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BIOAVAILABILITY OF LITHIUM FROM LITHIUM CITRATE SYRUP VERSUS CONVENTIONAL LITHIUM CARBONATE TABLETS

P. J. M. GUELEN*§, T. J. JANSSEN*, T. C. M. DE WITTE*, T. B. VREE† AND K. BENSON‡

*Farma Research B.V., Snelliusstraat 6, 6533 NV Nijmegen, The Netherlands
†Department of Clinical Pharmacy, Academic Hospital Nijmegen, Geert Grooteplein Zuid 8, 6525 GA Nijmegen, The Netherlands
‡R.P. Drugs, Braithwaite Street, Leeds LS11 9XE, England

ABSTRACT

The bioavailability of lithium citrate syrup was compared with that of regular lithium carbonate tablets in 18 healthy male human volunteers. Blood samples were collected up to 48 h after dosing. Lithium serum concentrations were determined by means of AAS. The absorption rate following oral administration of the syrup was greater (t_{max} 0·8 h) than following administration of regular tablets (t_{max} 1·4 h). Maximum lithium serum concentrations, however, were only about 10 per cent higher after syrup dosing and serum concentrations resulting from syrup and tablets were almost superimposable from 2 h after dosing. The terminal half-life of lithium was found to be 22 h after syrup as well as after tablet dosing. No side-effects were observed during the study. The bioavailability of lithium from syrup relative to tablets was found to be bioequivalent with respect to the maximum lithium serum concentration and the extent of drug absorption (AUC).

KEY WORDS Lithium Syrup Tablets Bioavailability

INTRODUCTION

Lithium salts are indicated in the prophylactic treatment of bipolar depression, recurrent unipolar depression, and schizo-affective disorders.[1,2] After oral administration of conventional lithium carbonate solid dosage forms, lithium is rapidly and almost completely absorbed. Peak plasma concentrations are attained within c. 3 h after dosing.[1,3]

Lithium is not metabolized or protein-bound and it is almost completely excreted by the kidneys. The elimination half-life ranges from 12 to 48 h depending on the duration of treatment, kidney function, and age.[1,3] The therapeutic range of lithium is very narrow and is defined as serum lithium concentrations from 0·6 to 1·2 mmol l^{-1}. If no clinical effects are observed and no side-effects are reported the lithium dosage may be elevated up to a corresponding serum lithium level of 1·5 mmol l^{-1}.

§Addressee for correspondence.

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The administration of oral liquid concentrates or syrups is an alternative way of administering medication to children, to patients having difficulty in swallowing the lithium tablets (e.g. the elderly), or to the noncompliant patient in the psychiatric setting.

Only limited data on the pharmacokinetics and bioavailability of lithium containing liquid dosage forms are available in literature.[4]

STUDY OBJECTIVE AND DESIGN

The aim of this study was to investigate and compare the disposition of equivalent single oral doses of lithium from lithium carbonate regular tablets and lithium citrate syrup in healthy adult male volunteers.

A two-way crossover design was used, with 18 subjects receiving both products in a randomly determined order. Each subject received a single oral 13·6 mmol Li^+ dose on two occasions separated by a 2-week washout period. Lithium concentrations in serum were determined by means of atomic absorption spectroscopy (AAS) up to 48 h after dosing. The resulting serum concentration–time curves for the two treatments were compared with respect to the area under the serum concentration–time curve, the maximum and the time to reach the maximum concentration of lithium.

MATERIALS AND METHODS

Subjects

Eighteen healthy male volunteers between the age of 19 and 33 years participated in this study. All subjects were selected after successful completion of a thorough history and physical examination, and after demonstration of clinically normal results following a battery of tests consisting of a blood chemistry examination, complete blood count, and urinalysis. Potential subjects were excluded from participation if they had a known sensitivity/idiosyncrasy to the drug, a history of psychiatric disorders, or of acute or chronic systemic disease, had donated blood or participated in any drug study within 60 days of the start of the study, had received any medication within 14 days before the first dosing, or had a known history of abuse or current abuse of drugs or alcohol or solvents.

Each volunteer signed an informed consent form, after written and oral presentation with full details of the research. The mean age $\pm$ SD and weight of the subjects at the time of the study were 25·1 $\pm$ 4·2 years and 76·1 $\pm$ 7·3 kg, respectively.

