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THE PHARMACOKINETICS OF LITHIUM IN THE BRAIN, CEREBROSPINAL FLUID AND SERUM OF THE RAT

O. WRAAE[1]

Unity Laboratory, Department of Human Biology and Health, University of Surrey, Guildford, Surrey, GU2 5XH

1 Addition of lithium carbonate (55 mmol/kg dry wt.) to the diet of rats for 4 days resulted in ratios between lithium in the brain and serum and between the cerebrospinal fluid (CSF) and serum of approx. 1 and 0.4, respectively. The relationships between the concentrations were linear.

2 After single intraperitoneal injections of lithium chloride (5 mmol/kg body wt.) the concentration of lithium in the CSF was greater than that of the brain for 2 h.

3 Repeated subcutaneous injections of lithium chloride (0.9 mmol/kg body wt.) resulted in steady state ratios corresponding to those observed when lithium was given in the diet. The rate of elimination from the CSF was intermediate between that of the serum and cerebral tissue until a new equilibrium was reached after approx. 24 h. At that time the ratios between lithium in the brain and serum, and in the CSF and serum were increased to approx. 5 and 0.8, respectively.

4 These results are consistent with passive transfer kinetics of lithium in the CSF and elimination of lithium from the cerebral tissue via the CSF.

5 The results may explain some of the phenomena observed in patients during intoxication with lithium.

Introduction

In the treatment of patients for manic depressive disease it is normally assumed that the effectiveness of lithium salts (lithium) is related to the concentration achieved in the brain. This cannot be monitored and so it is usual to measure the concentration of the ions in the serum, which is the closest site in which repeated observations can be made safely. However, it has been shown in rats that when the lithium concentration in the serum changes rapidly, it does not correlate well with that found in the brain (Frazer, Mendels, Secunda, Cochrane & Bianchi, 1973).

Paul, Pilz & Munz (1973) and Watanabe, Taguchi, Ebara, Iguchi & Otsuki (1973) found a high correlation at steady state between the lithium concentrations in the serum and in the cerebrospinal fluid (CSF). These authors assumed that the concentration in the CSF would reflect the cerebral concentration better than that found in the serum. Therefore, it was decided to compare directly in rats the concentration of lithium in the serum, the CSF and the brain at steady state and also to examine the relationship between these concentrations during the uptake and elimination of lithium. These data could be compared with findings in patients and in previous experiments on cerebral slices of rats *in vitro* (Wraae, Hillman & Round, 1976).

[1] Present address: Department of Psychiatry, University Hospital, 5000 Odense C, Denmark.

Methods

Administration of lithium

Male Wistar albino rats weighing 250 to 400 g were used. (1) For measurement of lithium at steady state, 8 rats were given a powdered standard diet (Spratt's no. 2) for 4 days, followed by a further period of 4 days during which they were given a similar diet to which lithium carbonate (55 mmol/kg dry food) and sodium chloride (300 mmol/kg dry food) had been added. (2) In one series of kinetic experiments a single intraperitoneal injection of lithium chloride (500 mmol/l, 5 mmol/kg body wt.) was given to 35 rats. (3) In a second series of kinetic experiments 56 rats were given subcutaneous injections of lithium chloride (150 mmol/l, 0.9 mmol/kg body wt.) every 6 h for 2 days, corresponding to approx. 8 half lives ($T_{1/2}$). In (2) and (3) the rats were given pellets of the above standard diet without any additions and

had access to a solution of sodium chloride (155 mmol/l) during and after the administration of lithium. The addition of extra sodium chloride to the diet, or access to a sodium chloride solution has been shown to prevent intoxication during administration of lithium to rats (Thomsen & Olesen, 1974). The rats were allowed to drink water *ad libitum*.

Preparation of tissue

All rats were anaesthetized with ether and blood samples of approx. 5 ml were taken by cardiac puncture and centrifuged without the addition of anticoagulants. Samples of CSF were drawn from the cisterna magna by the technique described by Smith & Balagura (1972), slightly modified by the use of a disposable tuberculin syringe connected to a mouthpiece. By slight suction it was possible to take samples of approx. 0.1 ml, which increased the sensitivity of the measurements. The samples were transferred to preweighed tubes and weighed immediately afterwards. Samples that were blood stained were discarded. The necks of the rats were then dislocated and the brains were rapidly removed and placed on moist filter paper in a petri dish.

