Single-dose bioavailability of two extended-release lithium carbonate products

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Abstract: The single-dose bioavailabilities of two extended-release lithium carbonate products and an immediate-release product were compared.

Nonsmoking healthy volunteers ages 20–31 ($n = 12$) were randomly assigned to one of three groups and given three treatments, each separated by a one-week period. The treatments, which were given to each group in a different sequence, consisted of three 300-mg immediate-release lithium carbonate tablets (Lithotab), two 450-mg extended-release lithium carbonate tablets (Eskalith CR), and three 300-mg extended-release lithium carbonate tablets (Lithobid). Blood samples were collected just before drug administration and at intervals up to 48 hours afterward. Urine was collected for 96 hours. Plasma and urine lithium concentrations were determined by flame-emission spectrophotometry, and lithium pharmacokinetic values and the cumulative urinary excretion of lithium were computed.

Mean maximum plasma lithium concentration (C_{max}) differed significantly among all three lithium carbonate products. Eskalith CR produced a 40% lower C_{max} and Lithobid a 25% lower C_{max} than Lithotab; Lithobid produced a 23% higher C_{max} than Eskalith CR. Lithotab had a significantly shorter mean time to maximum plasma lithium concentration than either extended-release product. Mean cumulative urinary excretion of lithium did not differ significantly among the three products.

Two extended-release lithium carbonate products were not bioequivalent when given in single doses to healthy volunteers.

Index terms: Antimanic agents; Blood levels; Dosage forms; Dosage schedules; Drugs, availability; Equivalency, generic; Excretion: Lithium carbonate; Sustained-action medications

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A major factor in the development of extended-release lithium products was the emergence of adverse effects associated with lithium therapy (e.g., gastrointestinal complaints, tremors, polyuria, polydipsia).[1] The first published report suggesting a correlation between gastrointestinal adverse effects and peak serum lithium concentrations appeared in 1967.[2] Subsequently, many studies with multifarious formulations and results have been published. Caution must be exercised when evaluating the results, because heterogeneous patient populations were studied, sample sizes were small, different lithium salts and dosage forms were compared, blood-sampling times were not consistent, and standardized scales for rating adverse effects were not used. Nevertheless, gastrointestinal adverse effects appear to be related to the rate of lithium absorption[3-11] and the extent of absorption,[5] and tremors are associated with the rate of absorption,[4,5] the maximum plasma lithium concentration,[8] and the extent of absorption.[5] The frequency of nausea is reportedly higher after administration of immediate-release lithium products than when extended-release preparations are given.[6,7] Conversely, abdominal pain,[9] diarrhea, and loose stools[5,6,10,11] occur more frequently in association with extended-release lithium products. The authors of studies of once-daily lithium therapy concluded that slower absorption produced fewer adverse effects.[12,13] However, Lyskowski and Nasrallah[14] did not observe any difference in the frequency of adverse effects between immediate-release and extended-release products.

Lithium is most frequently prescribed as the carbonate salt as a 300-mg (8.12-meq) capsule or tablet; until recently, Lithobid 300 mg and Eskalith CR 450 mg (12.18 meq) extended-release dosage forms were both available. In May 1993 Ciba-Geigy announced that it would no longer distribute Lithobid.[3] The only lithium solution is manufactured as the citrate salt.[15]

Previously, common reasons for therapeutic interchange between the two extended-release lithium products included intolerable adverse effects, formulary

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restrictions, and cost. Until now, a comparison of the bioavailabilities of the extended-release lithium carbonate products that have been marketed in the United States has not been published. Such information would be useful to practitioners when switching patients who were on a stable Lithobid regimen to another lithium product. The purpose of this study was to compare the single-dose bioavailabilities of two extended-release lithium carbonate products and a reference immediate-release product.

