Br. J. clin. Pharmac. (1988), **25**, 375–380

Steady-state pharmacokinetics of lithium carbonate in healthy subjects

R. HUNTER
MRC Brain Metabolism Unit, Royal Edinburgh Hospital, Morningside Park, Edinburgh EH10 5HF

1 The pharmacokinetics of lithium in six healthy volunteers stabilised on lithium were investigated and appropriate pharmacokinetic parameters calculated.
2 The results illustrate important differences in single and multiple dose lithium pharmacokinetics; the implications for minimising lithium-induced renal damage are discussed.

Keywords lithium pharmacokinetics healthy subjects

Introduction

Lithium is now widely used for the prophylaxis of manic-depressive illness and its efficacy is well established (Baastrup *et al.*, 1970; Prien *et al.*, 1973). Our knowledge of lithium pharmacokinetics comes mainly from single-dose studies, many of which have serious methodological shortcomings including diagnostic heterogeneity of the sample, infrequent blood sampling and lack of information about concomitant drug use (Shaw *et al.*, 1974; Tyrer *et al.*, 1976; Bennie *et al.*, 1977). Although recent work has overcome some of these problems (Shelley & Silverstone, 1986), it was restricted to single dose pharmacokinetics and, therefore, of limited value in understanding pharmacokinetics in subjects stabilised on lithium. In two studies (Mellerup *et al.*, 1979; Johnson *et al.*, 1982), serum lithium pharmacokinetics have been investigated in patients stabilised on lithium, however, they gave no information on diagnosis or concomitant medication, both of which may significantly alter lithium pharmacokinetics. The present study attempts to address these criticisms by investigating lithium pharmacokinetics in healthy subjects stabilised on lithium.

Methods

Six normal subjects, four males and two females, with no history of psychiatric disorder, gave their informed consent to take part in the study. All were examined to ascertain that they were physically and psychiatrically well. Laboratory investigation revealed no abnormality, in particular, serum creatinine concentrations were all within normal limits. However, serum creatinine is an insensitive measure of glomerular function and as much as 50% reduction in glomerular filtration rate (GFR) may occur before serum creatinine exceeds the normal range (Enger & Blegen, 1964). To overcome this limitation, creatinine clearance (ml min^{-1}) was calculated from serum creatinine concentration as a measure of GFR, using the method of Cockcroft & Gault (1976) which also takes account of age, sex and weight. This information is summarised in Table 1. On entry to the study, all subjects were free of medication including oral contraceptives.

Subjects took lithium carbonate (Camcolit-400) every 12 h for 21 days in a dose sufficient to achieve serum concentrations in the 'therapeutic range' which was defined as 0.5–1.0 mmol l^{-1}. Blood for lithium estimation was taken every 5 days, at about 12 h after the last dose. Side effects, volunteered and elicited, were scored for severity and their time and duration noted.

After 21 days on lithium, subjects fasted overnight, and at 08.30 h an intravenous cannula was inserted into a peripheral vein to allow blood to be taken for lithium estimation. Blood was removed (a) just before administration of last dose of lithium, (b) every 0.5 h for 6 h after administration and (c) at 12, 24, 36, 48 and 72 h. Serum lithium concentrations were measured

Table 1 Sex, age, weight and GFR for the six subjects with their last dose of lithium carbonate

Subject	*Sex*	*Age (years)*	*Weight (kg)*	*GFR (ml min^{-1})*	*Last lithium dose (mmol)*
1	M	20	73.0	138	21.7
2	F	40	50.8	90	10.9
3	M	36	64.9	105	21.7
4	M	29	63.5	106	21.7
5	F	35	55.0	66	10.9
6	M	37	82.5	107	10.9

GFR is glomerular filtration rate (creatinine clearance) calculated from serum creatinine (see text).

using absorption spectrophotometry in the same laboratory which normally undertakes lithium estimation.