In (1) the rats were killed after 4 days on the lithium diet. In (2) the rats were killed from 0.25 h to approx. 48 h after injection, and in (3) 6 h to approx. 48 h after the last injection.

All samples were stored at 4°C for a maximum of 5 days before the measurement of lithium. Then the serum was diluted by 6 to 150 times with a solution of sodium chloride (155 mmol/l), and 0.7 to 1.2 ml of this solution was added to all the samples of CSF. The brains were blotted with filter paper, and specimens of whole brain, weighing 100 mg to 800 mg, were homogenized in 2 to 4 ml of 6% TCA.

Measurement of lithium

Lithium was measured by atomic absorption spectrophotometry, as previously described (Wraae *et al.*, 1976). In addition to the standards with TCA for the cerebral tissue mentioned there, standards for the measurement of lithium in the serum and CSF were made up in sodium chloride (155 mmol/l), as the latter standards had been shown in recovery experiments to give reproducible results with all the dilutions used in the present experiment. Double determinations were made on the samples of serum and cerebral tissue, the relative standard deviations being 2% and 5% respectively; the samples of CSF were too small for double determination.

Lithium carbonate was dissolved in HCl to make up the lithium chloride solutions and acid solutions were neutralized with NaOH pellets, if they were to be administered to rats. All chemicals were of analytical grade.

Calculations

Concentrations of lithium are referred to the wet weight of the cerebral tissue or to the total volumes of the CSF or serum.

The analysis of variance was used when more than two means were compared (Tables 1 and 2). Prior to that, a test for the homogeneity of variance was performed (Bartlett, 1937). If the analysis of variance showed a significant variation of the combined result, the individual means were compared by a multiple range test (Duncan, 1955).

Results

Steady state

The lithium concentrations measured in the cerebral tissue, CSF and serum after oral administration of lithium carbonate for 4 days are shown together with the corresponding ratios between these values. There was no significant difference between the concentrations in the brain and in the serum, but that of the CSF was almost one third of these values (Table 1(i)). There were considerable inter-individual differences in the concentrations, whereas the intra-individual ratios between the concentrations showed smaller variations (Table 1(ii)). Linear plots of lithium in the cerebral tissue and CSF relative to lithium in the serum had correlation coefficients of 0.93 and 0.96, respectively.

Single injections

The concentration of lithium in the brain slowly reached a maximum of approx. 1.5 mmol/kg between 9 h and 24 h. In the CSF, the maximum concentration of 1.2 mmol/l was seen between 45 min and 2 h. Between 15 min and 2 h the concentration of lithium in the CSF was greater than that of the brain. Serum concentrations were maximal, approx. 8 mmol/l, when the first sample was taken after 15 min.

The elimination of lithium from the brain, CSF and serum took place at different rates even from 24 h to 50 h, when the half-life was found to be 12 h, 10 h and 7 h respectively. From the kinetic curve (Figure 1) it may be difficult to determine when the elimination became linear, because of the rather large variation. Relating the concentrations of lithium in the brain and in the CSF to the corresponding concentrations in the serum reduced the scatter (Figure 2). From this figure it can be seen that the ratios of concentrations of lithium in the CSF and serum, and in the cerebral tissue and serum at steady

Table 1 Steady state concentration of lithium in the rat brain, CSF and serum

	(a) *Brain*	(b) *CSF*	(c) *Serum*	*P value of differences*
(i) Concentration	0.482 ± 0.043 (8)	0.172* ± 0.018 (7)	0.435 ± 0.030 (8)	<0.01
(ii) Relative to serum concentration	1.114 + 0.033 (8)	0.407 ± 0.013 (7)	1	<0.001

Values are expressed as mmol/kg of wet cerebral tissue or as mmol/l of serum or CSF and represent the mean ± s.e. mean. The number of samples is shown in parentheses.
* Significantly different from (a) and (c); the analysis of variance and a multiple range test was used (Duncan, 1955).

state (Table 1) were reached between 10 h and 20 h, but the ratios continued to rise until an apparent equilibrium was reached around 40 h. However, only the elimination of lithium in the serum could be shown to be linear from 40 h to 50 h ($T_{1/2}$ = 12 h, r = 0.90, n = 6), while the corresponding fitted regression lines for the elimination of lithium from the CSF and the cerebral tissue were not statistically significant.

