Section: Pharmacology

Research

# ALTERED PHARMACOKINETIC ATTRIBUTES OF LITHIUM IMIPRAMINE WITH CONCOMITANT USE OF DOMPERIDONE IN HUMAN VOLUNTEERS

**Preet Sood[1], SC Chopra[2]**

[1]Professor, Department of Pharmacology, Sriguru Ramdass Institute of Medical Sciences, Vallah, Amritsar, Punjab, India
[2]Ex. Professor, Dayanand Medical College, Ludhiana, Punjab, India

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Corresponding Author:
**Dr. Preet Sood,**
Email: preetsood2015@gmail.com
ORCID: 0000-0001-5489-8109

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## Abstract

**Background:** Lithium is used in psychiatry in manic depressive disorder along with imipramine. This combination decreases not only the side effects of lithium and increases efficacy. Domperidone is used for dyspepsias as it increases the gastric motility. Its effect of lithium levels is not much studied. **Materials and Methods:** 30 normal human volunteers divided in 3 groups (10 in each group) were administered with the study drugs. The effect on lithium levels were estimated by using ion selective electrodes. Changes in pharmacokinetic parameters of lithium i.e.$c_{max}$, $t_{max}$, AUC, kel etc were calculated. **Result:** Domperidone attenuated the imipramine induced fall in serum lithium concentration at ½ h and 1 h. It also normalized the imipramine induced fall in Cmax and increase in tmax. Domperidone significantly reduced $K_{el}$ and increase the $t_{1/2}$ of lithium. **Conclusion:** As concomitantly used domperidone can potentially influencing factor of lithium serum concentrations.

## INTRODUCTION

Lithium being a versatile drug in Psychopharmacology and used in variety of psychiatric disorders like prophylaxis of Bipolar affective disorders, manias and schizoaffective disorders. Various antidepressants like imipramine, Fluoxetine and many Psychotropic drugs like resperidone are used along with lithium. These combinations increase the efficacy but decreases the dose resulting in the reduction of Adverse drug reactions.

Pharmacokinetics of lithium is little different. It absorbed quickly and completely from GIT, not bind to plasma and tissue protein, not metabolized in the body. Reabsorption from kidney and elimination half-life fluctuates in mania and depressive attacks (20-24 hrs). It possesses narrow therapeutic index and mild distressing side effects like lethargy, irritability and tremors even occurs at therapeutic concentration(Cp) 0.5-1.25meq/lt.

In manic depressive psychosis imipramine is usually combined with lithium and together called as Normothymotics i.e mood stabilizers.it effects pharmacokinetic parameters like AUC, $K_e$l& $_{t1}$/2resulting in delay in lithium reaching its site of absorption in GIT.

This study was planned to study the effect of Domperidone,[1] which is very commonly used for gastrointestinal causes in day-to-day life. Its effect on lithium bioavailabilty using different pharmacokinetic parameters ($C_{max}$,$t_{max}$, AUC, $K_{el}$,$K_{abs}$,$t_{1/2el}$).

## MATERIALS AND METHODS

This work was performed in Dayanand medical college and hospital, Ludhiana. The study was approved by institutal ethics committee.

30 normal human volunteers of either sex who were physically healthy were enrolled. After obtaining informed written consent, subjects were divided into three groups of 10 each.

Drug used-Lithium Carbonate- (LiCab, torrent 300mg tablets)

-Imipramine hydrochloride (Depsonil, S Gpharma 25 mg tablets)

-Domperidone (Domstal, Torrent 10mg tablets)

Drug administration Protocol

| Group | (-60 min) | 0hr |
|---|---|---|
| 1 | | Lithium 900mg |
| 2 | | Lithium 900mg+Imipramine25mg |
| 3 | Domperidone 10mg | Lithium 900mg+Imipramine25mg |

After overnight fast, drugs were administered with 200ml of plain water according to the protocol. Using aseptic technique ,5 ml blood samples each were collected at 0,1/2,1,2,4,6and 24 hrs after lithium administration. At the time of sample


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collection jelco cannula was inserted at forearm and after first sample withdrawn at 0hr heparin 1ml was injected to maintain the patency of cannula. Serially all the blood samples were collected after discarding first 1ml blood to remove heparin. After collecting the sample, 1ml of heparin (1:1000) was injected every time.

