A study of the transport of lithium across the erythrocyte membrane *in vivo* and of the effects of the ion transport inhibitors digoxin and dipyridamole

A. J. WOOD, J. K. ARONSON, C. BUNCH¹ & D. G. GRAHAME-SMITH

MRC Unit and University Department of Clinical Pharmacology, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE and ¹Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford OX3 9DU

1 We have given an oral load of lithium carbonate to healthy volunteers in order to investigate the transport of lithium across the erythrocyte membrane *in vivo* and the effects of known inhibitors of that transport.

2 Using this technique we have shown that pretreatment with either digoxin, an inhibitor of the sodium/potassium pump, or dipyridamole, an inhibitor of the anion transporter, does not alter the plasma or erythrocyte lithium concentration profiles, nor any of the pharmacokinetic variables derived from these data, and we conclude that these two transport pathways do not contribute significantly to the *in vivo* handling of lithium by erythrocytes.

3 We have also shown that erythrocyte lithium concentrations measured directly differ significantly from the predicted concentrations calculated using the two-compartment pharmacokinetic model which has been used in some earlier comparisons of *in vitro* and *in vivo* lithium handling.

4 We suggest that the *in vivo* administration of lithium carbonate may permit a specific measure of the *in vivo* activity of the sodium/sodium countertransport pathway.

Keywords lithium erythrocyte digoxin dipyridamole sodium countertransport

Introduction

The major pathways by which lithium is transported across the erythrocyte membrane have been investigated in a series of *in vitro* experiments and are depicted in Figure 1. Lithium influx is thought to occur via two pathways – predominantly by passive diffusion down a concentration gradient, and to a small extent (approximately 25%) via the bicarbonate-sensitive anion transport pathway (Duhm & Becker, 1977a, b; Pandey *et al.*, 1979). Lithium probably enters via this pathway as $(\text{LiCO}_3)^-$. Approximately 75% of lithium efflux *in vitro* is via the sodium/sodium countertransport pathway (Haas *et al.*, 1975; Duhm *et al.*, 1976), and the remaining fraction of lithium efflux is thought to occur via the sodium/potassium pump enzyme Na^+, K^+ -ATPase (Duhm & Becker, 1977b),

although the extent of this contribution is not clear (Ehrlich & Diamond, 1979). The investigation of lithium fluxes *in vitro* has been based on the use of specific inhibitors of individual pathways and the important inhibitor compounds are also shown in Figure 1 (for reviews see Ehrlich & Diamond, 1979; Pandey *et al.*, 1979).

The contribution of these individual pathways to the transmembrane flux of lithium *in vivo* is not known. However, one group of workers has measured plasma lithium concentrations *in vivo*, analysed the data using a two-compartment pharmacokinetic model (Figure 2), and compared the derived *in vivo* rate constants with the rate constants measured in *in vitro* assays (Mallinger *et al.*, 1985). Their results suggest some similarity between erythrocyte lithium handling *in vitro*

Figure 1 The major pathways for the transmembrane movements of lithium ions in the erythrocyte. The standard inhibitor of each pathway is also shown.

Figure 2 The two-compartment pharmacokinetic model previously used by others for modelling lithium disposition. In our study we have tested the hypothesis that erythrocytes are representative of the peripheral compartment.

and *in vivo*, but to date no-one has measured intracellular lithium concentrations directly in order to assess the adequacy of such a model.

The activities of some of these individual pathways for cation transport have been investigated in patients suffering from a variety of clinical conditions. *In vitro* studies have shown changes in Na^+, K^+ -ATPase activity in erythrocytes from patients with essential hypertension, renal failure, thyroid disease, and manic-depressive illness (Edmonson *et al.*, 1975; Welt *et al.*, 1968; Cole, 1973; Khan & Baron, 1987; Naylor *et al.*, 1973, 1976). More recently we have developed a method of measuring the *in vivo* cation transport activity of Na^+, K^+ -ATPase, and have used this to extend the earlier *in vitro* studies in a similar range of clinical illnesses (Boon *et al.*, 1984, 1986; Wood *et al.*, 1987).