Elimination from steady state (Figure 3)

The steady state levels in the cerebral tissue, serum and CSF, obtained after repeated subcutaneous injections, as described in methods, were 0.9 mmol/kg, 0.8 mmol/l and 0.3 mmol/l respectively, as estimated from the first three sets of concentrations from 6 h to 7 h after the last injection. From then on, elimination from the three compartments took place at different

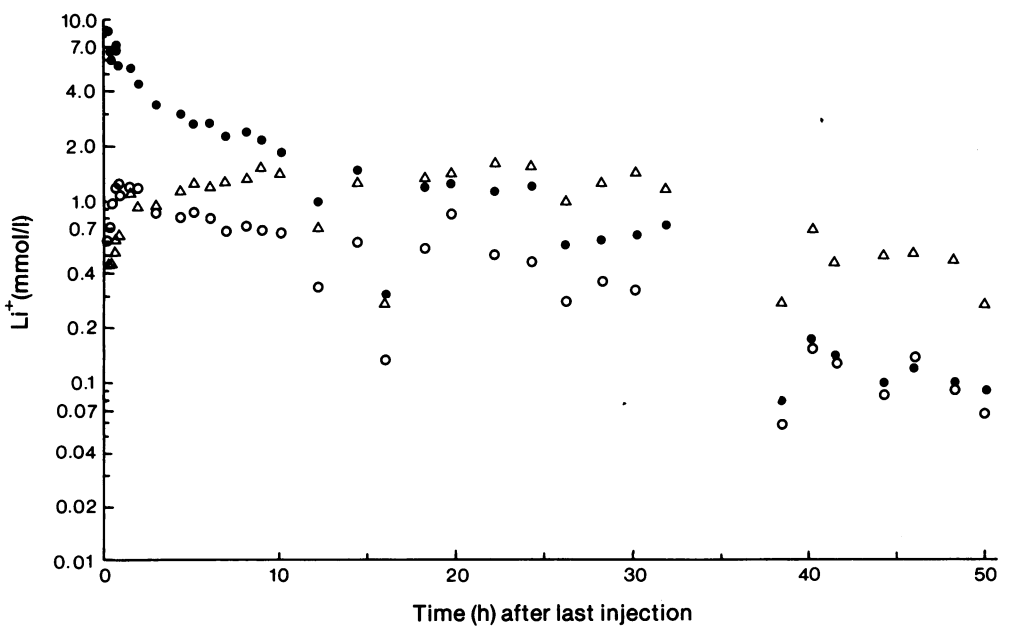

Figure 1 Concentration in rats of Li^+ after single intraperitoneal injections of LiCl (5 mmol/kg body wt.) In all figures the Li^+ was measured in serum (●) and CSF (○) as mmol/l, and in whole brain (△) as mmol/kg wet tissue.

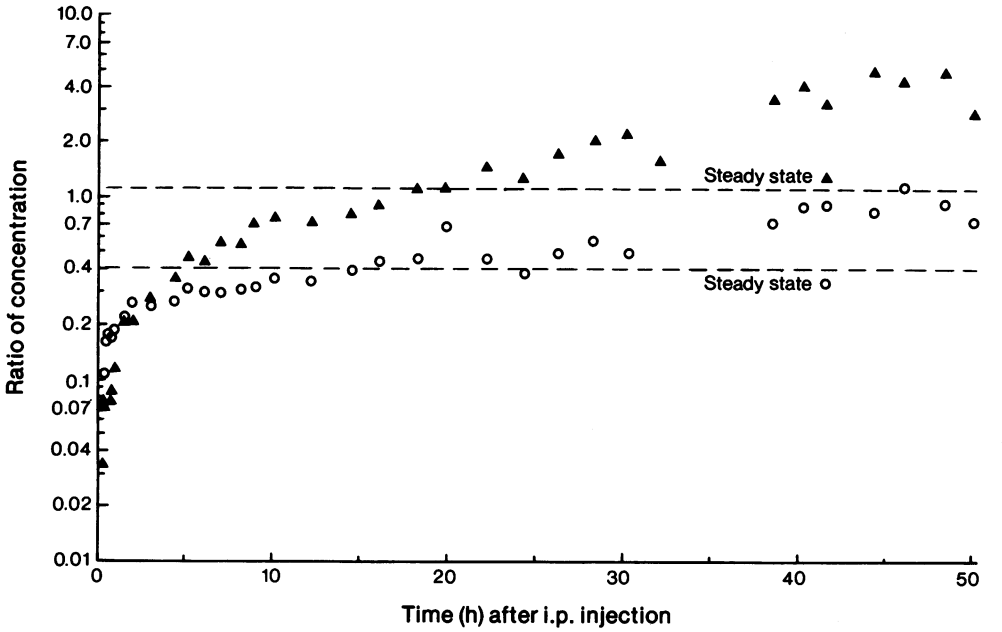

Figure 2 Ratios of concentrations after single injections of Li^+ (Figure 1) replotted as Li^+ in CSF/serum (○), and brain/serum (▲), respectively. The broken lines represent the steady state values (Table 1).