Methods

Twelve nonsmoking healthy volunteers (five women and seven men) ages 20–31 years (mean ± S.D., 24.8 ± 4 years) participated in the study. The subjects weighed 50–91 kg (mean ± S.D., 63.6 ± 11.2 kg). The protocol was approved by the institution's review board, and written informed consent was obtained from the volunteers.

The participants underwent physical examinations, and complete blood and urine chemistries were obtained. Individuals were excluded if they had upper-gastrointestinal-tract disease, renal or thyroid impairment, supraventricular tachycardia, convulsant disorders, mental illness, hypersensitivity or allergy to lithium, or pregnancy. All female subjects agreed to avoid conception during the study. The subjects were drug- and alcohol-free for one week before the study and during it. Each subject was instructed to maintain a constant intake of dietary sodium throughout the study.

The study had an open-label, randomized, three-treatment-crossover design. Each subject was randomly assigned to one of three groups and given three treatments, each consisting of the administration of a total of 900 mg (24.36 meq) of lithium carbonate, in the following sequences: treatments A, B, and C (group 1); B, C, and A (group 2); and C, A, and B (group 3). One-week intervals separated the drug treatments. Treatment A consisted of three 300-mg immediate-release lithium carbonate tablets (Lithotab, Reid-Rowell Laboratories, Baudette, MN, lot 66850). Treatment B consisted of two 450-mg extended-release lithium carbonate tablets (Eskalith CR, SmithKline & French Laboratories, Philadelphia, PA, lot 96J10). Treatment C consisted of three 300-mg extended-release lithium carbonate tablets (Lithobid, Ciba-Geigy Pharmaceutical Company, Summit, NJ, lot 66367).

The subjects fasted for eight hours before and three hours after ingesting the immediate-release product and for five hours after ingesting each extended-release product. Blood samples were collected in heparin-treated tubes immediately before drug administration and 0.5, 1, 2, 3, 4, 5, 7, 9, 12, 24, and 48 hours afterward. The plasma was harvested and frozen at –20 °C until analyzed. Urine was collected during the following periods after lithium ingestion: 0–24, 24–48, 48–72, and 72–96 hours. After the volume of the urine collected was measured, a 10-mL portion was frozen at –20 °C until analyzed.

Lithium concentrations in the plasma and urine were determined by flame-emission spectrophotometry with a cesium internal standard (model 943 flame photometer, International Laboratories, Lexington, MA). All samples were diluted 100-fold with an aqueous solution of cesium chloride (0.0015 M) to provide a lithium concentration in the range of 0 to 10 meq/L. The lower limit of detection of the assay was 0.06 meq/L. For plasma, the precision of the assay (measured as the coefficient of variation) at lithium concentrations of 0.28, 0.55, and 1.10 meq/L was 8.2% (n = 19), 6.0% (n = 21), and 4.5% (n = 19), respectively. For urine, the precision of the assay at lithium concentrations of 0.5, 3.0, and 7.0 meq/L was 4.9% (n = 7), 1.2% (n = 6), and 1.5% (n = 6), respectively. The accuracy of the assay (measured as the percent difference between mean and nominal concentrations) for the same plasma controls was 0%, 1.8%, and 0.9%, respectively; the accuracy for the same urine controls was 12.0%, 3%, and 2.6%, respectively.

The maximum plasma lithium concentration (C_{max}) and the corresponding time to maximum lithium concentration (t_{max}) were determined by visual inspection of the data. The area under the plasma lithium concentration-versus-time curve from 0 to 48 hours (AUC_{0-48}) was calculated by using the trapezoidal rule. The cumulative urinary excretion of lithium was determined for the period from 0 to 96 hours after the lithium carbonate ingestion (ur_{0-96}). At baseline and 1, 2, 4, 9, and 24 hours after each lithium carbonate dose, the subjects were asked, "Have you noticed any changes in your health?" If an adverse event was reported, the subject was asked to rate its severity.

