patient drug charges are based only on doses actually consumed and consequently drug waste is minimized. However,

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