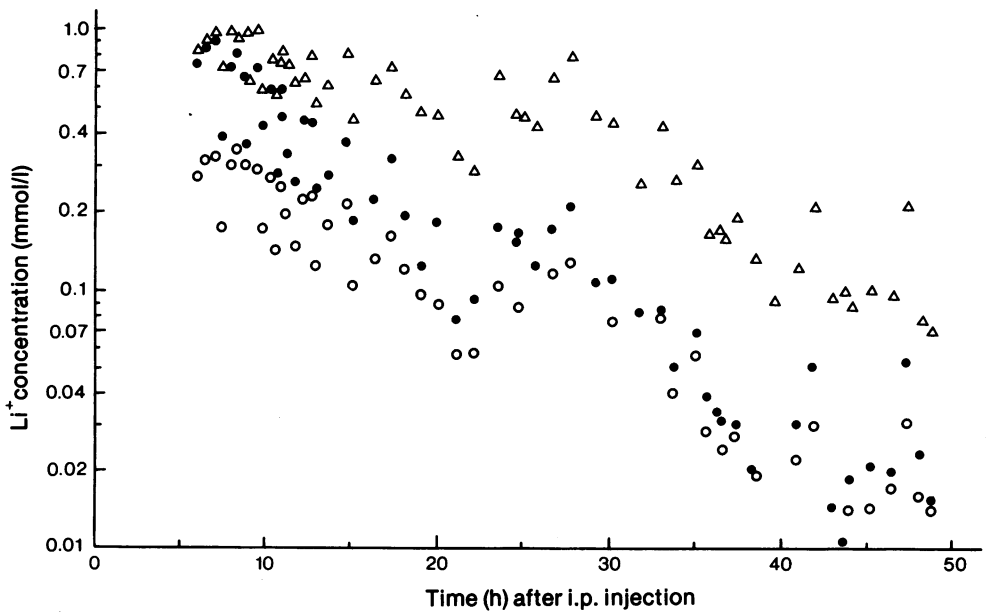

Figure 3 Elimination of Li^+ after steady state. Rats were given LiCl subcutaneously (0.9 mmol/kg body wt.) every 6 h for 2 days (approx. 8 half lives). At the times indicated after the last injection, Li^+ was measured in serum (●), CSF (○) and whole brain (△).

