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Original Research Article

Effect of Loperamide on Imipramine Induced Modification in Lithium Bioavailability in Healthy Volunteers

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Abstract

Introduction: Lithium along with imipramine has a pivotal role in Psychopharmacology in disease like mania, schizo affective disorders etc. Lithium being on ion is unique and it possesses narrow therapeutic index.

Aim & Objectives: Imipramine as Coad ministered with Lithium in Psychiatric disorder. In previous studies found to lower the C_{max} & T_{max} . Further, loperamide is commonly used OTC drugs for various GIT problems. This study was planned to evaluate loperamide effect on Lithium bioavailability in healthy volunteers.

Material & Methods: 30 normal human volunteers were enrolled & randomised in 3 groups of 10 each. Assigned drug to the particular group was administer and samples to estimate lithium were taken & serum level of lithium were determined by using ion selective electrode(Synchron EL-ise)

Objectives & Results: Loperamide accentuated the imipramine induced reduction in absorption rate of Lithium, as evidenced by a further reduction in C_{max} & increased in T_{max}. Fall in AUC of lithium has also been observed.

Conclusion: Sustained release preparation of lithium to retard its absorption & minimize the drug interaction of Lithium seems the only solution.

Keywords: Lithium, Loperamide, Therapeutic index, mania depressive psychosis.

Introduction

Lithium has a pivotal position in Psychopharmacology. It is used in variety of psychiatric ailments like Bipolar affective disorders, manias and schizoaffective disorders. Other non-psychiatric uses include cluster headaches, cancer chemotherapy induced leucopenia and Syndrome of inappropriate secretion of anti-diuretic hormone (SIADH).

Further, Lithium being a narrow therapeutic index drug. Concomitant use of drugs for any purpose can leads to increase or decrease in the concentration resulting in change in efficacy and adverse drug reactions. Various formulation of lithium has found beneficial in treatment of neurodegenerative brain diseases.

As Lithium is extensively used by Psychiatrists as well as Physicians due to its high efficacy in the management of Mania and Depression.

Concomitant administration of two or more drugs always has the possibility of Pharmacokinetic or pharmacodynamic interactions which can benefit or limit the final therapeutic.

The present study was carried out as only a few studies are there for gastrointestinal drugs with lithium, Loperamide being a commonly used drug is important among the gastro intestinal drugs.

In psychiatric practice, Imipramine is usually combined with lithium in manic depressive psychosis and they are together termed as normo thymotics i.e. mood stabilizers.

Loperamide is an over-the-counter, peripherally-acting, μ-opioid receptor agonist commonly used in the treatment of diarrhea. As loperamide with other drugs induce secondary QT syndrome, its relation with lithium is yet to be find.

Polypharmacy in the bipolar affective disorders is a common practice. As majority of patients require Supplement anti-depressants, anti-manic, anti-Psychiatric and phobia medication. This combination itself for the life-threatening adverse drug reaction. Keeping in mind the above scenarios, even the drugs for common ailments can alter the lithium levels if repeatedly used.

Material and Methods

The study was conducted in 30 normal human volunteers of either sex who were physically healthy. The volunteers were divided into 3 groups

of 10 each and drugs were administered as per table 1.

Drug used were:

- Lithium Carbonate - (LiCab, Torrent 300mg tablets)
- Imipramine hydrochloride (Depsonil, SG Pharma 25 mg tablets)
- Loperamide (Diarlop, Jagson Pal 2 mg tablets)

Trial Design:

Table 1: Drug administration protocol:

Group	(-60 min)	0hr	
I		Lithium 900mg	
II		Lithium + Imipramine 900mg	25mg
III	Loperamide (2mg)	Lithium + Imipramine 900mg	25mg

Table 1: After overnight fast, Lithium (900 mg) & Imipramine (25 mg) were administered to each volunteer with 200 ml water except in group I where only Lithium was administered. In group III, Loperamide was administered 1 hour prior to Lithium administration.