For each subject the following pharmacokinetic parameters were measured:

(a) t_{max} (h): time to maximum serum concentration after last lithium dose.
(b) C_{max} (mmol l^{-1}): maximum serum concentration
(c) Serum lithium concentration at 12 h and 24 h
(d) The area under the 24 h serum curve (AUC 0–24) was estimated using the trapezium rule,
as a measure of bioavailability.
(e) The elimination half-life ($t_{½}$) in h was calculated from the plot of log serum lithium concentration against time.
(f) Total body clearance (CL) was calculated from the formula D/AUC 0–12 where D was the last dose taken (see Table 1) and AUC 0–12 the area under the 12 h serum curve.
(g) The apparent volume of distribution (V) was calculated from the formula: $V = (CL \times t_{½})/\ln 2$.

Results

Figure 1 shows the serum lithium concentrations for each subject from time of the last dose (0 h) until 72 h, while Figure 2 shows mean serum concentrations (± s.e. mean) for the same data. Serum concentrations follow the same pattern in all subjects, rising to a peak as the drug is absorbed, then falling with subsequent distribution and elimination. Plots of log concentration *vs* time (not illustrated) clearly indicate two distinct and separate phases of distribution and elimination. Figure 1 shows that rates of absorption were similar in most subjects, except subjects 1 and 2, where absorption was slower and C_{max} occurred at about 3 h. Peak serum lithium concentrations (C_{max}) range from 1.0 to 1.94 mmol l^{-1} (mean ± s.d. 1.49 ± 0.31) and occur (t_{max}) at 1.2 to 3.0 h (2.1 ± 0.5) after the last dose of lithium. This is shown in Table 2 together with other pharmacokinetic parameters.

During the 3 weeks of the study, few side-effects were reported and none was serious. Over 21 days, side-effects were reported on only ten occasions and consisted almost equally of occasional nausea, usually 1–2 h after taking lithium, loose bowel motions and difficulty concentrating. Nausea and poor concentration appeared to be time-related to peak lithium concentrations but there was no association between severity of side-effects and C_{max}.

Discussion

Although this is a small study, it illustrates a broad range of lithium pharmacokinetic profiles. Absorption rates were similar, but the low absorption rate of subject 2 resulted in the lowest peak serum lithium concentrations of the group. Lithium elimination was also slow in this subject, resulting in only a small reduction in serum lithium concentration between four and 48 h. The long elimination half-life and large apparent volume of distribution reflect the low GFR of subject 2 (90 ml min^{-1}), which is below the normal range for a female of this age (100–140 ml min^{-1}). The other female subject, (5), had an even lower estimated GFR (66 ml min^{-1}), which explains the high serum lithium concentrations during the elimination phase (see Figure 1) and resulting high bioavailability. The remaining four subjects, all male, had similar pharmacokinetics, reflecting similar glomerular function, despite quite diverse ages and weights.

There have been several single-dose studies of lithium pharmacokinetics which, although useful

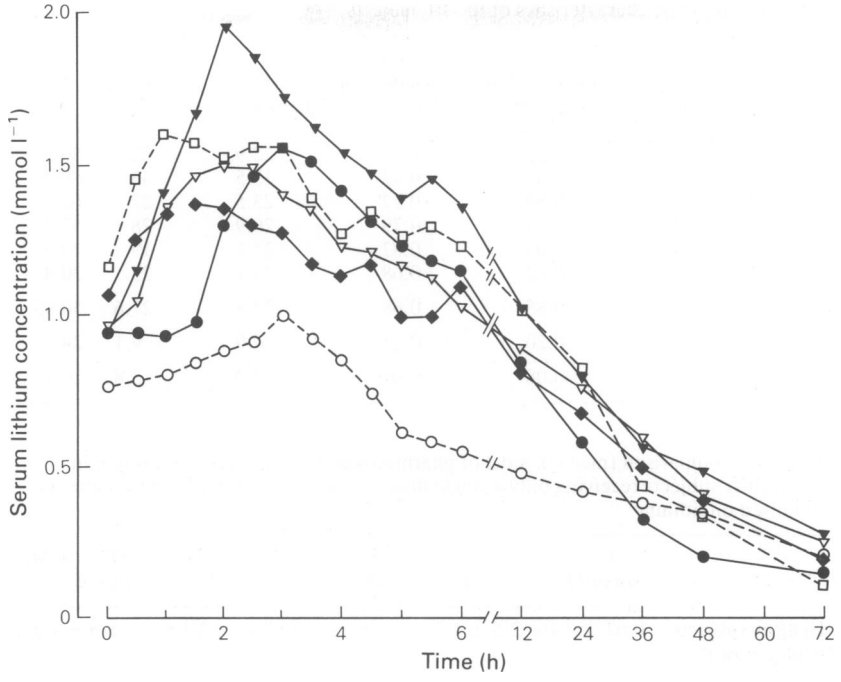

Figure 1 Serum lithium concentrations for each of the six subjects over 72 h from last lithium dose (0 h).

