# $^{7}$Li MR Studies of Codrug Effects on Plasma and RBC Lithium of Rats Under Li prophylaxis

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## Introduction

Lithium (Li) is largely considered as the first–line long-term treatment for bipolar or manic depressive illness (1). Patients who fail to respond to lithium monotherapy are often supplemented with a co-drug (2,3). The effect of the codrug on Li in different tissue compartments and the intra and extra cellular RBC compartments are not fully understood. In this study, a mammalian model is used to study the drug effect on Li concentrations. Since frequent monitoring of blood lithium is a requirement for Li maintenance therapy, we are studying the changes in plasma and RBC lithium. Additionally the similarities between red blood cells (RBCs) and neurons, such as their transport mechanisms, make RBCs a suitable model for the brain. Intracellular lithium levels such as those in RBCs are believed to be a better indicator of tissue lithium levels than plasma levels. We have successfully used MR technique to study the lithium in plasma and RBC (4-6) of rats. This study design consists of coadministration of Li with fluoxetine (SSRI antidepressant), Citalopram, (SSRI antidepressant with a different chemical structure), fluphenazine (antipsychotic), clozapine (atypical antipsychotic), and, valproic acid (anticonvulsant and antiepileptic) drugs. Here we report the codrug effects on the RBC and plasma lithium of rats under Li prophylaxis using $^{7}$Li MR technique and a shift reagent. The differential effect of co-drug on RBC and plasma Li concentrations are discussed.

## Methods

***Animal Preparation:*** Male Sprague Dawley rats weighing 200-300g were used in the study. Animals were housed in cages and provided with food and water *ad libitum*. The room was kept at a temperature of 23°C on a 12-hour light/dark cycle. Lithium chloride (LiCl) was administered IP at a dose of 2meq/kg twice daily for the first two days followed by a single dose in the morning of the third day. Each Li administration was immediately followed by an injection of a codrug. All codrugs were administered IP at a dose of 20mg/kg with the exception of valproic acid which was administered at 180 mg/kg. A total of 43 animals were used in the study, with one Li-alone treated rat serving as control in each group. Blood samples were taken 8 hours after the last injection. An aliquot of blood sample was used to determine plasma Li using the Vitros 950 system (Johnson and Johnson Clinical Diagnostics, Inc). Another aliquot was used to determine plasma and RBC lithium independently by MR technique. Lithium standards were used to obtain the concentrations in plasma and RBC.

***Preparation of blood samples for NMR:*** The volume of blood drawn from each animal was measured. Approximately 20 mg of shift reagent ($TmDoTP^{5-}$) was added in small NMR vials to 1.4ml of blood containing anticoagulant CPD. All samples were studied by $^{7}$Li MR on the day blood was drawn.

***NMR:*** All NMR studies were performed on Bruker 7 T instrument operating at 116.75 MHz for $^{7}$ Li nucleus. A home built 7 turn solenoid coil (1.5 cm diameter and 3cm long) was used. The $^{7}$ Li NMR data were collected using 4K data points, a 30 μs pulse, 900 acquisitions, and inter pulse delay of 2 s. The peak integrals were used to compute the RBC and plasma lithium concentrations

## Results and Discussion

The changes in plasma and RBC lithium upon addition of comedication to Li regimen are shown in Figure 1. Quantitative analysis of changes in Li concentration with the addition of fluoxetine showed an increase in plasma Li of 62 % (p=0.002) and RBC Li of 69 %( p=0.002). Fluphenazine showed an increase in plasma Li of 53 %( p=0.003) but no significant change in RBC lithium. Citalopram, an SSRI antidepressant, did not show significant changes in either plasma or RBC Li. The co drug valproic acid, an anticonvulsant, showed an increase in RBC lithium of 52 %( p=0.008) with no change in plasma Li. Finally the atypical antipsychotic agent, clozapine, did not lead to significant changes in either plasma or RBC Li.

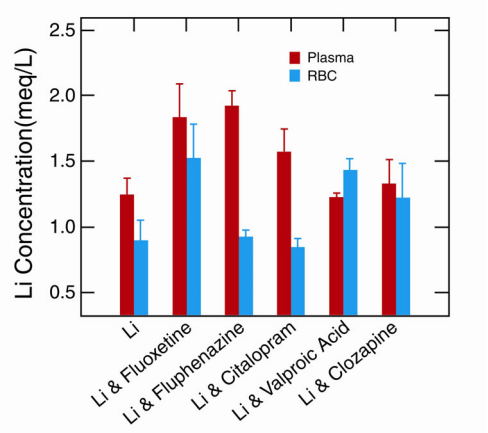


**Figure 1**: A bar chart indicating Li concentrations in plasma and RBC under combination treatments.

## Conclusions

$^{7}$Li MR studies of blood samples clearly demonstrate different effects of codrugs on plasma and RBC Li concentrations. The study can provide useful information on the effect of codrugs on Li in different compartments and hence provide additional information in maintenance therapy involving codrugs. $^{7}$Li MR offers a convenient nondestructive way of measuring these changes in a single study.

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