Study drugs

The test product (liquid lithium 10·8 mEq. per 5 ml, containing 10·8 mmol Li^+ per 5 ml) and reference product (Camcolit®, lithium carbonate 250 mg,

Table 1. Allocation of subjects to the two groups

Group	Number of subjects	Treatments Phase 1	Phase II
1	9	A	B
2	9	B	A

A = single oral dose of two Camcolit tablets (13·6 mmol lithium).
B = single oral dose of 6·3 ml Liquid Lithium (13·6 mmol lithium).

containing 6·8 mmol Li^+ per tablet) were supplied by R. P. Drugs Ltd, Leeds, England.

Randomization and treatments

The 18 subjects were randomly allocated to two groups of equal size by use of computer randomization of subject code (SAS, Procedure Plan) as summarized in Table 1.

Dosing and blood sampling

Subjects arrived at the study centre at 10.00 pm on the day preceding each phase of the trial. After a supervised overnight fast (the intake of tap water was allowed *ad libitum* until 2 h before dosing) each subject received a single oral dose of 13·6 mmol Li^+ between 8.00 and 9.00 am with 200 ml of tap water.

All subjects remained at the study facility until 32 h after drug administration where they were monitored for side-effects. Subjects were ambulatory but were not permitted to engage in strenuous physical exercise. The fast was maintained until 3 h after dosing when a standardized breakfast was served. All food intake was standardized until 32 h after dosing. Fluid intake was standardized until 7 h after dosing. Throughout each study period, alcohol-containing foods and drinks were prohibited.

Blood samples (10 ml) were drawn via an indwelling Venflon® 2 IV cannula, inserted in a forearm vein, into non-heparinized glass tubes just before drug administration and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 15, 24, 33, and 48 h after dosing. The blood samples were allowed to clot and centrifuged at about 2700 g for 10 min. Serum was transferred into labelled polypropylene tubes and stored at $\leqslant -20°$ pending analysis.

Drug analysis

The quantitative determination of lithium was carried out by means of an atomic absorption spectrometric method. The instrument, a Perkin Elmer Type 400 atomic absorption spectrophotometer, was equipped with a Lithium Hollow

Cathode lamp (670·8 nm). The slit setting was 0·7 mm, the oxidant was air, and the fuel was acetylene.

Quantification was done by means of the standard addition method in the lithium concentrations of 0, 100, 500, and 1000 μmol l^{-1}. The linear range of the method was 25–2500 μmol l^{-1}. The limit of quantification (LOQ) was set at 25 μmol l^{-1}, based on the repeatability of 16 per cent (RSD) at 16 μmol l^{-1}, 8 per cent at 33 μmol l^{-1} and 8 per cent at 65 μmol l^{-1}.

Reproducibility (between run variation) of the method was 3 per cent at 100 μmol l^{-1}, 1 per cent at 500 μmol l^{-1}, and 1 per cent at 1000 μmol l^{-1}, based on relative standard deviation (RSD) calculated over eight consecutive runs.

Pharmacokinetic parameters and statistical methods

Calculations and statistical analysis of the data for test and reference product were performed by using standard and user-modified procedures of the Statistical Analysis System (SAS-Institute).

The following pharmacokinetic parameters for lithium were derived from the individual serum concentration–time profiles:

C_{max}: maximum drug concentration.
t_{max}: time to reach the maximum drug concentration.
$t_{½}$: elimination half-life associated with the terminal slope of a semilogarithmic concentration–time curve (ln2/z).
$AUC_{0\to48}$: area under the serum concentration–time curves calculated (linear trapezoidal method) until 48 h after dosing.
AUC_{∞}: area under the serum concentration–time curve from zero to infinity, calculated by addition of the residual area (C_{48h}/z) to $AUC_{0\to48}$.

Pharmacokinetic parameters and serum concentrations for each time point were analysed by means of analysis of variance (ANOVA), with a model appropriate for a balanced two-period, two-treatment crossover design (source of variability: treatments, periods, subjects per sequence and sequence). The statistical power[6] to detect inter-formulation differences of at least 20 per cent for the mean AUC and C_{max} values at $\alpha = 0{\cdot}05$ was calculated. Classical 95% confidence intervals (95% CI) and 90% confidence intervals (90% CI)[8], operationally equivalent to the two one-sided test procedure,[9] for the relative bioavailability were calculated using the AUC and C_{max} data, expressed as per cent of the reference product.