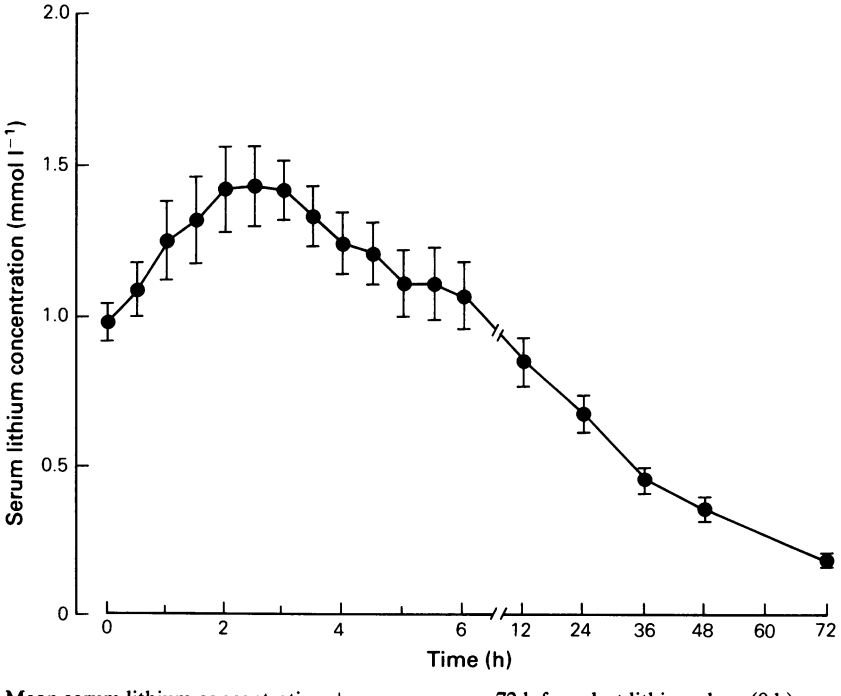

Figure 2 Mean serum lithium concentration ± s.e. mean over 72 h from last lithium dose (0 h).

Table 2 Pharmacokinetic characteristics of the six subjects

Subject	t_{max} *(h)*	C_{max} *(mmol l^{-1})*	*12 h concentration (mmol l^{-1})*	*24 h concentration (mmol l^{-1})*	*AUC (mmol l^{-1} h)*	$t_{1/2}$ *(h)*	V *(l)*	*CL (l h^{-1})*
1	3.0	1.55	0.84	0.58	22.9	22	50.9	1.62
2	3.0	1.00	0.48	0.42	13.5	45	89.4	1.39
3	2.0	1.49	0.89	0.77	23.5	27	62.5	1.62
4	2.0	1.94	1.01	0.79	26.9	28	53.2	1.33
5	1.3	1.61	1.03	0.82	27.1	19	19.3	0.71
6	2.0	1.37	0.82	0.68	23.1	25	30.4	0.85
Mean	2.1	1.49	0.85	0.68	22.8	27.6	50.95	1.25
s.d.	0.5	0.31	0.20	0.15	4.9	9.1	24.7	0.40
s.e. mean	0.2	0.13	0.08	0.06	2.0	3.8	10.1	0.16

Table 3 Comparison (mean ± s.d.) of pharmacokinetic parameters of lithium in (a) healthy subjects receiving only a single dose, (b) healthy subjects and (c) patients stabilised on lithium