Methods of collecting the blood sample: Under aseptic conditions, in an accessible vein of the forearm of the volunteers Jelco cannula was inserted. The first blood sample (0 hrs) was withdrawn at the same time and then heparin (1 ml) was injected to maintain the patency of cannula. Serially all the blood samples were collected at ½ hr, 1 hr, 4 hr, 6 & 24 hr. After 6 hrs sample, Jelco cannula was taken out and volunteer was sent back home and asked to come back again at 9.00 a.m. the next day for collection of the 24 hrs. sample. 1ml blood was discarded so as to remove heparin and after collecting the sample, 1ml of heparin (1:1000) was injected.

A standard breakfast was given 1 hour after lithium administration. Serum was separated after allowing. The blood to clot for an hour in the vacutainer in which it was collected and then it was centrifuged at 300 rpm. Serum levels were determined by the using Ion selective electrode (Synchron EI-Ise).

Instrument: Synchron El-Ise system is a multi-analytic discrete analyzer used to measure the concentration of electrolytes (Na. K, Cl, Li).

Instrument is standardized with known value of lithium calibrator to give us reading in mEq/1. A precise volume (50µl) serum was used to estimate the lithium.

E (at lithium electrode) = constant + slope (log Li).

The system was set to perform all the calculations internally to produce the final report. The serum data was analyzed for various pharmacokinetic parameters (K_{el}, $t_{½}$, AUC) using one compartment model (Shargel, 1941). Peak plasma concentration (C_{max}) and time to reach maximum concentration (T_{max}) were noted directly from the raw data.

Standard plasma concentration vs time graph as plotted to calculate various parameters, like rate constant of elimination from the terminal part of the graph (K_{el}), half-life of elimination (t_{el}), area under plasma concentration time graph (AUC) by trapezoidal rule (Rowland and Tozer, 1996).

Statistical Analysis: Mean, standard deviation (SD) and standard error of mean (SEM) of all the parameters of the fifty patients divided in the five group of ten each were calculated. The comparisons were then made with the Lithium alone, Lithium and Imipramine and the lithium and Imipramine and Loperamide. Unpaired t-test was applied and significance was determined from the t-table. Results were taken be significant if p was found to be less than 0.05 at the 18 ($n_1 + n_2 - 2$) degrees of freedom

Observations: The serum concentration assayed and various Pharmacokinetics like C_{max}, t_{max}, k_{el}, $t_{½}$ and AUC were calculated for each volunteer.

Group- I (Lithium): The mean serum lithium concentration at various time intervals is shown in Table 2. The peak plasma concentration of 75mEq was attained in 1 h and followed by a fall which continued throughout the 24 h observation period. Fig 1 shows the concentration time graph of lithium.

Lithium concentration (mEq/1) after a single dose of lithium versus Lithium + imipramine versus Lithium + Imipramine + loperamide (n=30) are tabulated in table2

Group- II (Lithium and Imipramine): The comparison of mean lithium concentration versus lithium and Imipramine versus lithium imipramine and loperamide is shown in table 3 while parameters are compared in table 4.

The treatment with Imipramine produced a significant decrease in C_{max} ($P<0.01$), increase in t_{max} ($P<0.001$) and a significant fall in AUC ($P<0.001$) of lithium. There was no significant change in K_{el} and hence no change in t 1/2 was observed. Direct calculation of K_{abs} was not performed as there was only one data point between 0 time and C_{max}.

Group- III (Lithium + Imipramine + Loperamide): The mean Lithium concentration is shown in Table 9 and significant change in Gp-1 (LI) versus group V (LI + IMP + LOP) in plasma concentration at ½ h ($P<0.01$), 1 h ($P<0.001$) and at

2h (P<0.01) has been observed while in comparison to Gp- II (LI + IMP) only significant fall in concentration at initial (P<0.05) at 2h (P<01) have been observed. Loperamide is accentuated the Imipramine induced fall in serum lithium concentration as shown in Fig 5 at all the sampling point except at 4 h. the diffrences was statistically significant at 1, 2 and 24 h (P<0.05). Loperamide also produced a non-significant reduction in C_{max} and a significant increase in t_{max} (P<0.01).

Loperamide increase K_{el} and reduced the half-life (P<0.01) when compared with lithium alone. AUC was further reduced in the group III (LI + IMP + LOP).

Table 2: Lithium concentration (mEq/1) after a single dose of lithium versus Lithium + Imipramine versus Lithium + Imipramine + Loperamide (n=30).