Changes in the *in vitro* activity of the erythrocyte sodium/sodium countertransporter have

been demonstrated in essential hypertension and in manic depressive illness, as well as during treatment of patients with lithium salts (Canessa *et al.*, 1980, 1987; Ostrow *et al.*, 1978; Meltzer *et al.*, 1977; Rybakowski *et al.*, 1978), and some of these authors have suggested that the observed changes may be relevant to the pathogenesis of the clinical condition.

We have therefore given an oral dose of lithium carbonate to healthy volunteers in order to study lithium kinetics across the erythrocyte membrane *in vivo*. By this technique we have been able to investigate (1) the effects of digoxin and dipyridamole on erythrocyte lithium handling *in vivo*; (2) the adequacy of the two-compartment model (Figure 2) for describing erythrocyte lithium handling by direct measurement of erythrocyte lithium concentrations; (3) the possibility of developing a useful technique for the *in vivo* assessment of erythrocyte sodium/sodium countertransport activity.

Methods

We have studied lithium handling *in vivo* in six healthy male volunteers (ages 30–51 years). Each volunteer took three separate lithium loads during the study. The dose of lithium was 600 mg of the carbonate salt (Li_2CO_3) (Analar grade, BDH, Athelstone, Warwickshire), equivalent to 16.2 mmol of lithium, and this was given as a single oral dose dissolved in 200 ml of deionized water. Venous blood was taken into ammonium heparin as anticoagulant at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 32 and 48 h after the administration of lithium.

Plasma and erythrocytes were separated by centrifugation at 1000 g. The erythrocyte pellet was subsequently treated to remove trapped plasma according to a modification of the method of Ehrlich & Diamond (1979). Briefly, a volume of the erythrocyte pellet was pipetted onto the surface of ice-cold choline/sucrose solution in a centrifuge tube. This solution contained 700 mM sucrose and 166 mM choline chloride and had a density intermediate between plasma and erythrocytes. The tube was centrifuged at 3500 g at 4°C for 10 min and the supernatant plasma and washing solution were discarded. The volume of plasma trapped in the erythrocyte pellet after this washing procedure was less than 1%. Plasma and erythrocytes were then diluted with deionized water and lithium concentrations were measured in the diluted plasma and erythrocyte lysate by atomic absorption spectrophotometry.

A Perkin Elmer 2380 spectrophotometer incorporating an HGA 400 graphite furnace was

used throughout (Perkin Elmer, Beaconsfield, Bucks). An atomization temperature of 2500°C was used in the plasma assay and 2300°C in the erythrocyte assay. All the samples were measured in triplicate and comparisons were made against standard solutions, which contained known concentrations of lithium prepared in equally-diluted samples of the subjects' own plasma or erythrocytes taken before the lithium load. Erythrocyte lysate solutions contained 200 μl of the detergent Triton X100 (BDH, Athelstone, Warwickshire) in order to ensure maximum fragmentation of the membranes and to minimize interferences due to irregularity of the solute matrix. Erythrocyte lithium concentrations have been expressed as $\mu\text{mol l}^{-1}$ of packed cells. The limit of detection of lithium in this assay was 12 pg (1.7 pmol) in erythrocytes and 360 pg (51 pmol) in plasma. The interassay coefficient of variation was 4.6% in erythrocytes and 2.7% in plasma ($n = 7$).

The first lithium load was given in order to assess the normal handling of the cation under control conditions. Each subject then took dipyridamole and on a separate occasion digoxin, both orally over 24 h before the lithium load test was repeated. The total dose of digoxin was 20 $\mu\text{g kg}^{-1}$ body weight (i.e. a loading dose) and the total dose of dipyridamole was 300 mg. Each drug was given as three divided doses during the day before lithium administration. The order of drug administration was randomized and there was an interval of at least 2 weeks between each lithium load test. Venous blood was taken immediately before the administration of lithium, and serum digoxin and dipyridamole concentrations were measured by radioimmunoassay or high-performance liquid chromatography respectively.