	C_{max} *(mmol l^{-1})*	t_{max} *(h)*	$t_{1/2}$ *(h)*	V *(l)*	*CL (1 h^{-1})*	*AUC (0–24) (mmol l^{-1} h)*
Healthy subjects (single dose)*	0.62 ± 0.16	2.5 ± 1.2	18	79.7	3.1	8.6 ± 1.4
Healthy subjects (steady state)+	1.49 ± 0.31	2.1 ± 0.5	27.6 ± 9.1	50.9	1.25 ± 0.4	22.8 ± 4.9
Patients (steady state)/	1.71 ± 0.14	1.9 ± 0.8	21.9	27.8	0.89	24.3 ± 4.0

* Shelley & Silverstone (1986)
\+ Present study
/ Johnson *et al.* (1982)

for comparing different formulations, make only a limited contribution to understanding steady-state conditions. Patients are managed in steady-state lithium conditions and adequate assessment of serum lithium concentrations is essential for effective and safe prescribing. In Table 3, pharmacokinetic parameters from this study are compared with published data from patients stabilised on lithium (Johnson *et al.*, 1982) and from a recent single dose study (Shelley & Silverstone, 1986). In the three studies, absorption rates, as measured by t_{max}, are similar, but peak concentrations in the steady-state are more than two-fold greater than reported in the single dose study. Subjects stabilised on lithium have an increased half-life, although in the present study, this is largely accounted for by subject 2. However, bioavailability (AUC 0–24) is increased three-fold in the steady-state with corresponding decreases in total body clearance and apparent volume of distribution. Such comparisons illustrate the important differences in pharmacokinetics between single dose and steady-state conditions.

Our results show that for all subjects, serum lithium concentrations, as measured at 12 h after the last dose, lie within the 'therapeutic range'. In a 12 h dosing schedule, as used in this study, the serum lithium concentration at 12 h after the last dose represents the minimum lithium concentration in the daily serum lithium profile. In other words, apart from the 12 h nadirs, serum lithium concentrations are higher than the upper limit of the therapeutic range, at all times throughout the day. Elevated serum lithium concentrations can result in irreversible glomerular damage (Perry *et al.*, 1981; Bendz, 1983; Waller & Edwards, 1985) but the consensus from most studies is that if 12 h post-dose lithium concentrations are within therapeutic limits, then only a minority (5–10%) will suffer from mild glomerular impairment (Bendz, 1983).

Serum lithium concentrations are paralleled by considerably higher concentrations in the renal tubules and prolonged lithium treatment may impair the concentrating capacity of the tubules (Hetmar *et al.*, 1986). There is evidence that patients treated with single daily lithium

doses have less polyuria than those treated with multiple daily doses (Plenge *et al.*, 1982; Perry *et al.*, 1981; Schou *et al.*, 1982), perhaps by allowing restitution of tubular function during lower trough levels. However, it has been argued that single dose regimens of lithium expose the distal nephron to unacceptably high lithium concentrations which results in tubular damage and defective concentrating ability (Amdisen, 1977). Single doses of lithium result in greater peak to trough fluctuations and Johnson *et al.* (1982), suggested that multiple dose schedules are preferable because they produce more even elimination and less widely fluctuating serum levels. Our study shows that using a 12 h dosing regimen, lower peak serum levels occurred compared with the single daily dose schedule of Johnson *et al.* (1982), although in both studies, subjects received equivalent lithium doses. If low trough levels are important for tubular regeneration, then it is clear from our study that 12 hourly doses do not facilitate regeneration as the trough levels lie well within the therapeutic range.

Different treatment schedules produce different serum lithium profiles and affect the kidney differently. The pharmacokinetic data in this present study emphasises, that in deciding whether a single or multiple dose schedule is appropriate for a particular patient, it is important to consider the likely effects of different treatment schedules on the kidney. Single daily dose regimens may minimise tubular damage by allowing cellular restitution during low trough concentrations; however, if glomelular impairment is suspected, or conditions such that supervision will be less than optimal (Masterton *et al.*, 1987), then multiple daily doses may help avoid high peak serum concentrations.

I would like to thank Mr M. R. Scott of Norgine Ltd for helpful advice and financial support, Dr Daniel Simpson, Department of Clinical Chemistry, Royal Infirmary, Edinburgh for serum lithium estimation and Drs J. E. Christie, G. M. Goodwin and G. Masterton of the Royal Edinburgh Hospital for encouragement and helpful criticism of the manuscript. My thanks to Norma Brearley for the careful preparation of the manuscript.

