Localized ^{7}Li MR Spectroscopy: Correlation of *in vivo* Brain and Serum Concentrations in the Rat

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SYNOPSIS

The brain concentration of lithium (Li) in treated rats was measured by *in vivo* ^{7}Li PRESS localized MRS and compared to the corresponding serum concentration at two treatment times. The brain and serum Li concentrations were highly correlated with each other, more so than found previously for humans. The brain and serum Li concentrations also correlated with dose. The brain/serum Li ratios for rats were comparable to previous values found for humans. In some cases the ratios deviated substantially from the mean, suggesting that serum Li is not always a reliable indicator of brain Li.

INTRODUCTION

Lithium (Li) is the treatment of choice for acute manic illness and prophylaxis in bipolar disorder. Li treatment is usually monitored via the serum concentration of the ion. Treatment failures in the therapeutic serum range are common, and neurotoxicity is a constant concern. The magnitude of the pharmacologic effect of a drug depends on the concentration at the receptor sites in the target tissue, which may not be reflected in the serum concentration. In recent studies in humans[1,2] the correlation between serum and brain concentration, as measured by ^{7}Li MRS *in vivo*, was found to be weak, but statistically significant when a wide concentration range is considered. These results suggest that serum Li is a less than ideal measure of Li therapy, and that individuals with nominally therapeutic serum concentrations may have either sub-therapeutic or excessive (toxic) brain concentrations. The expected strong correlation between serum and brain Li has not been seen in humans, and the factors responsible are not understood. Here we have measured brain Li concentrations *in vivo* by ^{7}Li PRESS localized MRS, as well as serum Li concentrations in rats as a function of dose at two times after beginning treatment. The rat is a well controlled model with guaranteed drug delivery over a relatively wide dose range for Li.

METHODS

Brain Li concentrations were measured once or twice (at 6.6±0.44 and/or 16.1±1.6 days of treatment) in 44 male Sprague-Dawley rats (on a controlled diet) at daily doses of 1.0 (N=7), 1.75 (N=1), 2.0 (N=18), and 2.5 meq/kg (N=18) aqueous LiCl administered b.i.d. MRI/MRS measurements were performed on a GE Omega 4.7-T system with a two-channel ^{7}Li-^{1}H coil, designed specifically for rat head imaging and spectroscopy by Doty Scientific, Inc. (Columbia, SC). Rats were anesthetized using 15 mg/kg xylazine and 80 mg/kg ketamine IM, followed by 1.5% isoflurane in O_2. Conventional ^{1}H spin-echo MRI at 200 MHz was used to select an approximately 1-cm^{3} voxel in brain. Shimming was performed on the localized H_2O signal. Localized ^{7}Li spectra were acquired at 77.7 MHz using a PRESS sequence with TR=5 s, TE=6.8 ms, in 0.5-4 hours. Brain concentrations were measured relative to a standard Li phantom (of comparable concentration, T_1, and T_2) sampled similarly before or after the *in vivo* spectrum. Blood was sampled immediately after the MRS measurements once or twice in 37 rats. Serum concentrations were measured by atomic emission spectrophotometry.

RESULTS

Repeated-measures ANOVA showed no difference between brain or serum Li concentration, or their ratio, at 6.6 days and 16.1 days. Brain and serum Li concentrations measured at the same time were significantly different from, and strongly correlated with, each other (r=0.95, p=0.0000) (Figure 1) at both treatment times. Both brain and serum concentrations of Li correlated with dose at 6.6 and 16.1 days (r=0.63-0.69, all p<0.0002) (Figure 2). The average brain/serum Li ratio was 0.70±0.17 at 6.6 days and 0.65±0.11 at 16.1 days. The brain/serum Li ratio correlated weakly with dose at 16.1 days (r=0.48, p=0.016), but not at 6.6 days.

DISCUSSION

The correlation between brain and serum Li concentrations found here was substantially better than found previously for humans (r=0.65-0.68), although the mean ratios were comparable to previous values (0.76-0.80).[1,2] We attribute the better correlation of brain and serum Li found here to guaranteed drug delivery and controlled diet for the rat model. Although a close correlation of brain and serum values was generally maintained, the brain/serum ratio varied from 0.25 to 1.09. Although brain and serum Li concentrations correlated with dose, substantial interindividual variation was observed among animals given the same dose. For example, for a dose of 2.5 meq/kg, brain values varied from 0.32 to 1.86 mM (Figure 2), while serum values varied from 0.54 to 2.38 mM (not shown). Clearly, in individual cases neither the dose nor the serum value may be a reliable indicator of brain Li.

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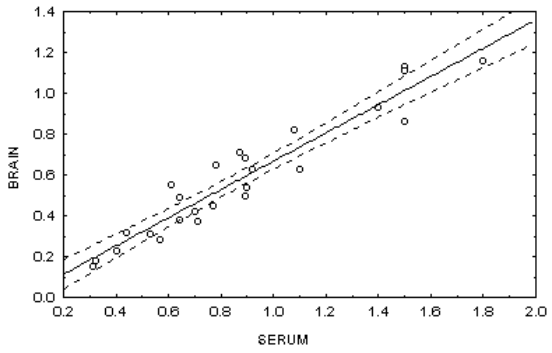


Figure 1. Brain vs. serum Li concentrations (mM) in rats at 16.1 days. Regression line:solid; 95% confidence interval:dashed.

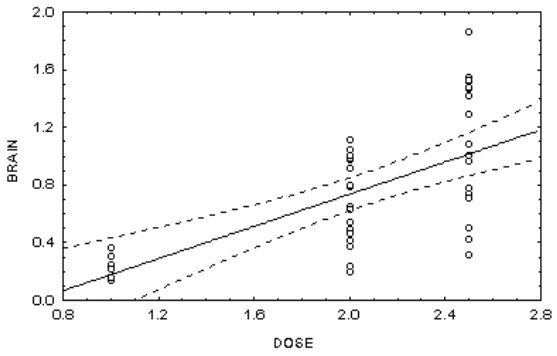


Figure 2. Brain Li concentration (mM) in rats vs. daily dose of LiCl (meq/kg) at 6.6 days. Regression line:solid; 95% confidence interval:dashed.