Time (h)	Group-I Lithium	Group-II Lithium + Imipramine	Group- III Lithium + Imipramine + Loperamide
0	0	0	0
0.5	0.29 ± 0.018	0.22 ± 0.025*	0.20 ± 0.017**
1	0.75 ± 0.013	0.52 ± 0.031***	0.39 ± 0.042***#
2	0.68 ± 0.017	0.60 ± 0.61**	0.48 ± 0.043***##
4	0.61 ± 0.08	0.48 ± 0.021***	0.51 ± 0.050*
6	0.48 ± 0.023	0.36 ± 0.025***	0.32 ± 0.0.8 ***
24	0.26 ± 0.022	0.17 ± 0.011***	0.12 ± 0.014***#

***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 3: Pharmacokinetic parameters of Lithium versus Lithium + Imipramine versus Lithium + Imipramine + Loperamide (n=30).

Pharmacokinetic Parameters	Group-I Lithium	Group-II Lithium + Imipramine	Group- III Lithium + Imipramine + Loperamide
C_{max}(mEq/1)	0.75 ± 0.01	0.62±0.016**	0.54±0.039***
t_{max}(hrs)	1 ± 0.0	2.1 ± 0.23***	3.4 ± 0.305***##
K_{el}(hrs^{-1})	0.039±0.0026	0.049 ± 0.0041	0.063±0.006**
$t_{½}$(hrs)	18.19±1.2053	14.97 ± 1.0422	11.85±1.129**#
AUC (mEq.h/1)	17.01±0.7586	11.01 ± 0.5933***	8.80±0.759***##

***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**

In table 3 highly significant change in Gp-1 (LI) versus Gp-3 (LI + IMP + LOP) in C_{max}, t_{max}, k_{el}, $t_{½}$ and AUC, K_{abc} (P<0.001) is seen there. While change in t_{max}, k_{el}, t_{max} (P<0.001) and AUC (P<0.01) have been seen.

Discussion

As studies proving the effect of various drugs on absorption of lithium are very few. Propantheline has been shown to increase the time to achieve maximum concentration (tmax) while reducing the peak plasma concentration (Cmax) indicating a reduction in the absorption rate of lithium. Change in AUC was small, indicating little effect on the extent of absorption [1]. Only 900mg of lithium was administered and Cmax was achieved as 1 h, indicating rapid absorption of lithium. This corresponds to many published reports that with conventional dose, lithium absorption is rapid while peak is attained in 0.5-3 h after single oral dose [2]. While in one report on 6 normal human volunteers where two preparations, conventional and sustained release was compared and wide variation has been and lower peak plasma concentration (Cmax) was attained. Here the author has opined that small number of volunteers, extremes of age and poor dietary control were the reasons [3].

Moreover, it has not been demonstrated clearly whether this is a drug specific effect or a non-specific effect due to alteration in the gastrointestinal motility.

1. As Imipramine significantly lowered the peak plasma concentration to (P<0.001) and delayed the attainment of peak plasma concentration i.e. increase in tmax of lithium when administered along with it (P<0.05).

The interaction of lithium and Imipramine is less studied but the combination is very popular and widely used [4] This is probably because of anticholinergic effect of Imipramine as it results in allowing in gastric emptying and increases transit time as lithium stays for more time in stomach but absorbed in intestine resulting in decreased rate and extent of absorption [5] manifested by decreased Cmax increase Cmax and AUC. However, there was no effect on Kel and AUC.

2. Loperamide appears to have added to the significant antimuscarinic effects of Imipramine

resulting in decrease in lithium absorption. Since there is a ceiling on the effects of competitive antagonists, a marked synergistic action could not have taken place.

3. The study thus demonstrates that antimotility drugs affect Imipramine induced decrease in lithium bioavailability along the expected lines and may result in toxicity or decrease in therapeutic efficacy of lithium thus possibility of drug interaction must be observed in prescribing drug affecting the gastrointestinal (GI) motility to the patients on lithium therapy with or without Tricyclic antidepressants (TCAs).

4. In addition, it appears to prepare sustained released (SR) preparation of lithium to retard its absorption and thus lower the Cmax which may be responsible for at least dome of the adverse drug reactions of lithium.

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