RESULTS

Clinical

Lithium was well tolerated by all 18 subjects after both treatments. No side-effects were reported by any subject or observed by the medical staff of the study facility. All subjects completed the study.

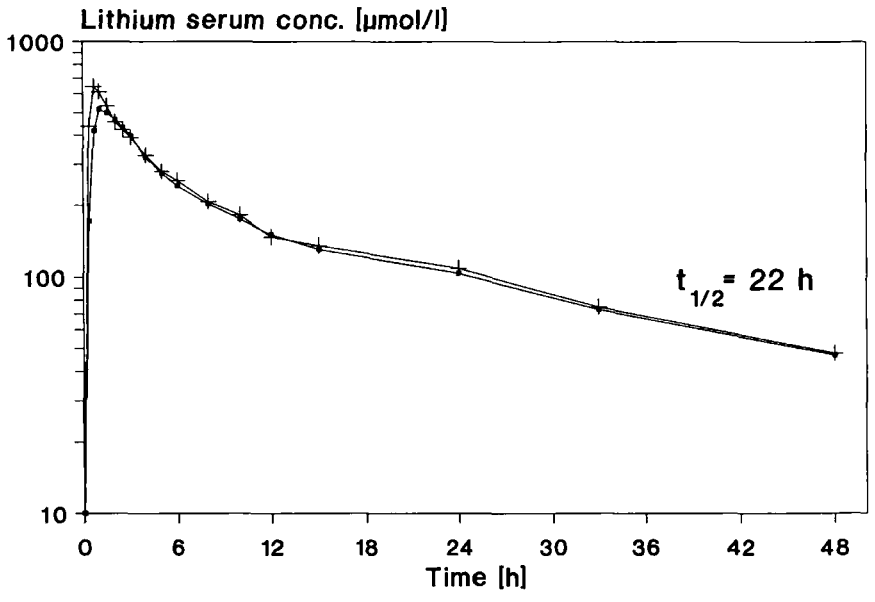

Figure 1. Average lithium serum concentration versus time plots after equimolar oral doses (13·6 mmol Li^+) of lithium citrate syrup (+) or lithium carbonate tablets (□) to 18 male subjects

Table 2. Mean (SD) lithium serum concentrations [μmol l^{-1}] after oral administration of 13·6 mmol Li^+

Time (h)	Reference*		Test†		Difference at 95% level ($p<0·05$)‡	
0·0	0		0			
0·33	171	(123)	436	(188)	S	($p<0·01$)
0·67	418	(193)	644	(90)	S	($p<0·01$)
1·0	516	(159)	612	(77)	S	($p=0·01$)
1·5	497	(105)	532	(60)	NS	($p=0·05$)
2·0	466	(96)	456	(47)	NS	($p=0·65$)
2·5	432	(53)	422	(38)	NS	($p=0·31$)
3·0	399	(62)	392	(49)	NS	($p=0·64$)
4·0	322	(49)	329	(29)	NS	($p=0·56$)
5·0	275	(29)	280	(36)	NS	($p=0·62$)
6·0	242	(29)	256	(26)	NS	($p=0·05$)
8·0	203	(24)	207	(32)	NS	($p=0·48$)
10·0	175	(20)	182	(24)	NS	($p=0·24$)
12·0	150	(22)	147	(22)	NS	($p=0·42$)
15·0	130	(20)	135	(23)	NS	($p=0·40$)
24·0	104	(17)	109	(18)	NS	($p=0·22$)
33·0	73	(11)	75	(17)	NS	($p=0·68$)
48·0	47	(12)	48	(13)	NS	($p=0·67$)

*Single oral dose of two 250 mg lithium carbonate containing tablets.
†Single oral dose of 6·3 ml liquid containing 10·8 mmol lithium per 5 ml.
‡ANOVA, degrees of freedom: treatments (1), periods (1), subject (group) (16), group (1), error (16).