In addition, two of the subjects took a fourth lithium load. During this fourth test the two subjects took dipyridamole for 24 h before lithium administration and continued to take the same dosage of dipyridamole (100 mg three times daily) throughout the 48 h of the lithium load test.

The profiles of lithium concentrations in the plasma and erythrocytes after the oral administration of lithium carbonate were analysed by weighted non-linear least-squares regression using the computer program NONLIN (Metzler 1969) run on a Sage III microcomputer under the UCSD p-system. From these data the plasma half-time, clearance, and apparent volume of distribution were calculated. From the pharmacokinetic analysis we were able to calculate the volume of the peripheral compartment of a two-compartment model (V_2) and the concentration

of lithium in that compartment (A_2/V_2). By this means we were able to compare directly the measured erythrocyte lithium concentration profile with the calculated concentration in the theoretical peripheral volume.

The maximal rate of sodium/sodium counter-transport activity *in vitro* was measured by the technique of Canessa *et al.* (1980). Briefly, pre-washed erythrocytes were loaded with lithium by incubation for 3 h in a buffered solution containing 150 mM lithium chloride. The rate of lithium efflux was then measured by suspending the rewashed cells in buffered solutions in the presence and absence of sodium, and sampling the buffer after 15 and 30 min for the estimation of (effluxed) extracellular lithium.

The results have been expressed as means with standard deviations, and differences have been assessed statistically using two-way analysis of variance.

The protocol for this study was approved by the Central Oxford Research Ethics Committee.

Results

The results of the pharmacokinetic analysis are shown in Table 1 and representative sets of plasma and erythrocyte lithium profiles from the same individual are shown in Figures 3 and 4.

There were no significant differences in the pharmacokinetics of lithium after the administration of either digoxin or dipyridamole. The mean (s.d.) plasma half-time for lithium after the baseline lithium load was 17.39 (9.05) h, the clearance

was 2.38 (1.23) ml min⁻¹, and the apparent volume of distribution was 39.4 (9.1) l.

The volume of the peripheral compartment (V_2) was not altered by pretreatment with either digoxin or dipyridamole (19.6 (7.3) for control conditions).

The drug concentrations measured in the plasma after pretreatment, and immediately before the administration of the lithium load were 1.2 (0.25) nM for digoxin and 1.19 (0.51) µM for dipyridamole.

As there is no inhibitor of the sodium/sodium countertransporter that we could use in our volunteer study, we compared the maximal rate of activity of this pathway *in vitro* measured by the method of Canessa *et al.* (1980) (data not shown) with both the partial rate constant for the efflux of lithium from the peripheral compartment (k_{21}) and the rate of decrease of erythrocyte lithium concentrations in the log-linear portion of the terminal phase (see Figure 4). There was no correlation between the *in vitro* measure of sodium/sodium countertransport activity and either of these *in vivo* measures of erythrocyte lithium handling.

The directly-measured erythrocyte lithium concentrations and those calculated from the two-compartment model are shown in Figure 5. There is a large discrepancy between the observed concentration profiles and those predicted from the pharmacokinetic analysis of the plasma concentration versus time data. Specifically, the *calculated* profile predicts a peak intraerythrocytic lithium concentration of 375 µmol l⁻¹ occurring between 4 and 8 h after lithium administration;

Table 1 The pharmacokinetics of lithium under baseline conditions and after pre-treatment with digoxin or dipyridamole. The results of statistical analysis by analysis of variance (*F* values) revealed no significant differences. The ratio of the *in vivo* rate constants for the efflux and influx of lithium into and out of the peripheral compartment (k_{21}/k_{12}) is also shown.

