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Analysis of the Pharmacokinetics of Lithium in Man

F. Nielsen-Kudsk and A. Amdisen

Institute of Pharmacology and the Psychopharmacological Research Unit of the University of Aarhus, Aarhus, Denmark

Summary. An analysis of the single and multiple dose pharmacokinetics of lithium in 7 healthy volunteers is presented. A solution of lithium chloride was administered in single dose experiments and the same solution and a sustained release preparation were employed in multiple dose experiments, which were carried out at steady state. A fixed dose of 24 mmol was used in the single dose experiments and in the subsequent multiple dose experiments in the same subjects the same dose was administered once daily for a week. Distinct two-compartment characteristics were found, with a mean disposition rate constant (β) of 0.035 h^{-1} ± 0.010 SD, corresponding to a mean biological half-life of about 19.8 h. The mean half-time of the distributory α-phase was about 1.15 h. The absorption of lithium from an orally administered solution took place with a half-time of about 0.15 h in the single dose experiments. The apparent volume of distribution of the central compartment (V_c) was 0.307 1 kg^{-1} ± 0.046 SD, less than half that of V_{de} at equilibrium. $V_{d\beta}$ (V_{darea}) was 0.829 l kg^{-1} ± 0.184 SD and mean total body clearance was 27.6 ml kg^{-1} h^{-1} ± 4.7 SD.

Key words: lithium, litarex; single dose, multiple dose, pharmacokinetics

Lithium salts are used in the treatment of mania (Gershon and Yuwiler, 1960; Noack and Trautner, 1951, Schou et al., 1954), and prophylactically to attenuate or prevent recurrences of manic-depressive disease (Baastrup and Schou, 1967; Baastrup et al., 1970; Schou, 1976).

Early pharmacokinetic lithium balance studies were carried out by Trautner et al. (1955), but the results probably suffer from analytical errors of considerable magnitude (Amdisen, 1977). Caldwell et al. (1971) compared three different formulations in an investigation of the absorption in 6 normal volunteers of a single dose of lithium carbonate dissolved in water, and found by pharmacokinetic analysis in four of the subjects that the serum lithium concentration curve fitted a two compartment open system. The disposition rate constant β was within the range 0.028–0.048 h^{-1}. Similar pharmacokinetic results were reported by Poust et al. (1976) in four volunteers. According to these and other authors (Amdisen, 1975b; 1977; Amdisen and Sjøgren, 1968; Fyrö et al., 1970; Otto et al., 1972) the gastrointestinal absorption and systemic availability of simple lithium salts ingested in various tablet formulations amounts to more than about 85%, and the absorption of lithium chloride from solutions in practice is complete (Amdisen, 1975a). The biological half-life of lithium during early day time (8 a. m. – 3 p. m.) has been found to vary between individuals (n = 226) from 7 and 40 h, with a left-skewed distribution, and a mode of 13 h, corresponding to β-values of 0.100 to 0.017 h^{-1} with the mode 0.0533 h^{-1} (Amdisen, 1975a). This author found that the serum lithium concentration – time profile after oral ingestion of a lithium chloride solution by normal subjects clearly showed two-compartment characteristics, but a confirmatory pharmacokinetic analysis was only reported for one representative case. Groth et al. (1974) also found a biexponential decline in serum lithium concentration curves in 3 healthy men after oral lithium carbonate, but no pharmacokinetic analysis was done. Altamura et al. (1977) analysed plasma lithium curves obtained after oral intake of simple lithium salts according to one-compartment pharmacokinetics, but the plasma concentrations were only followed for 12 h. Mason et al. (1978) also

