Pharmacokinetics and relaxivity of Lithium in Rat Thigh Muscle by MR Studies

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Introduction

Lithium (Li) salts are effective in the treatment and prophylaxis of mania and depression. The narrow therapeutic window of lithium requires frequent monitoring of lithium. Currently it has been the practice to monitor and maintain plasma lithium level in the range of 0.5-1.2 meq/L. The advances in magnetic resonance techniques have brought new possibilities of investigating the relevance of tissue lithium levels to clinical response. Since muscle tissue resembles nerve as an excitable cell, an evaluation of Li in muscle may serve as good predictor of therapeutic response and side effects (1).

Magnetic resonance techniques have been used to measure Lithium in animal models and humans (2-5). However, relatively little is known about lithium pharmacokinetics and properties of lithium in the cellular microenvironment of the muscle. The very early pharmacokinetic study at 5 meq/kg dose in rats used the atomic absorption technique to quantitate tissue lithium. Because the technique is invasive in nature, it is not a suitable method to monitor living systems. With the goal of studying Li levels in the muscle tissue, under the administration of lithium and codrugs, we are making Li measurements using MR spectroscopic method. The complete profile of absorption and elimination has been constructed and the details are discussed here. The transverse relaxation time (T_2) studies were performed to gain insight into the lithium environment in the muscle tissue.

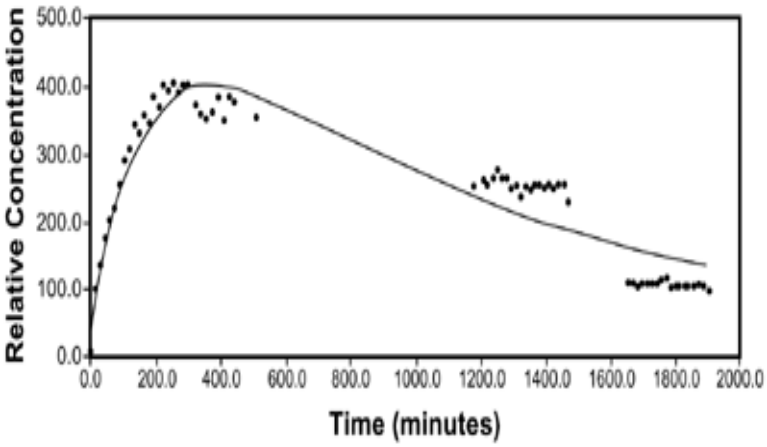
Methods

Animal preparation: Male Sprague Dawley rats weighing ~300g were used in this study. They were provided water and chow *ad libitum*. The rats were administered 10 meq/kg dose of LiCl and studied by in vivo ^{7}Li MR spectroscopy over time. All MR studies were performed using a 4.7T MR instrument operating at 77.75 MHz for ^{7}Li nucleus. A home built two-coil assembly, consisting of a 3-cm diameter single turn coil for ^{7}Li and a figure-eight-loop for the ^{1}H nucleus, was used. After positioning the animal inside the magnet, the field homogeneity was adjusted using the proton signal. The line widths obtained were in the neighborhood of 30Hz. A typical in vivo data collection lasted for about 4 hours with spectra being collected every 5 minutes. The transverse relaxation times were measured using the Hahn spin echo technique.

Results

The normalized intensities obtained on the rat thigh at various time points following Li administration is shown in Figure 1. Li intensities were measured for up to 30 hrs. The tissue Li intensity reached a maximum value around 3 hours post Li injection. The generation of the pharmacokinetic profile (shown as solid line) and related analysis was performed using the software for non-compartmental pharmacokinetic data analysis (6). The half-life of absorption and elimination were approximately 3 and 6 hours respectively. The pharmacokinetic profile closely resembles that obtained by Schou (7) where more than 40 animals were used to construct the profile. Our study demonstrates that the entire profile can be constructed by MR spectroscopy using two animals. This will allow us to choose appropriate time points for detailed investigation of codrug effects on tissue lithium by MR. The T_2 measurements show a biexponential behavior with a fast component of 5±4 ms and a slow component of 250 ± 29ms. As compared to the fast component in the head tissue, the corresponding value in the thigh muscle tissue indicates a highly restricted motion of the ions. The study indicates a possibility of two major environments for lithium in the muscle.

Figure 1.



Conclusions

Under a single 10 meq/kg dose of LiCl we monitored Li in the muscle tissue over time. The pharmacokinetic profile is closely similar to that reported by in vitro tissue analysis (7). The T_2 relaxation is biexponential in nature with a significantly fast component.

References

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