	Control	Digoxin	Dipyridamole	F value
k_{10} (h ⁻¹)	0.136 (0.098)	0.095 (0.032)	0.085 (0.016)	3.27
k_{12} (h ⁻¹)	0.220 (0.105)	0.251 (0.141)	0.174 (0.129)	2.99
k_{21} (h ⁻¹)	0.249 (0.192)	0.217 (0.055)	0.144 (0.068)	2.95
(k_{21}/k_{12})	1.153 (0.570)	0.999 (0.388)	1.028 (0.455)	0.30
Plasma half-time (h)	17.4 (9.1)	18.8 (6.3)	20.4 (2.5)	0.71
Clearance (ml min ⁻¹)	2.38 (1.23)	1.58 (0.50)	1.51 (0.28)	3.20
Volume of distribution (V_{ss}) (l)	39.4 (9.1)	35.2 (3.9)	36.9 (6.4)	2.05
Volume of central compartment (V_1) (l)	19.7 (5.1)	17.0 (3.4)	18.3 (5.4)	1.79
Volume of peripheral compartment (V_2) (l)	19.6 (7.3)	18.2 (4.1)	19.8 (3.5)	0.75

Figure 3 The profile of plasma lithium concentrations in one volunteer under the three experimental conditions (● control, ○ after digoxin, △ after dipyridamole). Plasma concentrations ($\mu\text{mol l}^{-1}$) are shown for times after the lithium load up to 48 h.

Figure 4 The profile of erythrocyte lithium concentrations in the same volunteer under the three experimental conditions (● control, ○ after digoxin, △ after dipyridamole).

by contrast the *measured* peak concentration was $124 \mu\text{mol l}^{-1}$ and occurred 1 h after the lithium load.

Discussion

We have shown that neither digoxin nor dipyridamole changes the erythrocyte or plasma concentration profiles of lithium in healthy volunteers. This suggests that there is no signifi-

cant pharmacokinetic interaction between lithium on the one hand and digoxin or dipyridamole on the other. Furthermore, these results suggest that the roles of the dipyridamole-sensitive anion transport pathway and the digoxin-sensitive Na^+, K^+ -ATPase are minor in modulating the *in vivo* handling of lithium by erythrocytes. This finding is consistent with the earlier *in vitro* data (Duhm & Becker, 1977a, b; Duhm *et al.*, 1976; Pandey *et al.* 1979; Ehrich & Diamond, 1979). We have also demonstrated directly that the

Figure 5 A comparison of the directly-measured erythrocyte lithium concentrations (●) with the concentrations predicted (○) by the two-compartment model (Figure 2) under control conditions. The data are taken from the same volunteer as those shown in Figures 3 and 4.

two-compartment pharmacokinetic model used in previous *in vivo* studies of lithium handling (Mallinger *et al.*, 1985) is a poor predictor of measured erythrocyte lithium concentrations.

It is possible that an effect of the inhibitor compounds was not observed because of the relatively short period of administration of the drugs, and because dosing did not continue throughout the period of the lithium load test. However, we have previously demonstrated an effect of the same regimen of digoxin treatment on the *in vivo* activity of Na^+, K^+ -ATPase, as reflected by the disposition of an oral load of rubidium chloride (Boon *et al.*, 1984). Because the half-time for digoxin is long (approximately 40 h) this demonstrated effect might be expected to last through the period of the lithium load test (48 h). The half-time for dipyridamole is much shorter (approximately 6 h), and so plasma dipyridamole concentrations will fall more quickly. Furthermore, the concentration of dipyridamole previously used in *in vitro* experiments is much higher than would be acceptable *in vivo*. However, the dose of dipyridamole used in this study is the maximum recommended for clinical purposes and produced plasma concentrations at the time of lithium loading which were as high as those found at steady state in clinical practice. Furthermore, we were able to show no change in the pharmacokinetics of lithium in the two volunteers who took a fourth lithium load during which they continued to take full doses of dipyridamole for the 48 h sampling period.