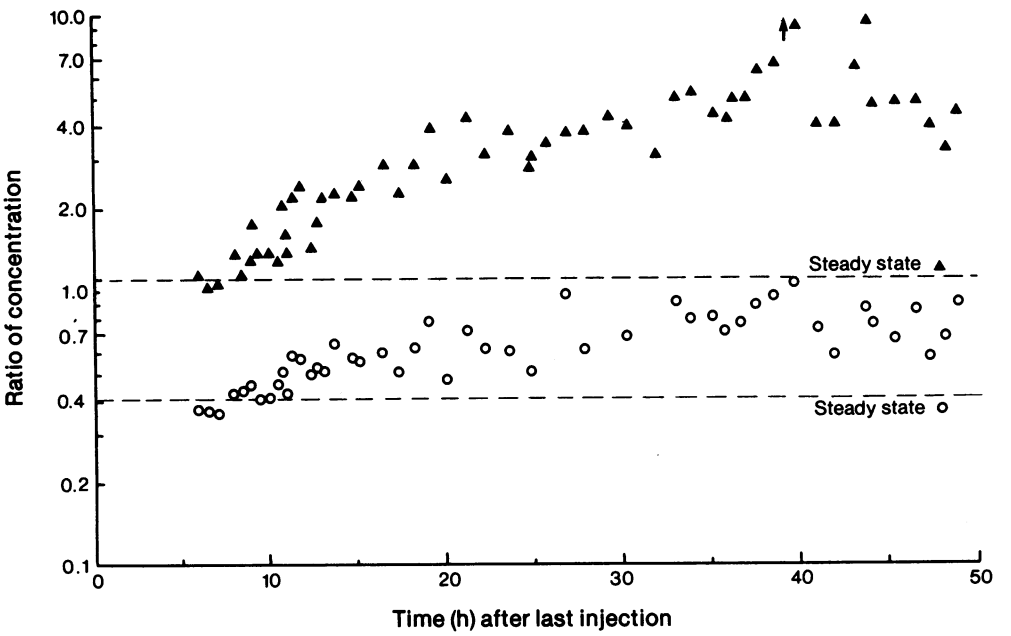

Figure 4 Elimination of Li^+ after steady state, ratios of concentrations. Concentrations of Li^+ (Figure 3) replotted as Li^+ in CSF/serum (○), and brain/serum (▲), respectively. The broken lines represent the steady state value (Table 1).

rates. Also in this experiment the points on the kinetic curve showed a large variation. Therefore, as in the previous experiment, the concentrations of lithium in the brain and in the CSF were related to the corresponding concentration in the serum in order to get a more precise impression of the changes (Figure 4). The initial values were very close to the values at steady state from the feeding experiment (Table 1). Thereafter the ratios increased until approx. 24 h when a fitted regression line was no longer significantly different from zero, indicating that a new equilibrium had been reached. The corresponding joint

Table 2 Statistical analysis of results in Figure 3

Time after last injection:	*Biological half-life (h)* *Mean*	*95% confidence limits†*	*No. of samples*
(i) 6 h to 24 h			
Serum	5.35*	4.47–6.65	29
CSF	7.18*	5.83–9.35	27
Brain	12.73*	9.86–17.99	29
(ii) 24 h to 48 h			
Serum	6.82 (NS)	5.43–9.18	28
CSF	7.57 (NS)	5.85–10.73	22
Brain	8.22 (NS)	6.88–10.21	28

* All three values were significantly different from each other. (Overall variation: $P < 0.001$; individual differences: $P < 0.05$). NS = not significant. The analysis of variance and a multiple range test was used (Duncan, 1955).

† The asymmetry around the means is due to the transformation from a semilogarithmic plot.

ratio between the concentrations in the cerebral tissue and serum was 4.71 ± 0.28, and in the CSF and serum was 0.773 ± 0.032 (mean ± s.e. mean of 25 and 21 ratios respectively).

The calculated elimination constants before and after 24 h are shown in Table 2. The elimination rate of lithium in the serum slowed down, that of the brain increased, and that of the CSF remained unaltered. After 24 h the constants were no longer significantly different, indicating that the β-phase of elimination had been reached.

Discussion

In the present experiments the concentration of lithium after single injections was higher in the CSF than that of the brain for approx. 2 h. These results are representative of average cerebral tissue, although different rates of uptake of lithium in various areas of the rat brain have been observed under similar experimental conditions (Mukherjee, Bailey & Pradhan, 1976). The bulk of evidence shows that the blood-CSF and the blood-brain barriers are similar with respect to the permeability to solutes so that most of the differences in the rate of penetration of solutes through the barriers could be explained by the more favourable area-to-volume relationship of the brain (Davson, 1967). Therefore, it would seem likely that initially the concentration of lithium in the extracellular fluid of the cerebral tissue is equal to, or higher than that of the CSF and that the delay in uptake is due to the neuronal and glial membranes, resulting in a concentration of lithium which appears to be low because it is referred to total wet weight in the present experiments. This view would be compatible with observations in cerebral slices on the uptake of lithium, which is relatively slow. (Wraae *et al.*, 1976).

Except during the first few hours after a single injection, the concentration of lithium was lower in the CSF than in both the cerebral tissue and serum. However, it is also obvious from a plot of the ratios (Figure 2) that one cannot draw meaningful conclusions about the steady state from experiments with single doses of lithium (Baker & Winokur, 1966; Smith & Balagura, 1972).

The ratios at steady state in the present experiments were reproducible for each of the two different routes of administration. However, from the ratios of the concentration in the CSF and serum during elimination after steady state (Figure 4) one can infer that, although the influence of a single dose is less in this situation, the magnitude of the dose and the interval after the last dose would influence the ratios, mainly, because of the fluctuations in the serum levels. This is the most likely explanation of the different ratios reported in the literature even under steady state conditions (Schou, Juel-Nielsen, Strömgren & Voldby, 1954; Gershon & Yuwiler, 1960; Paul *et al.*, 1973; Watanabe *et al.*, 1973). Consequently, the conditions under which the samples were taken should also be stated when lithium in the CSF is measured.

