

## MONITORING DRUG INTERACTION IN A CASE WITH BIPOLAR DISORDER TREATED WITH NIFEDIPINE IN PRETERM LABOUR

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### ABSTRACT

Lithium is used to treat bipolar disorder, which is also called manic-depression. The recommendation to continue or discontinue Lithium during Pregnancy is based on a variety of factors, such as the type and severity of the condition being treated, the likelihood of relapse without medication, the stage of pregnancy you are in, and other risk benefit considerations. Stopping lithium too quickly has been associated with relapse of symptoms in individuals with bipolar disorder and is not recommended. Here we monitored and reported a case with a woman treated with Lithium for her bipolar disorder and Nifedipine for preterm labour. She was at 33 weeks of gestation. The blood levels of lithium were monitored for any interaction of nifedipine during treatment. The results showed that there was no significant alteration in the pharmacokinetic parameters of Lithium before and after the initiation of nifedipine therapy.

**Keywords:** Lithium, Nifedipine, Interaction, Pharmacokinetics

### INTRODUCTION

Treatment of bipolar disorders during pregnancy has been safe till date<sup>1, 2</sup>. In recent years women with bipolar disorders have been advised to refrain from lithium during the first trimester of pregnancy and to resume it in the second trimester and this is because of the fact that there are case reports of lithium use during pregnancy and the development of a goiter (enlarged thyroid gland in the neck) in the mother. Nifedipine is a calcium channel blocker which inhibits the influx of calcium ions into myometrial and other cells and thereby reduces muscle contractility<sup>3</sup>. In recent years nifedipine has found its way in obstetrics and gynecology in the management of preterm labour. Its popularity in the management of preterm labour is at least partially based on the absence of tachyphylaxis and low incidence of side effects<sup>4</sup> several studies have shown the efficacy and safety of nifedipine in preterm labor<sup>5, 6, 7</sup>, but limited data are present about the safety and efficacy of nifedipine. This case is presented to provide and analyze the pharmacokinetic interactions of Lithium and nifedipine being treated simultaneously for two different therapeutic uses in which none of the therapy could be neglected.

### MATERIALS AND METHODS

Women aged 30years at 33 weeks of gestation was under maintenance of Lithium therapy for every second day, scheduled as per the monitored Lithium levels in blood. She presented with the signs of preterm labour and was administered nifedipine with an initial oral loading dose of 30 mg (10mg sublingual and 20 mg oral) and a maintenance oral dose of 20 mg every 6 h.<sup>8</sup> Maintenance of Nifedipine dose of 10-20mg orally; 6-8hourly was done at 4-6hours after the last sublingual dose for not more than 7days. Blood levels for lithium were monitored again after initiation of nifedipine therapy at predose 00.00 hrs ,and post dose at 00.25, 00.50, 00.75, 01.00, 01.50, 02.00, 02.50, 03.00, 03.50, 04.00, 05.00, 06.00, 08.00, 10.00, 12.00, 24.00 hrs, 36.00, 48.00 & 72.00 hrs. The volume of blood collected at each time point of post dose was 04 mL. After collection of blood samples at each time point, the blood samples were centrifuged at 4000 RPM for 10 minutes at 4°C to separate the plasma and the plasma samples were transferred into pre-labeled polypropylene tubes. These samples were stored at temperature below -30°C at the clinical site and were transferred to the bio analytical facility and stored at a temperature below -70°C in ULTF until completion of analysis. Lithium in plasma was analyzed using a validated ICP MS method. Pharmacokinetic analysis was performed using WinNonlin<sup>®</sup> software version 5.3 of Pharsight Corporation, USA for pharmacokinetic parameters  $C_{max}$ ,  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $t_{max}$ ,  $t_{1/2}$ ,  $V_d$  and  $D$ .