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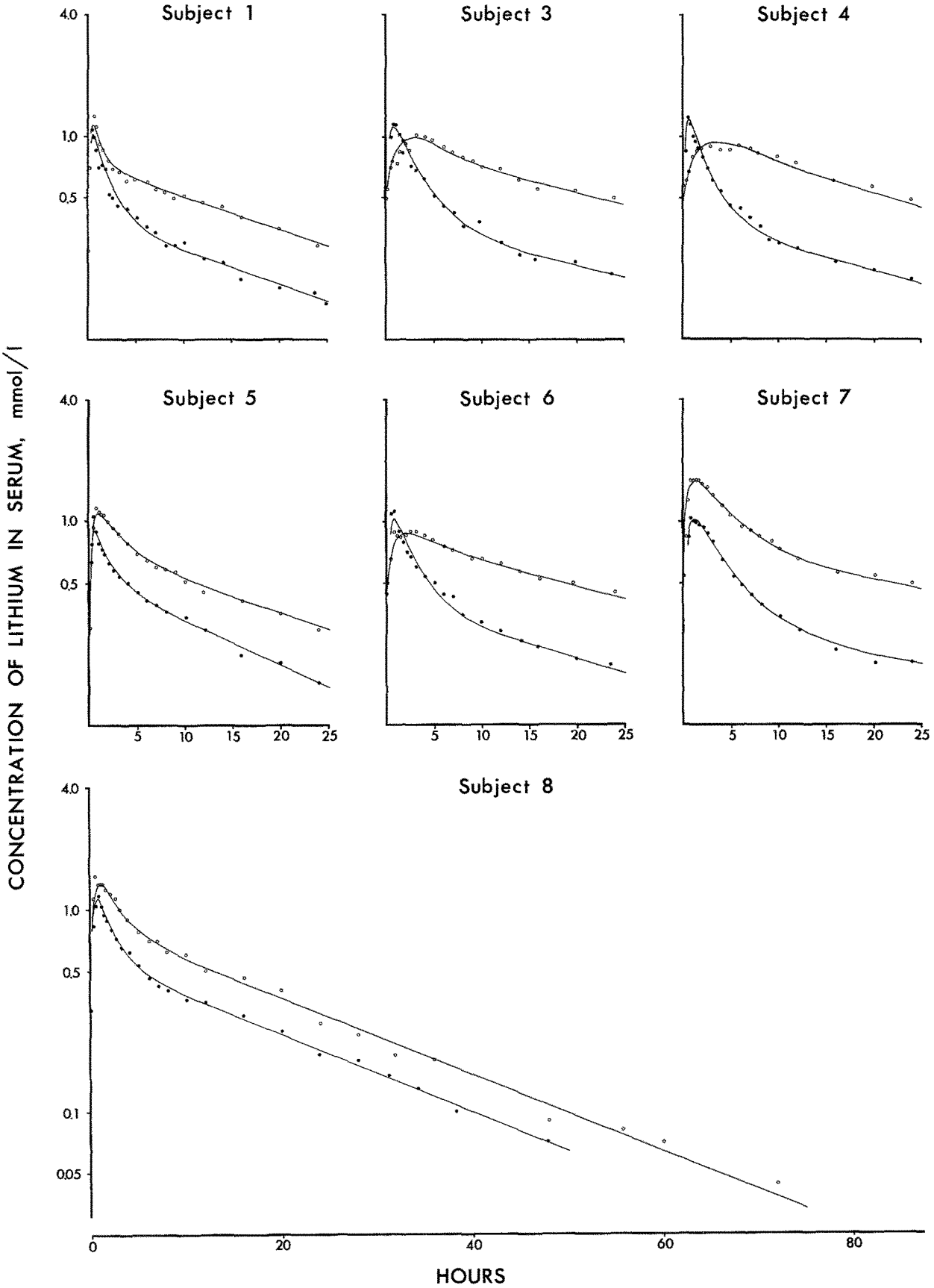

Fig. 1. Serum concentrations of lithium after oral administration of lithium chloride 24 mmol in water to seven normal, fasting volunteers – shown as black dots in the lower semilogarithmic plot in the figures marked with the subject numbers 1–8. The serum concentrations plotted as open circles were obtained in the same subjects at steady state after ingestion of the last of a series of daily doses of lithium 24 mmol administered for 8 days. Lithium was administered as lithium chloride solution to subjects 1, 5, 7 and 8, and subjects 3, 4 and 6 received lithium citrate in a sustained release preparation (Litarex®). Although not shown in the first six figures, serum lithium concentrations were followed for up to 49 h in the single dose experiments and for 72–96 h in the steady state experiments. The theoretical curves of best fit also shown are based upon pharmacokinetic analysis of serum concentrations measured throughout the investigation.