The data were transformed logarithmically. The mean pharmacokinetic values for the three lithium products were evaluated by analysis of variance (ANOVA) with SAS version 6.0 (SAS Institute, Inc., Cary, NC). Significant differences by subject, treatment, period, and treatment sequence were analyzed. Tukey's test was used for multiple comparisons. The a priori level of significance was <0.05. The 90% confidence intervals for comparing the two extended-release products were calculated by using two one-sided t tests, as is currently advocated by FDA for bioequivalence testing.[16]

Results

All 12 subjects completed the three treatments. The mean plasma lithium concentration-versus-time curves for the three lithium carbonate products are shown in Figure 1. Mean values for C_{max}, t_{max}, AUC_{0-48}, and ur_{0-96} are presented in Table 1. The power of the ANOVA to detect a difference in C_{max}, t_{max}, AUC_{0-48}, and ur_{0-96} among the three lithium carbonate products was 90%, 47%, 68%, and 69%, respectively.

Mean C_{max} values differed significantly among the three lithium carbonate products. Eskalith CR produced a 40% lower C_{max} and Lithobid a 25% lower C_{max} than Lithotab, the immediate-release product. Lithobid

produced a 23% higher C_{max} than Eskalith CR.

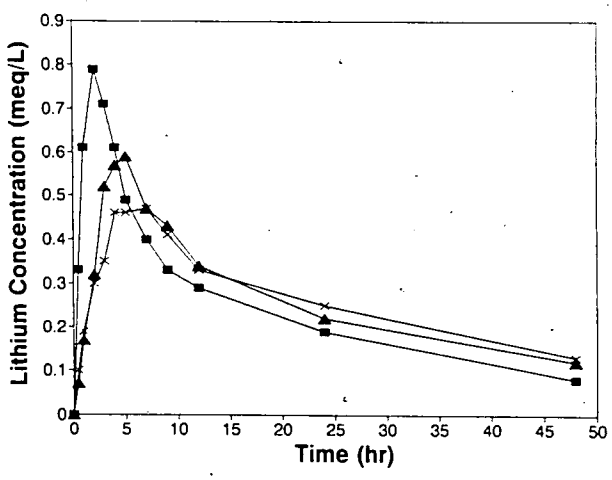
Lithotab had a significantly shorter mean t_{max} than either extended-release product. The difference in mean t_{max} values for the two extended-release products was not significant. There were no significant differences in mean values for AUC_{0-48} among the treatments.

Urine collections for two subjects were incomplete; these subjects were not included in the analysis of cumulative urinary excretion of lithium. Of the lithium ingested, the amount excreted over 96 hours, as calculated from the mean data, was 68%, 78%, and 79% for Eskalith CR, Lithotab, and Lithobid, respectively. Mean ur_{0-96} values did not differ significantly among the three lithium carbonate products.

The ratios for Lithobid and Eskalith CR were within the 0.8–1.2 range accepted by the FDA. These values are in direct contrast to the results of the statistical comparison made by using the 90% confidence intervals. The 90% confidence intervals for mean differences between the two extended-release products were within acceptable limits (0.8–1.2) only for t_{max} (0.91–0.95).

Two subjects reported mild polyuria and polydipsia after ingesting the immediate-release product. One reported moderate nausea at the time of C_{max} after Lithobid ingestion.

Figure 1. Mean plasma concentration-versus-time curves for 12 healthy subjects after ingestion of immediate-release lithium carbonate (Lithotab) (■) and two extended-release products, Eskalith CR (×), and Lithobid (▲).



Discussion

The bioavailabilities of extended-release preparations of a variety of lithium salts (carbonate, sulfate, fumarate, and acetate) have been evaluated over a period of more than two decades.[7-11,12,17-29] The results of these trials are difficult to compare because of differences in study patient populations and diagnoses, lack of demographic information, the use of concomitant medications, and the lack of appropriate study design (crossover treatment groups, divided daily doses, an adequate number of samples for assessing pharmacokinetic variables, and valid statistical analysis).