References

Amdisen, A. (1977). Serum level monitoring and clinical pharmacokinetics of lithium. *Clin. Pharmacokin.*, **2**, 73–092.

Baastrup, P. C., Poulsen, J. C., Schou, M., Thomsen, K. & Amdisen, A. (1970). Prophylactic lithium: double-blind discontinuation in manic-depressive and recurrent-depressive disorders. *Lancet*, **ii**, 326–330.

Bendz, H. (1983). Kidney function in lithium-treated patients. A literature study. *Acta psychiat. Scand.*, **68**, 303–324.

Bennie, E. H., Manzoor, A. K. M. & Scott, A. M. (1977). Serum concentrations of lithium after three proprietary preparations of lithium carbonate (Priadel, Phasal, Camcolit). *Br. J. clin. Pharmac.*, **4**, 479–483.

Cockcroft, D. W. & Gault, M. H. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*, **16**, 31–41.

Enger, E. & Blegen, E. M. (1964). The relationships between creatinine clearance and serum creatinine in renal failure. *Scand. J. clin. lab. Invest.*, **16**, 273–280.

Hetmar, O., Bolwig, T. G., Brun, C., Ladefoged, J., Larsen, S. Rafaelsen, O. J. (1986). Lithium: long-term effects on the kidney. *Acta psychiat. Scand.*, **73**, 574–581.

Johnson, G. F. S., Hunt, G. E., Lewis, J. & St. George, B. (1982). Pharmacokinetics of standard (Lithi carb) and sustained-release (Priadel) lithium carbonate preparations in patients. *Aust. N.Z. J. Psychiat.*, **16**, 64–68.

Masterton, G., Warner, M. & Roxburgh, B. (1987). Supervising lithium: a comparison of a lithium clinic, psychiatric outpatient clinics and general practice. *Br. J. Psychiat.*, (in press).

Mellerup, E. T., Dam, H., Wildschiodtz, G. & Rafaekseb, O. J. (1979). Lithium effects: Relation to lithium dose and to plasma peak levels. *Acta psychiat. Scand.*, **60**, 177–184.

Perry, P. J., Dunner, F. J., Hahn, R. L., Tsuang, M. T. & Berg, M. J. (1981). Lithium kinetics in single daily dosing. *Acta psychiat. Scand.*, **64**, 281–294.

Plenge, P., Mellerup, E. T., Bolwig, T. G., Brun, C., Hetmar, O. Ladefoged, J., Larsen, S. & Rafaelsen, O. J. (1982). Lithium treatment: does the kidney prefer one daily dose instead of two? *Acta psychiat. Scand.*, **66**, 121–128.

Prien, R. F., Caffey, E. M. JR., & Klett, C. J. (1973). Prophylactic efficacy of lithium carbonate in manic depressive illness. *Arch. gen. Psychiat.*, **28**, 337.

Schou, M., Amdisen, A., Thomsen, K., Vestergaard, P., Hetmar, O., Mellerup, E. T., Plenge, P. & Rafaelsen, O. J. (1982). Lithium treatment regimen and renal water handling. The significance of dosage pattern and tablet type examined through comparison of results from two clinics with different treatment regimens. *Psychopharmacology*, **77**, 387–390.

Shaw, D. M., Hewland, R., Johnson, A. L., Hilary-Jones, P. & Howlett, M. R. (1974). Comparison of serum levels of two sustained-release preparations of lithium carbonate. *Curr. med. Res. Opin.*, **2**, 90–94.

Shelley, R. K. & Silverstone, T. (1986). Single dose pharmacokinetics of 5 formulations of lithium: a

controlled comparison in healthy subjects. *Int. clin. Psychopharmac.*, **1**, 324–331.

Tyrer, S. P., Hullin, R. P., Birch, N. J. & Goodwin, J. C. (1976). Absorption of lithium following administration of slow-release and conventional preparations. *Psychol. Med.*, **6**, 51–58.

Waller, D. G. & Edwards, J. G. (1985). Investigating renal function during lithium treatment. *Psychol. Med.*, **15**, 369–375.

(Received 12 May 1987, accepted 30 October 1987)