Table 1. Pharmacokinetics of lithium in 7 normal subjects who took a single oral dose of lithium chloride 24 mmol in water. The symbols used are defined in the text. Serum lithium was followed for up to 49 h

Pharmaco-kinetic parameter	Subject no.								
	1	3	4	5	6	7	8	Mean	SD
Sex	M	F	M	F	F	F	F		
Age (y)	48	18	33	39	44	26	37		
BW (kg)	85	58	56	59	65	51.5	52	60.9	±11.6
A′	0.8502	1.1114	0.4873	0.6224	1.0398	1.0982	1.0859	0.8993	± 0.2543
B′	0.4048	0.3932	0.4004	0.5441	0.4096	0.3282	0.5849	0.4379	± 0.0915
C′ (mmol l^{-1})	− 1.2550	− 1.5046	− 1.5985	− 1.1665	− 1.4494	− 1.4264	− 1.6708	− 1.4387	± 0.1788
α	0.5800	0.3711	0.4873	0.6572	0.4444	1.0982	0.6237	0.6088	± 0.2385
β	0.0386	0.0265	0.0298	0.0515	0.0331	0.0209	0.0443	0.0350	± 0.0106
k_a	7.9501	3.5251	5.2564	5.8550	3.5002	2.4814	3.7503	4.6169	± 1.8620
k_{10}	0.1009	0.0795	0.0951	0.0966	0.0918	0.0681	0.1024	0.0906	± 0.0125
k_{12}	0.2960	0.1945	0.2695	0.2615	0.2256	0.1446	0.2956	0.2410	± 0.0562
k_{21} (h^{-1})	0.2217	0.1236	0.1524	0.3507	0.1601	0.0849	0.2701	0.1948	± 0.0921
V_c	0.2371	0.2988	0.2886	0.3726	0.2811	0.3581	0.3112	0.3068	± 0.0464
V_{de} (V_{dss})	0.5536	0.7691	0.7988	0.6504	0.6771	0.9682	0.6517	0.7241	± 0.1349
$V_{d\beta}$(V_{darea})	0.6203	0.8972	0.9226	0.6982	0.7802	1.1675	0.7185	0.8292	± 0.1841
V_{pe} (1 kg^{-1})	0.3166	0.4702	0.5102	0.2778	0.3960	0.6100	0.3405	0.4173	± 0.1187
AUC (mmol l^{-1} h)	11.806	17.424	15.613	11.308	14.311	19.099	14.487	14.864	± 2.813
Clearance (ml kg^{-1} h^{-1})	23.92	23.75	27.45	35.97	25.80	24.40	31.86	27.59	± 4.66

fitted their experimental plasma lithium elimination data to a one-compartment open model. The few serum lithium elimination curves showed by Birch et al. (1978) probably exhibited biexponential decline, although this was neither stated nor further investigated.

The objective of the present study was to investigate and analyse the pharmacokinetics of lithium in normal healthy subjects after oral administration of a single dose of lithium chloride, and after multiple doses administered to establish a steady state in the same subjects. For comparative purposes the multiple dose pharmacokinetics of a sustained release preparation were also investigated.

Materials and Methods

Seven normal, healthy volunteers of either sex, between the ages of 18 and 48 years, and weighing 51.5 to 85 kg, participated in the study. Informed consent was obtained from all subjects.

The investigation was carried out in two parts. In the first experiments a single dose of lithium chloride 24 mmol in water solution (about 200 ml) was administered to each of the seven fasting subjects, who were allowed after 3 h to eat and drink as usual. The serum lithium concentration – time course was monitored during the following 24 h or longer (up to 49 h). Serum lithium concentrations were determined in capillary blood samples drawn from the ear lobe and treated and analysed according to the method of Amdisen (1967).