### RESULTS

The pharmacokinetics describes the quantitative relationship of concentration- time profiles in different body fluids.<sup>20</sup> The volume of distribution,  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ , the measured capacity of elimination, and the rate of elimination were found to be 493438.2543ml and 496674.2975ml, 12262.9259ng\*hr/ml and 11184.6363ng\*hr/ml, 13731.915ng\*hr/ml and 13489.4123ng\*hr/ml, 21710.4126 and 22101.7854 for Lithium after treatment with nifedipine and before treatment with nifedipine respectively. All the Pharmacokinetic parameters do not have significant difference for us to expect any pharmacokinetic interaction of lithium with nifedipine. However The  $C_{max}$  and  $t_{max}$  was found 1075.2417ng/ml and 2.5hrs after nifedipine therapy and 1364.6875ng/ml and 1.00hrs before nifedipine therapy respectively and this difference is expected as it is dependent upon the external factors and physiological factors and cannot be directly relayed upon to suspect any interaction. There is no interference of nifedipine with lithium as half life of lithium was approximately 15 hrs before and after nifedipine therapy. Linear plot of individual plasma concentration vs time for Lithium Carbonate before Nifedipine therapy is provided in Fig.1. And after Nifedipine therapy is provided in Fig.2. The semi log plot of individual plasma concentration vs time for Lithium Carbonate before Nifedipine therapy is provided in Fig.3 and after Nifedipine therapy is provided in Fig.4.

### DISCUSSION

Although lithium continues to be regarded as the treatment of choice for bipolar disorder<sup>9</sup>, the clinical use of this mood stabilizer is associated with a narrow therapeutic range. Conventional lithium carbonate tablets produce rapid and relatively high peakserum lithium levels which results in adverse effects<sup>19</sup>. Lithium has drug interaction with antipsychotics, antidepressants, other mood stabilizers, angiotensin converting enzyme (ACE) inhibitors, and diuretics<sup>10</sup>. Safety of lithium co administration is of a major concern<sup>11</sup>. Lithium has been reported with interactions with diclofenac, ketoprofen, mephenamic acid, piroxicam<sup>12</sup> and acetazolamide<sup>13</sup>. However the cases of interactions that lithium could hold, it has central importance in psychiatric diseases. In general adding drugs effecting glomerular filtration and electrolyte exchange in nephrons may influence pharmacokinetic disposition of lithium. In our case it was found that the plasma levels of lithium was not altered significantly before the treatment of nifedipine and as well as after the treatment of nifedipine. Nifedipine is the first CYP3A4 substrates to be identified<sup>14,15</sup> and has been the subject of large number of drug-drug interaction studies. The most

interactions of nifedipine were reported with itraconazole<sup>16</sup>, grapefruit juice<sup>17</sup>, and inducers such as barbiturates<sup>18</sup> and rifampin. The other interactions of nifedipine are not significantly proven. Our data of lithium levels are obtained and compared between a single dose of lithium before and after the nifedipine therapy moreover the

nifedipine levels were also not monitored for us to understand the lithium interaction with nifedipine but as far as this case report is concerned we report that nifedipine does not have significant effect on the blood levels of lithium when both the drugs has been co administered to a patient with preterm delivery symptom.

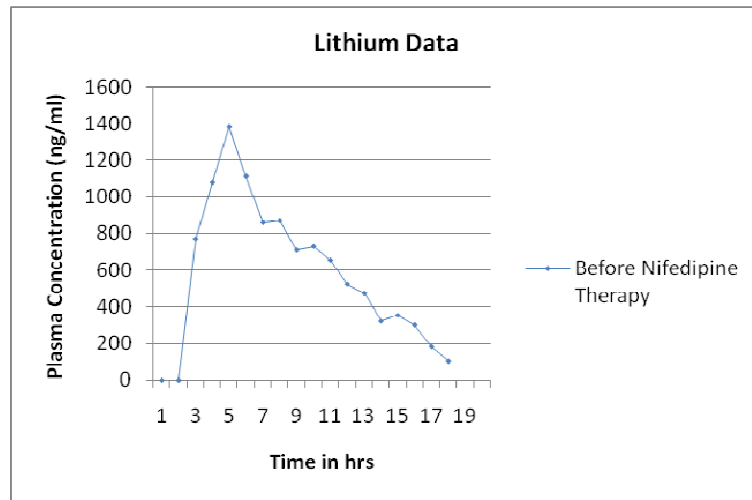


Fig. 1: Linear plot of individual plasma concentration vs time for Lithium Carbonate before Nifedipine therapy