Two bioavailability studies have been performed to compare immediate- and extended-release formulations of lithium carbonate. Cooper et al.[30] reported that a single dose of Lithobid produced a significantly lower C_{max} and AUC_{0-48} and a larger t_{max} than the immediate-release product; however, since $AUC_{0-\infty}$ values were equal, the two products were judged to be equally bioavailable. Caldwell et al.[31] found that steady-state blood concentrations of an immediate-release lithium carbonate product fluctuated 1.4 times more than blood levels produced by Eskalith CR.

The findings of the present study are consistent with those of previous trials showing that C_{max} is lower with extended-release lithium carbonate products than with immediate-release products. Interestingly, the mean C_{max} after a single dose of Eskalith CR was significantly lower than that for Lithobid on the basis of both ANOVA and confidence-interval testing. Differences in C_{max} between the extended-release products may be important in patients who experience adverse effects that

Table 1.
Pharmacokinetic Data for Three Lithium Carbonate Products in 12 Subjects

Pharmacokinetic Variable[a]	Mean ± S.D. Value for Indicated Lithium Carbonate Product (Raw Data)			Ratio[b]	90% Confidence Interval[c]
	Immediate-Release (Lithotab)	Extended-Release (Eskalith CR)	Extended-Release (Lithobid)		
C_{max} (meq/L)	0.86 ± 0.18	0.51 ± 0.11[d,e]	0.64 ± 0.12[d]	0.80	0.91–1.72
t_{max} (hr)	2.25 ± 0.75	5.25 ± 1.86[d]	5.17 ± 1.70[d]	1.02	0.91–0.95
AUC_{0-48} (meq · hr/L)	11.6 ± 2.2	12.4 ± 4.2	12.2 ± 3.3	1.02	0.70–1.44
ur_{0-96} (meq)[f]	18.9 ± 2.3	16.5 ± 5.5	19.2 ± 2.5	0.86	0.82–1.84

[a] C_{max} = maximum plasma lithium concentration, t_{max} = time to maximum plasma lithium concentration, AUC_{0-48} = area under the plasma lithium-versus-time curve from 0 to 48 hours, and ur_{0-96} = cumulative urinary excretion of lithium from 0 to 96 hours after ingestion.
[b] Pharmacokinetic value for Eskalith CR divided by value for Lithobid.
[c] 90% Confidence interval for mean difference between Eskalith CR and Lithobid. Calculated by using logarithmically transformed data.
[d] Significantly different from corresponding value for Lithotab.
[e] Significantly different from corresponding value for Lithobid.
[f] $n = 10$.

may alter medication compliance, especially tremors.[32] Therefore, patients who have adverse effects associated with higher peak plasma lithium concentrations with an immediate-release product might experience fewer problems if they took instead the only currently available extended-release product, Eskalith CR.

The time to maximum lithium concentration was significantly shorter for the immediate-release product than for the extended-release products. Both ANOVA and confidence-interval testing showed no difference in t_{max} between the two extended-release products. Eskalith CR had the greatest variability in t_{max}; this may have been due to differences in drug absorption among the products and the subjects. Further study is needed to determine whether this variability has clinical significance. ANOVA of AUC_{0-48} and ur_{0-96} values showed that lithium absorption did not differ significantly between the extended-release products; however, variability among subjects was demonstrated by confidence-interval testing. Confidence-interval testing of C_{max} and AUC_{0-48} values indicated that the extended-release products are not bioequivalent. A comparison of the pharmacokinetics and adverse effects of the extended-release lithium carbonate products given in multiple doses to a larger sample would have been necessary to determine the clinical significance of the difference in bioequivalence.

Conclusion

Two extended-release lithium carbonate products, Lithobid and Eskalith CR, were not bioequivalent when given in single doses to healthy volunteers.

[3]De Leonardis M, Ciba-Geigy Corporation. Personal communication. 1993 May 24.

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