In the second part of the study a single, daily dose of diluted lithium chloride 24 mmol was given to 4 of the experimental subjects, and the same daily dose of lithium citrate in a sustained release preparation (Litarex®) was administered to the other 3 subjects, in both instances for 8 days in order to establish steady state conditions. At that time lithium administration to all seven subjects was stopped, and the serum lithium concentration was followed for a further 72 to 96 h.

For pharmacokinetic analysis of the experimental results we developed and used a program for a minicomputer, Compucorp® alpha 327. The program incorporates exponential nonlinear regression analysis of the time/concentration values corresponding to the β-phase, and of the time/residual values defining the α-phase and the k_a-phase of the serum concentration curves.

The serum concentration/time profile in the single dose peroral experiments could be fitted to a pharmacokinetic model using one first order input step in conjunction with an open two compartment system, and with elimination taking place from the central compartment. According to the model the serum lithium in the central compartment expressed as a function of time is given by:

Table 2. Pharmacokinetics of lithium in 4 normal subjects (nos. 1, 5, 7 and 8) after daily oral administration for 7 days of lithium chloride 24 mmol. In a further three normal subjects (no. 3, 4 and 6) the lithium was administered as a sustained release preparation (Litarex®), but under otherwise similar conditions. Serum lithium was followed for 72–96 h. Further information is given in the text

Pharmaco-kinetic parameter	Subject no.						Subject no.		
	1	5	7	8	Mean	SD	3	4	6
Sex	M	F	F	F			F	M	F
Age (y)	48	39	26	37			18	33	39
BW (kg)	85	59	51.5	52	61.9	±15.8	58	56	59
A″	0.9645	0.7100	1.3494	1.5365	1.1401	± 0.3727	1.3725	0.3898	0.4314
B″	0.7246	0.7527	0.7589	0.8812	0.7794	± 0.0695	0.8920	0.8311	0.8495
C″ (mmol l^{-1})	− 1.3898	− 1.1808	− 1.4033	− 2.1106	− 1.5211	± 0.4060	− 1.7886	− 0.7555	− 0.8501
α	1.1199	0.4056	0.2436	0.6075	0.5942	± 0.3808	0.3669	0.1259	0.3738
β	0.0368	0.0374	0.0201	0.0439	0.0346	± 0.0102	0.0262	0.0259	0.0283
k_a	5.0020	2.5591	1.9004	1.9078	2.8423	± 1.4725	0.6000	0.6792	0.9710
k_{10}	0.0965	0.0783	0.0766	0.1110	0.0906	± 0.0163	0.0559	0.0403	0.0446
k_{12}	0.6328	0.1710	0.1232	0.2999	0.3067	± 0.2298	0.1654	0.0306	0.1202
k_{21} (h^{-1})	0.4274	0.1937	0.0640	0.2405	0.2314	± 0.1505	0.1717	0.0809	0.2373
V_c	0.2412	0.3933	0.3184	0.2870	0.3100	± 0.0640	0.4444	0.6376	0.6055
V_{de} (V_{dss})	0.5983	0.7404	0.9313	0.6450	0.7288	± 0.1474	0.8723	0.8783	0.9121
$V_{d\beta}$(V_{darea})	0.6320	0.8234	1.2122	0.7250	0.8482	± 0.2550	0.9493	0.9915	0.9536
V_{pe} (1 kg^{-1})	0.3571	0.3471	0.6129	0.3580	0.4188	± 0.1295	0.4280	0.2407	0.3067
AUC (mmol l^{-1} h)	12.127	13.213	19.121	14.494	14.739	± 3.078	16.657	16.688	15.078
Clearance (ml kg^{-1} h^{-1})	23.28	30.79	24.37	31.84	27.57	± 4.37	24.84	25.68	26.98