Although we have shown no effect of digoxin

or dipyridamole on the pharmacokinetics of lithium in this experimental paradigm, it is possible that long-term administration of either drug may alter the pharmacokinetics or pharmacodynamics of lithium. Lithium administration is known to lead to a gradual change in the activity of both the Na^+, K^+ -ATPase enzyme (Naylor *et al.*, 1974; Wood *et al.*, 1986; 1988) and the sodium/sodium countertransport pathway (over approximately 21 days) (Meltzer *et al.*, 1977; Rybakowski *et al.*, 1978). These adaptive changes may be important to the maintenance of stable tissue lithium concentrations and perhaps also to the mechanism of action of the drug in affective illness, and they may themselves be altered by the concurrent administration of inhibitor drugs. Indeed, Chambers *et al.* (1982) showed that patients with affective illness, taking digoxin and lithium together, were significantly less symptomatically improved over 7 days than those taking lithium along with inactive placebo.

It is also possible that the activities of the various specific pathways are different in different tissues, and that our failure to demonstrate any change in the plasma profile of lithium after the administration of digoxin or dipyridamole is a reflection of balancing changes in individual tissues. Known differences in both the *in vitro* activity of Na^+, K^+ -ATPase (Bonting *et al.*, 1961) and the transmembrane electrical gradient might contribute to altered handling of lithium by different tissues *in vivo*. However, we must conclude that the contribution of the two active pathways we have tested is small in the erythrocyte, since we found no change in actual intraerythrocytic

lithium concentrations measured after the administration of the inhibitor drugs.

The likelihood that changes in the *in vivo* activity of the sodium/sodium countertransport pathway will be reflected in the results of this lithium load technique could not be tested directly. However, the demonstration that inhibitors of the anion transport pathway and the Na^+ , K^+ -ATPase enzyme do not alter the lithium concentration profile in either the plasma or in erythrocytes is an important step in establishing the specificity of the test.

The two-compartment model is obviously a very poor predictor of erythrocyte lithium handling (Figure 5). The difference between the calculated and the measured concentrations is striking and suggests that the *in vivo* constants calculated in the earlier study of Mallinger *et al.* (1985) are likely to be inaccurate. Furthermore, those authors demonstrated a correlation between their *in vivo* rate constants and the ratio of the rate constants for sodium/sodium countertransport activity and passive membrane permeability, derived from *in vitro* measurement of lithium efflux from preloaded erythrocytes. Under these circumstances intracellular electrolyte concentrations are unphysiological (Canessa *et al.*, 1980) and furthermore, lithium efflux occurs against the prevailing transmembrane electrical gradient. For both these reasons, 'leak' measured as lithium efflux is likely to be quantitatively different from true passive influx measured *in vitro*. Thus, the demonstrated correlation between *in vivo* and *in*

vitro rate constants in their study is also likely to be spurious.

By contrast, we were unable to demonstrate any quantitative correlation between our direct measures of lithium efflux from erythrocytes *in vivo* and the *in vitro* measure of lithium efflux via the sodium/sodium countertransport pathway measured by the method of Canessa *et al.* (1980). Our failure to demonstrate any correlation suggests that the *in vivo* regulation of erythrocyte lithium handling, and specifically the efflux of lithium via the sodium/sodium countertransport might be qualitatively and quantitatively different from that predicted by *in vitro* experiments.

However, this does not imply that the use of an oral dose of lithium to assess the activity of the sodium countertransport pathway *in vivo* is excluded on theoretical grounds, simply that a more empirical approach to the investigation of its potential value is necessary. It will therefore be important in the future to apply the lithium load test to the *in vivo* study of patients suffering from clinical illnesses (e.g. essential hypertension) in which altered sodium countertransport activity has been reported from *in vitro* studies. Such studies are in progress in our laboratory.

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