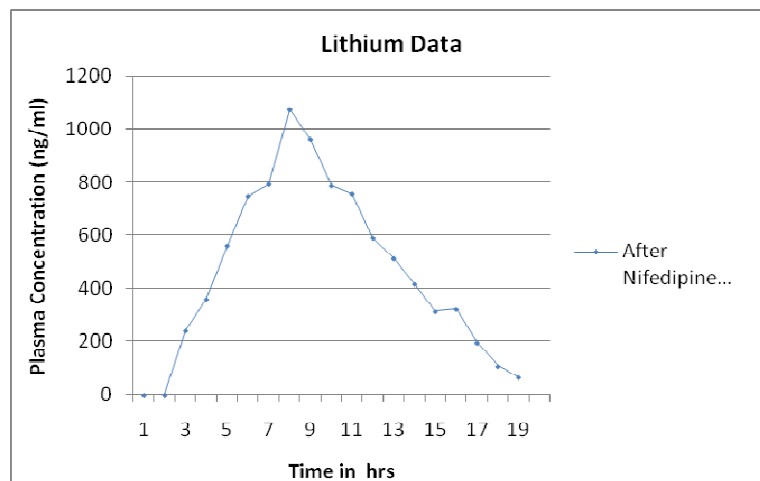


Fig. 2: Linear plot of individual plasma concentration vs time for Lithium Carbonate after Nifedipine therapy.

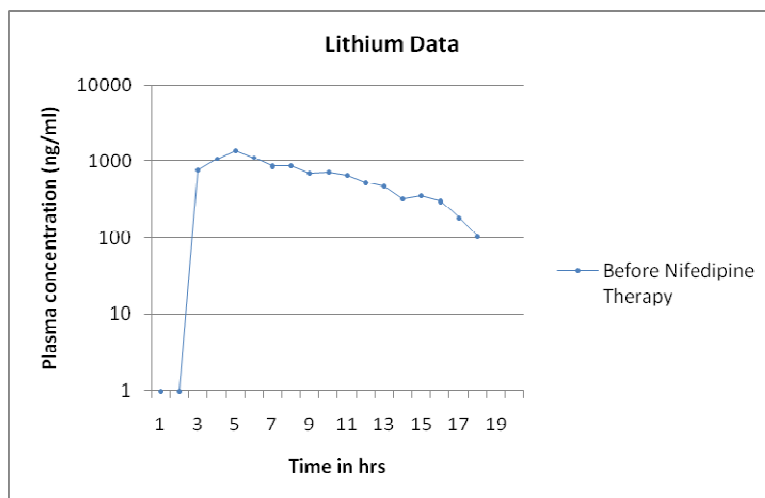


Fig. 3: Semilog plot of individual plasma concentration vs time for Lithium Carbonate before Nifedipine therapy

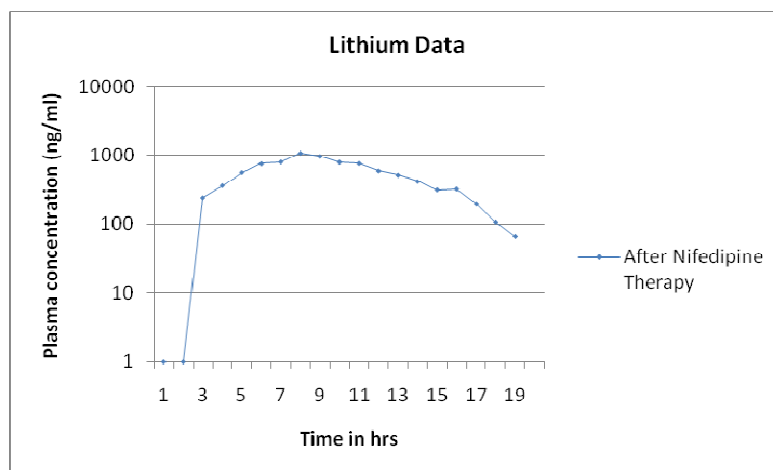


Fig. 4: Semilog plot of individual plasma concentration vs time for Lithium Carbonate after Nifedipine therapy

## CONCLUSION

In the present study simultaneous administration of nifedipine and Lithium to pregnant women which was under unavoidable circumstances did not register any adverse effects possibly related to neither the Nifedipine nor Lithium. This observation in the present study could be useful for practitioners as a decision making guide for patients simultaneously administered nifedipine and Lithium drugs.

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