$$c_1 = \frac{k_a a_o (k_{21} - \alpha)}{(\beta - \alpha)(k_a - \alpha) V_c} e^{-\alpha t} + \frac{k_a a_o (k_{21} - \beta)}{(\alpha - \beta)(k_a - \beta) V_c} e^{-\beta t} + \frac{k_a a_o (k_{21} - k_a)}{(\alpha - k_a)(\beta - k_a) V_c} e^{-k_a t} \quad (1)$$

where the coefficients for the exponential expressions define the backward projections (A′, B′ and C′) at the initial function zero (corresponding to the termination of a possible lag-time) of the extrapolated concentration, or residual values corresponding to the α, β, and k_a-phases of the curve described by the function. The three extrapolated true zero time concentration constants A*, B*, and C* and the corresponding rate constants (α, β, k_a) are all calculated first by means of the program, which then permits simulation of the function corresponding to Eq. (1), whereby a final manual curve fitting procedure involving successive minor changes in k_a and C*, together with a simultaneous determination of function zero and a possible lag-time, is made possible. Lag-time is here defined by the zero value of the fitted first order model function. The backward projection values (A′, B′ and C′), corresponding to the end of the lag-time period, when $c_1 = 0$, are then exchanged with A*, B* and C* and an f-value is calculated as:

$$f = -A'(k_a - \alpha)/(B'(k_a - \beta)) \quad (2)$$

The non-composite rate constants k_{21}, k_{10} and k_{12} are then calculated according to the equations:

$$k_{21} = (\alpha - f\beta)/(1 - f) \quad (3)$$

$$k_{10} = \alpha\beta / k_{21} \quad (4)$$

and

$$k_{12} = \alpha + \beta - k_{10} - k_{21} \quad (5)$$

The area under the function-fitted serum concentration curve is calculated as:

$$AUC_{po} = (A'/\alpha) + (B'/\beta) + (C'/k_a) \quad (6)$$

The systemic availability of lithium in water was assumed to be 100% in the single dose experiments, and in the multiple dose experiments both with sustained release tablets and simple solutions it was judged comparatively from the ratio of the areas under the serum concentration curves corresponding to equal peroral doses in the two types of experiment. After calculation of the systemic available dose (a_o), the apparent volume of the central compartment is calculated as:

$$V_c = k_a a_o (k_{21} - \beta)/(B'(\alpha - \beta)(k_a - \beta)) \quad (7)$$

The various other apparent volumes of distribution are determined by the equations:

$$V_{d\beta} (= V_{darea}) = V_c k_{10}/\beta \quad (8)$$

$$V_{de} (= V_{dss}) = V_c[1 + (k_{12}/k_{21})] \quad (9)$$

$$\text{and } V_{pe} = V_{de} - V_c \quad (10)$$

V_c is as a control measure also calculated as

$$V_c = a_o/(AUC\ k_{10}) \quad (11)$$

Body clearance of lithium is calculated as

$$Cl = \beta\ V_{d\beta} \quad (12)$$

Before determination of f, k_{21}, k_{10}, k_{12} and the other pharmacokinetic parameters related to the multiple dose, steady state experiments, the concentration constants A″, B″ and C″, found as the backward projections at the time for ingestion of the last dose (corrected for possible lag-time), are transformed by the program to the corresponding single dose constants by multiplication by the factor $(1 - e^{-k_i T})$, where k_i represents α, β or k_a, and T is the dose interval. In the multiple dose experiments the areas under the serum concentration curves corresponding to a dose interval were also measured directly and compared with those calculated from the fitted theoretical functions.

Results

The serum concentration of lithium as a function of time after peroral administration of a single dose of lithium chloride 24 mmol to the seven normal volunteers is plotted semilogarithmically as dots in Figure 1, which also shows the fitted theoretical concentration curves (lower curve in each figure) based upon the corresponding pharmacokinetic parameters listed in Table 1. Although not shown in Figures 1.1–1.7, serum concentration was followed for up to 49 h. The coefficients of determination calculated in the exponential regression analyses carried out on the terminal concentration values and on the residual values ranged from 0.8595–0.9974. The pharmacokinetic analyses clearly show that in all cases, the serum lithium concentration/time course fitted the linear kinetics of an open two-compartment model, with elimination from the central compartment and first order absorption into that compartment.