Table 3. Individual AUC and C_{max} values of lithium after oral administration of 13·6 mmol Li^+

Subject	$AUC_{0\to48}$ (mmol.h l^{-1})			AUC_{∞} (mmol.h l^{-1})			C_{max} (mmol l^{-1})		
	Ref.*	Test†	T/R	Ref.	Test	T/R	Ref.	Test	T/R
1	6073	6313	1·04	7363	8037	1·09	580	728	1·26
2	6591	6145	0·93	8036	7098	0·88	531	500	0·94
3	6907	6592	0·95	8755	7598	0·87	675	737	1·09
4	7770	8454	1·09	10455	10264	0·98	609	742	1·22
5	6688	7096	1·06	7723	9072	1·17	734	665	0·91
6	6539	6734	1·03	7835	8126	1·04	497	530	1·07
7	6290	6322	1·01	7570	7651	1·01	817	854	1·05
8	6392	6096	0·95	7680	7563	0·98	653	684	1·05
9	5818	6407	1·10	7474	8318	1·11	543	609	1·12
10	6055	8132	1·34	6939	10876	1·57	655	649	0·99
11	8098	8272	1·02	9818	11032	1·12	873	740	0·85
12	5880	6793	1·16	7618	8398	1·10	493	574	1·16
13	5998	6400	1·07	7392	7459	1·01	540	629	1·16
14	5912	5894	1·00	6573	6853	1·04	529	708	1·34
15	6067	5951	0·98	7438	6743	0·91	522	521	1·00
16	7142	7614	1·07	9539	9495	1·00	513	733	1·43
17	6536	6796	1·04	7485	7681	1·03	603	689	1·14
18	5244	6517	1·24	6831	7999	1·17	445	673	1·51
Mean	6444	6807	1·056	7918	8348	1·054	601	664	1·11
RSD (%)	10·9	11·7		13·3	15·6		19·3	13·8	

*Single oral dose of two 250 mg lithium carbonate containing tablets.
†Single oral dose of 6·3 ml liquid containing 10·8 mmol lithium per 5 ml.

Table 4. Individual t_{max} and $t_{½}$ values of lithium after oral administration of 13·6 mmol Li^+

Subject	t_{max} (h) Ref.	Test	T/R	$t_{½}$ (h) Ref.	Test	T/R
1	1·00	0·33	0·33	20·96	24·79	1·18
2	1·00	0·67	0·67	20·64	17·47	0·85
3	1·50	0·67	0·45	23·72	18·84	0·79
4	2·00	0·67	0·34	27·19	21·03	0·77
5	2·00	0·67	0·34	17·77	24·34	1·37
6	3·00	1·00	0·33	19·60	21·36	1·09
7	0·67	0·33	0·49	21·51	22·69	1·05
8	0·67	0·67	1·00	20·59	23·61	1·15
9	1·50	1·00	0·67	24·22	26·55	1·10
10	1·00	1·00	1·00	17·84	26·34	1·48
11	1·00	1·00	1·00	20·79	27·12	1·30
12	0·67	1·00	1·49	25·02	21·95	0·88
13	1·00	0·67	0·67	22·24	18·58	0·84
14	1·50	1·00	0·67	16·04	19·68	1·23
15	3·00	1·00	0·33	21·64	16·41	0·76
16	1·00	0·67	0·67	26·74	22·68	0·85
17	1·00	0·67	0·67	17·38	16·70	0·96
18	1·50	0·67	0·45	25·94	23·17	0·89
Mean	1·39	0·76	0·55	21·66	21·85	1·009
RSD (%)	51·2	29·3		15·2	15·4	

*Single oral dose of two 250 mg lithium carbonate containing tablets.
†Single oral dose of 6·3 ml liquid containing 10·8 mmol lithium per 5 ml.

Lithium serum levels

Mean lithium serum concentrations and standard deviations achieved following administration of test and reference product are given in Table 2. Semilogarithmic plots of the mean concentrations as a function of time are presented in Figure 1. Individual pharmacokinetic parameters (AUC, C_{max}, t_{max}, and $t_{½}$ values), derived from the lithium serum concentration–time curves, with mean values and relative standard deviations, are given in Tables 3 and 4.

Statistical analysis

The individual AUC and C_{max} data for test and reference product were statistically tested for bioequivalence. The results are given in Table 5.

DISCUSSION

Absorption from the liquid oral dosage form (test) was more rapid (mean t_{max} = 0·76 h) than from the solid oral dosage form (reference) (mean t_{max} = 1·39 h).