The ratio of lithium in the CSF and serum varies because of the factors mentioned above but it is consistently less than one. Lithium is not bound to the proteins in the serum so that the CSF does not represent simply an ultrafiltrate of the serum with respect to lithium. On the other hand, there was a linear relationship at steady state between the concentration in the serum and the CSF both in the present experiments and in patients treated with lithium (Paul *et al.*, 1973; Watanabe *et al.*, 1973). This is in contrast to the constant composition of the CSF with respect to potassium, calcium and magnesium, and is generally taken as indicating passive transfer (Davson, 1967). Prockop & Marcus (1972), from their experiments on rabbit choroid plexus *in vitro*, and from ventriculo-cisternal perfusion in dogs, concluded that simple diffusion and bulk flow could account for most of the clearance of lithium from the CSF. The passage of water into the CSF is very rapid (Davson, 1967), whereas the entry of lithium is slow, as demonstrated in the present experiments. This difference alone in the rate of entry of water and lithium would be sufficient to explain the continuous removal of lithium by bulk flow of the CSF through the arachnoid villi back to the serum, and hence the ratio.

The expendymal tissue offers very little resistance to solutes (Davson, 1967) so that the extracellular fluid of the cerebral tissue can be considered in equilibrium with the CSF, having concentrations which are probably not much higher. This would mean that a concentration gradient exists between the cerebral cells and the surrounding fluid at steady state. Such a gradient has been observed between lithium in cerebral slices and the incubation medium (Kjeldsen, Lund-Andersen & Hertz, 1973; Wraae *et al.*, 1976).

Lithium is probably eliminated from the cerebral tissue via the CSF. The concentration ratio between the brain and the CSF would favour this pathway and removal from the CSF by bulk flow would be independent of the concentration of lithium in the serum. Elimination through the blood-brain barrier directly to the serum would seem unlikely under normal circumstances. The kinetic findings in the present experiments are consistent with the former possibility. Firstly, the initial rate of elimination from the CSF was intermediate between that of the serum and the cerebral tissue (Table 2a). Secondly, the ratio of lithium between the CSF and serum, and between the brain and CSF during the β-phase were both approx. twice the corresponding ratios at the steady state, as can be inferred from Figure 4.

The ratio of lithium between the CSF and serum

at steady state in the present experiments was 0.41. In long term treatment of patients with lithium, Paul *et al.*, (1973) and Watanabe *et al.* (1973) found corresponding ratios of 0.30 and 0.25, respectively. Lithium was measured in the CSF and serum of patients from 1 h to 72 h after a single dose of lithium carbonate (0.2 mmol/kg body wt.) by Lehman, Scherber & Graupner (1976). Taking into account the differences due to the dose and route of administration, the temporal relationship between lithium in the CSF and the serum in the present experiments after a single dose (Figure 1) was very similar to that found by these authors. In view of such similarities between the measurements of lithium in patients and in rats, it would seem reasonable to try to draw conclusions about the concentrations in the cerebral tissue in patients under comparable conditions. In rats, after a large single dose of lithium, the steady state ratio between lithium in the cerebral tissue and serum is reached after approx. 20 h. A similar pattern would explain the frequent absence of clinical signs in patients after an acute overdosage of lithium, although the serum values of lithium are high. When lithium was discontinued after repeated doses the ratio of lithium between the brain and serum in the present experiments increased to more than 4 times the ratio at steady state. The latter finding might explain why the clinical signs of lithium intoxication may persist for several days after serum concentrations of lithium have fallen. However, it does not explain why some patients take weeks to recover. Also, the use of haemodialysis in the treatment of lithium intoxication modifies the kinetics very much, by increasing greatly the rate of elimination of lithium from the serum, after which it falls to low values. This would lead to a ratio near one between lithium in the CSF and serum during haemodialysis, and a ratio approximating that at steady state afterwards (Amdisen & Skjoldborg, 1969; Hansen & Amdisen, 1978). Therefore, it would appear that the concentration in the cerebral tissue is approximately that of the serum some hours after redistribution of lithium in the tissue following haemodialysis. In these circumstances, measurement of lithium in the CSF would not reflect the concentration of lithium in the brain more accurately than measurement in the serum.

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