The results of pharmacokinetic analysis of the seven single dose experiments just refered to are listed in Table 1. The average values of the composite rate constants α and β and k_a were $0.6088\ h^{-1} \pm 0.2385$ SD, $0.0350\ h^{-1} \pm 0.0106$ and $4.6169\ h^{-1} \pm 1.8620$, respectively. The mean biological half-life of lithium was 19.8 h, with the considerable range of 13.5 to 33.2 h. The α-phase, with a mean half-life of 1.14 h, was very distinct in the experiments, and it was subjected to a greater interindividual variation than the β-phase.

As expected the absorption of lithium was very fast, with a mean half-life of about 0.15 h, although pronounced variation was found. The maximum serum lithium concentration occured within about 0.5–1 hours and no lag-time was found.

The mean value of $V_{d\beta}$ (V_{darea}), the apparent volume of distribution at pseudoequilibrium during the β-phase, was $0.8292\ l\ kg^{-1} \pm 0.1841$ SD. The mean total body clearance ($\beta\ V_{d\beta}$) was thus 27.59 ml kg^{-1} $h^{-1} \pm 4.66$. It further appears from Table 1 that the central compartment V_c constituted less than half of the calculated total volume of distribution at equilibrium (or steady state) V_{de}. The pronounced two-compartment behavior characteristic of lithium is also clearly demonstrated by a mean k_{10}/β ratio of 2.6. The microscopic, uncomposite rate constants k_{10}, k_{12} and k_{21} exhibited coefficients of variation of 14–47%. The calculated areas under the serum lithium concentration curves agreed well with the areas measured by cutting and weighing plus terminal extrapolation.

The upper plot (open circles) in the individual panels of Figure 1 represent the results of the multiple oral dose steady state experiments in the same volunteers in which either lithium chloride in solution (subjects 1, 5, 7 and 8) or lithium citrate in a sustained release preparation, Litarex® (subjects 3, 4 and 6) was administered. Although shown only for subject 8, serum lithium concentrations were followed for 72–96 h after the last dose, which had then been given for 8 days in a single daily dose of 24 mmol. The concentration/time data could be analysed according to the two-compartment characteristics of lithium found in the previous experiment, and the simulated theoretical serum lithium concentration curves shown in the figures are based upon the pharmacokinetic parameters so obtained (Table 2).

The mean of all the disposition rate constants (β) is $0.0312\ h^{-1} \pm 0.0083$ (Table 2), which is slightly lower than the value found in the single dose experiments. The difference is not significant, and the mean of the β-values in the subjects (1, 5, 7 and 8) who received lithium chloride solution, is identical to that found after administration of single doses. The greatest intraindividual difference in β-values was found in subject 5. The corresponding half-lives were about 13.5 and 18.5 h, which represents a difference of 5 h in the two biological half-lives of lithium found in this subject.

The mean absorption rate constant found for subjects 1, 5, 7 and 8 was lower than that found in the single dose experiments, but the difference was not significant. As expected, a much lower absorption rate was found in the three subjects (3, 4 and 6), who received the sustained release lithium preparation.

While the mean values of the rate constants k_{10}, k_{12}, k_{21} and α found in subjects 1, 5, 7 and 8 were close to those found in the single dose experiments, there was an apparent difference in subjects 3, 4 and 6, in who particularly k_{10} and k_{12} were lower. V_c and also V_{de} seemed to be markedly higher and V_{pe} somewhat lower in subjects 3, 4 and 6; their body clearances seemed not to differ significantly from the values found in the single dose experiments.

The calculated areas under the serum lithium concentration curves given in Table 2 are in good agreement with the areas actually measured, which, in subjects 1, 5, 7, 8, 3, 4 and 6, were 11.98, 12.76, 19.34, 14.90, 16.78, 17.11 and 15.60 mmol l^{-1} h, respectively. On comparison with the areas measured in the single dose experiments (Table 1) it is apparent that the systemic availability of lithium in the two types of experiments was equally at about 100%.