Table 5. Statistical power, ratio of the means, relative bioavailability, and confidence intervals for AUC and C_{max} values after oral administration of 13·6 mmol Li^+ to 18 healthy male subjects

	T†/R*	Power‡	F_{rel} (T/R*100%)	95% CI	90% CI
$AUC_{0\to48}$	1·056	1·000	106%	101·0–110·2%	101·9–109·4%
AUC_{∞}	1·054	1·000	105%	98·4–112·5%	99·6–111·2%
C_{max}	1·107	0·999		102·6–118·7%	104·1–117·3%

*Single oral dose of two 250 mg lithium carbonate containing tablets.
†Single oral dose of 6·3 ml liquid containing 10·8 mmol lithium per 5 ml.
‡Statistical power to detect an inter-formulation difference of at least 20 per cent at $\alpha = 0·05$.

ANOVA on lithium serum concentrations at each time point demonstrates a significant difference ($p \leqslant 0·05$) between formulations at 0·33, 0·67, and 1·0 h after dosing. In addition, t_{max} was found to be less variable after test (range: 0·33–1·0 h) than after reference administration (range: 0·67–3·0 h). The rapid and consistent absorption from the liquid product was expected since the lithium in liquid oral dosage form is in solution and therefore immediately available, whereas lithium in the solid oral dosage form is not. The findings are in agreement with those previously reported in the scientific literature.[4]

From 2 h after dosing, mean serum concentration versus time profiles resulting from the test and reference formulations overlap. Low inter-subject variability in lithium serum concentrations at each time point is observed for both formulations.

The terminal half-life of about 22 h observed after dosing of both formulations, is consistent with half-lives reported in literature.[9] Pharmacokinetic parameters $AUC_{0\to48}$, AUC_{∞}, and C_{max} of lithium showed relatively low inter-subject variability (RSD) after administration of both the liquid dosage form (11·7 per cent, 15·6 per cent, and 13·8 per cent, respectively) and the solid oral dosage form (10·9 per cent, 13·3 per cent, and 19·3 per cent, respectively).

The results of the data evaluation were good (Table 4). Power of the study to detect inter-formulation differences of at least 20 per cent for the mean AUC and C_{max} values with $\alpha = 0·05$ was excellent ($>0·99$). The 90 per cent confidence intervals as well as 95 per cent confidence intervals were well within the accepted limits (80–120 per cent). The relative bioavailability of the liquid oral dosage form to the solid oral dosage form on the ratio of mean AUC_{∞} was 105 per cent.

The results of this study clearly indicate that the liquid oral dosage form of lithium is a safe and bioequivalent alternative in lithium therapy.

REFERENCES

1. W. A. Nolen and G. M. J. van Kempen. Lithium. *Geneesmiddelenbulletin*, **18**, 19–24 (1984).

2. C. J. Slooff, T. K. Bouman, G. J. Niemantsverdriet-van Kampen, J. Ormel, Lithiumprofylaxe, O. K., Maar Hoe Lang? *Ned. Tijdschr. Geneeskd.*, **129**, 1729–1733 (1985).
3. R. Hunter, Steady-state pharmacokinetics of lithium carbonate in healthy subjects, *Br. J. Clin. Pharmac.*, **25**, 375–380 (1988).
4. R. Hunter and A. Taylor, Lithium citrate syrup—a safe alternative formulation. *Br. J. Pharm. Pract.*, April, 146–149 (1989).
5. H. C. Caldwel, W. J. Westlake, R. B. Schriver and E. E. Bumbier, Steady-state lithium blood level fluctuations in man following administration of a lithium carbonate conventional and controlled-release dosage form. *J. Clin. Pharmacol.*, **21**, 106–109 (1981).
6. C. D. Hardison, D. Quade and R. D. Langston (1983). *Nine functions for probability distributions, SUGI Supplemental Library User's Guide*, 1983 edn, SAS Institute Inc., Gary, NC (1983).
7. D. J. Schuirmann, Pharmacometrics. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J. Pharmacokin. Biopharm.*, **15**, 657–680 (1987).
8. V. W. Steinijans and E. Diletti, Statistical analysis of bioavailability studies: parametric and non-parametric confidence intervals. *Eur. J. Clin. Pharmacol.*, **24**, 127–136 (1983).
9. T. S. Foster, R. E. Crass, F. A. Bustrack, R. B. Smith and J. W. Munson, Evaluation of two lithium carbonate formulations. *Am. J. Hosp. Pharm.*, **37**, 1528–1531 (1980).