Then 6hr cannula was taken out and volunteer were asked to come back at same time next morning (+_9am) for 24 hr sample.

After serum separation and centrifugating at 3000rpm, lithium level was determined by using ion selective electrode (Synchrone El-Ise).[2]

50µ litre of sample was mounted on a sample tray and buffered solution loaded automatically. Instrument is standardized with known value of lithium calibrator.

The system was set to perform all the calculation internally to produce final report.

A standard breakfast was given 1 hour after lithium administration.

## RESULTS

The comparison of the mean Lithium concentraraion in group I (Li), group II (Li+IMP) and group III (Li+IMP+DOM) is shown in [Table 1]. Statistically significant decrease in the lithium concentration at ½ h ($p<0.001$), 2h ($P<0.05$), 4 h 6 h (($p<0.001$) with Gp-I (Li) versus Gp-III (Li + IMP + DOM) while in comparison to Gp-II (Li +IMP) and Gp-III (LI + IMP + DOM) statistical significant decrease was seen at ½ h and 1h ($P<0.001$) and 24h ($P<0.01$).

[Figure 1] showing the effect of Domperidone on the Imipramine modified Lithium bioavailability. Domperidone treatment attenuated the Imipramine induced fall in serum lithium concentration at ½ h and 1 h. The serum lithium concentration at 24 h was hiogher in the group III (LI+IMP+DOM) as compared to group II (LI + IMP). It is also normalized the Imipramine unduced fall in. Cmax and increase in tmax.

Domperidone significantly reduced the Kel and increase the t½ of Kithium as compared to Lithium and Lithium Imipramine groups.

AUC was also higher in the Lithium Imipramine group as compared to Lithium Imipramine.

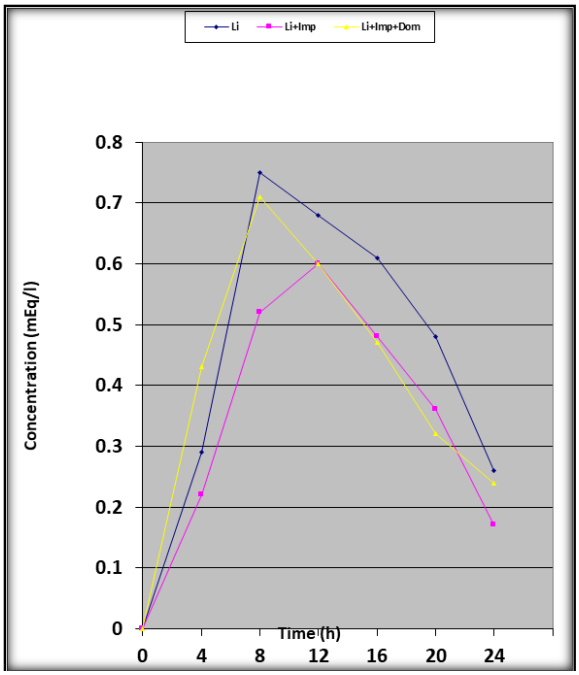


**Figure 1: Effect of Domperidone on the imipramine modified lithium bioavailability**

**Table 1: Lithium concentration (mEq/1) after a single dose of lithium versus Lithium + imipramine versus Lithium + Imipramine + Domperidone (n=30)**

| Time (h) | Group-I Lithium | Group-II Lithium + Imipramine | Group-III Lithium + Imipramine + Domperidone |
|---|---|---|---|
| 0 | 0 | 0 | 0 |
| 0.5 | 0.29 ± 0.018 | 0.22 ± 0.025* | 0.43 ± 0.002***### |
| 1 | 0.75 ± 0.013 | 0.52 ± 0.031*** | 0.71 ± 0.002### |
| 2 | 0.68 ± 0.017 | 0.60 ± 0.61** | 060 ± 0.031 |
| 4 | 0.61 ± 0.08 | 0.48 ± 0.021*** | 0.47 ± 0.031*** |
| 6 | 0.48 ± 0.023 | 0.36 ± 0.025*** | 0.32 ± 0.23*** |
| 24 | 0.26 ± 0.022 | 0.17 ± 0.011*** | 0.24 ± 0.019## |