Discussion

The experimental results clearly demonstrate the pronounced two-compartment characteristics of lithium, and so confirm and extend the previous rather sparse pharmacokinetic analyses of Amdisen (1975a), Caldwell et al. (1971) and Poust et al. (1976). Dosage regimen calculations and pharmacokinetic predictions should be based upon this concept, and not treated according to the one-compartment pharmacokinetics reported and used by Altamura et al. (1977) and Mason et al. (1978). Analysis of serum lithium data by one-compartment pharmacokinetics may, for example, lead to overestimation both of the volume of distribution (by extrapolation) and the disposition rate constant, and therefore of body clearance. There is a consequent serious risk of erroneous dose calculation, especially considering the near toxic therapeutic dose level.

The mean disposition rate constant β of 0.035 h^{-1} as well as the corresponding range of 0.0209–0.0515 h^{-1} found in the single dose experiments in the present study, are in full agreement with the previous single dose data of Caldwell et al. (1971) and Poust et al. (1976), and furthermore they are in fairly good accordance with the range of 0.017–0.100 h^{-1} (mode 0.053 h^{-1}) found by Amdisen (1975a), considering the day/night variation and skewed distribution in the 226 subjects. This result is confirmed by the fact that the mean β-value in the multiple dose experiments did not differ significantly from the value found in the single dose study.

During steady state conditions the ratio between the amount of lithium in the central compartment to that in the whole body is expressed by $V_c/V_{de} = k_{21}/(k_{12} + k_{21})$, it amounted to about 0.43 in the experiments in question. The "average" amount ($\bar{A}_\infty$) of lithium accumulated in the body under steady state conditions may be calculated as $\bar{A}_\infty = a_o V_{de}/(T\beta V_{d\beta})$, where T is the dose interval. Substituting the relevant mean pharmacokinetic parameters from Table 2 (or Table 1) into this formula gives an estimate of $\bar{A}_\infty$ about 25 mmol, assuming a daily absorbed dose of lithium of 24 mmol.

The measured apparent volume of the central compartment V_c of about 0.31 l kg^{-1} is far greater than the physiological extracellular volume, just as the apparent volume of distribution at steady state V_{de} of about 0.73 l kg^{-1} is greater than the volume of total body water. The experimental results thus appear to be consistent with the assumption that the lithium ion is easily distributed from the plasma water phase to organs and tissues with a high rate of blood flow, and that some tissues may attain a concentration of lithium higher than in plasma.

It is interesting to note that the concentration of lithium in the erythrocytes of normal humans in steady state is about 0.45 times the concentration in serum, and perhaps is slightly higher in some manic-depressives (Frazer et al., 1978). The pharmacokinetics in erythrocytes seem to imply that they are representative of the peripheral compartment (Poust et al., 1976), and consequently their lithium concentration only declines in parallel with serum lithium during the β-phase of elimination. Monitoring of erythrocyte lithium does not seem, therefore, to offer any advantage in dosage guidance over monitoring serum lithium.

The results obtained in the multiple dose experiments with the sustained release preparation show that although a fairly reasonable three-exponential curve-fitting could be achieved, there was a moderate but distinct deviation of the apparent volumes of distribution V_c, V_{de} and V_{pe} derived from the corresponding volumes found in the single dose experiments. Introduction of an extra input step representing the disintegration and dissolution of the preparation in the pharmacokinetic analysis might possibly have corrected these differences, but the actual steady state serum lithium data did not permit confident analyses based upon this more complicated model system. The experimental results, however, do clearly demonstrate that the pharmacokinetic parameters obtained in the single dose experiments were

predictive of the time course of the serum lithium concentrations actually observed after multiple dose administration of lithium chloride to produce steady state.

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Dr. F. Nielsen-Kudsk
Institute of Pharmacology
University of Aarhus
DK-8000 Aarhus/Denmark