*P<0.05, **P<0.01, ***P<0.001 as compared to group I #p<0.05, ##P<0.01, ###P<0.001 as compared to group II

**Table 2: Pharmacokinetic parameters of Lithium versus Lithium + Imipramine versus Lithium + Imipramine + Domperidone (n=30).**

| Pharmacokinetic Parameters | Group-I Lithium | Group-II Lithium + Imipramine | Group-III Lithium + Imipramine + Domperidone |
|---|---|---|---|
| $C_{max}$ (mEq/1) | 0.75 ± 0.01 | 0.62±0.016** | 0.72±0.0136### |
| $T_{max}$(hrs) | 1 ± 0.0 | 2.1 ± 0.23*** | 1.2 ± 0.1333## |
| $K_{el}$ ($hrs^{-1}$) | 0.039±0.0026 | 0.049 ± 0.0041 | 0.028±0.0023**### |
| $T_{½}$(hrs) | 18.19±1.2053 | 14.97 ± 1.0422 | 25.86±1.9481**### |
| AUC (mEq.h/1) | 17.01±0.7586 | 44.01 ± 0.5933*** | 17.14±1.5724## |

*P<0.05, **P<0.01, ***P<0.001 as compared to group I
#p<0.05, ##P<0.01, ###P<0.001 as compared to group II


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## DISCUSSION

Adding domperidone increased C max (P<0.001) and reduced tmax (p<0.001) as compared to lithium imipramine group. It may be due to prokinetic nature of domperidone, increased gastric motility may results in faster delivery of lithium at the site of absorption (small gut). This view is strengthened by the animal study in which oral imipramine, coadministered with metoclopramide intraperitoneally decrease the tmax by 63% while increase in AUC by 100%.[3]

The longer t1/2 life of lithium in group 3 vs group 2 indicates a reduction in elimination of lithium. lithium being an element it is not metabolized so its excretion could have been affected.[4,5]

A study has demonstrated marked fall in GFR by 12%, increase in ERPF (end renal perfusion fraction) by 38%and increase in UNAV (sodium excretion rate) by 100%by domperidone. All these factors result increase in sodium excretion. Sodium and lithium having same radius, increase in sodium excretion may lead to increase lithium reabsorption resulting in a lowered Kel and longer t1/2 life. The increase in AUC as of Domperidone administration appears to be net effect of increase in lithium absorption and reduction in excretion.

Much human studies on lithium with gastric motility modifying drugs on humans have been reported. But with others drugs like ACE inhibitors, angiotensin II receptor antagonists (sartans), diuretics, and non-steroidal anti-inflammatory drugs (NSAIDs) have reported to increase the lithium levels.[6-9] A study with amiloride is recommended as it blocks entry of lithium through the epithelial sodium channel in the collecting duct. This reduces lithium accumulation and may improve kidney function in patients on long-term treatment.[10,11]

Study with diuretics such as the osmotic methylxanthine (e.g. theophylline) and loop (e.g. furosemide (frusemide)) and potassium-sparing (e.g. spironolactone) diuretics may also alter lithium concentrations. Acetazolamide for intraocular pressure, glaucoma and epilepsy has been shown to significantly increase lithium levels.[12]

## CONCLUSION

Lithium has an important role in the treatment of mood disorders.More bioavailability studies with gastric motility drugs should be conducted so that its effect on the lithium levels can be analysed.

Prescribers need to be mindful of its potential drug interactions and the impact they can have on patients. Improved knowledge of and confidence with monitoring will contribute to better patient outcomes.

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