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# BULLETIN ON ADVERSE DRUG REACTIONS

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## Letter from the Editor

*Dear Friends and Colleagues*

*I am happy to present to you the third and the final issue of the year of the 'Bulletin on Adverse Drug Reactions'.*

*In this issue we have included articles on Pharmacogenetics and Therapeutic Drug Monitoring and their role in Pharmacovigilance.*

*We are thankful to the Medicine department to provide the case study on Lithium toxicity for this issue which has been discussed in details. To add to it we have also included some related case studies on Lithium toxicity, published in international journals, for your ready information.*

*Other topics are also included with the intention of providing some more relevant information on drugs for their safer use in the patients.*

*I hope the readers would find the articles interesting and the information utilizable in their clinical practice.*

*I would also like to inform that we would be starting a series on vaccines and ADRs, in the issues next year, as per the suggestions from the Paediatrics department of other state medical colleges.*

*Finally, I would like to thank all the clinical departments for their valued contribution in Pharmacovigilance by reporting the adverse drug reactions identified in their wards and also to all the members of Department of Pharmacology for their efforts in bringing out current issue of the bulletin.*

*Thank you*

**Dr Sudhir Pawar**

# INSIGHT IN THE ROLE OF TDM IN PHARMACOVIGILANCE

Dr. Swati Patil and Dr. Smiti Mali, *Assistant Professors, Department of Pharmacology*

Therapeutic drug monitoring (TDM), the measurement and interpretation of drug concentration, has been used to individualize drug therapy since long. The International Association for Therapeutic Drug Monitoring and Clinical Toxicology defines TDM as "the measurement made in the laboratory of a parameter which, with appropriate interpretation, will directly influence prescribing procedures". Commonly, the measurement is in a biological matrix of a prescribed xenobiotic, but it may also be of an endogenous compound prescribed as replacement therapy in an individual who is physiologically or pathologically deficient in that compound.[1]

After initiating any therapy, drugs prescribed to patients produce certain effects other than the desired or expected effects which not only add to spiraling costs of medical treatments, but also cause a great deal of morbidity and mortality. Dosages should be individualized to the patients and drugs should be tailored to patient's need and not the vice versa. In cases with renal/hepatic impairment dosage adjustments must be made to prevent the adverse drug reactions.[2]

The indications for drug monitoring are enlisted in table no. 1

**Table 1:** Reasons for requesting drug concentration[3]

- Toxicity suspected-toxic concentrations?
- Potential drug interaction due to change in co medications
- Manifestations of toxicity and disease state are similar
- Change in clinical state of the patient
- Lack of response-sub therapeutic concentrations?
- Assessment of compliance with medication regimen
- Assess therapy following a change in dosage regimen
- Therapy cessation monitoring

Plasma drug concentration measurements alone may be helpful in several circumstances, although each indication may not apply equally to every drug, like prodrugs, hit & run drugs and drugs with irreversible actions.

**Basic principles of TDM:**

The aim of TDM is to optimize pharmacotherapy by maximizing therapeutic efficacy, while minimizing adverse events, in those instances where the blood concentration of the drug is a

better predictor of the desired effect(s) than the dose. The reasons why these principles have gained wide acceptance include:

- A better relationship, although imperfect, often exists between the effect of a given drug and its concentration in the blood, than between the dose of the drug and the effect.
- A recognition that inter-patient variability in the pharmacokinetic processes of drug absorption, distribution, metabolism and excretion results in a need for dosage individualization.
- The development of reliable and relatively easy-to-use drug monitoring assays.

In addition, TDM can aid in dosage adjustment that is required because of drug-drug or drug-food interactions as well as in situations where unintentional overdose is suspected. However TDM is of modest value when plasma level of the drug and its clinical effect has weak correlation.[4]

While conducting TDM for any drug, attention must be paid to the timing of blood sampling, the type of blood sample, the measurement technique and the interpretation of results.[5]

Saliva has been advocated as an alternative matrix to serum and there are many advantages to saliva as a matrix viz. its collection is simple and non-invasive and importantly measured concentrations reflect the free drug (pharmacologically relevant) concentration in blood. Saliva sampling has drawbacks like difficulty in measuring low concentration of drug, contamination with drug residue in the mouth and dubious results due to chemical nature of compound being measured.[6]

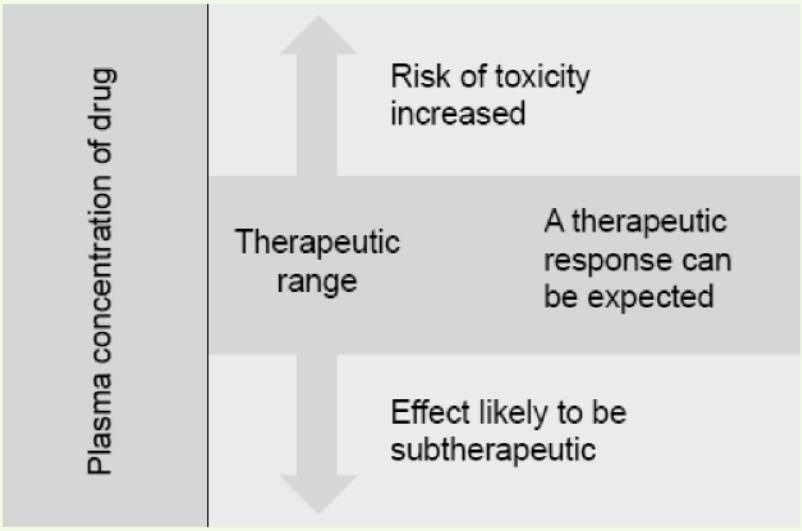
**TDM for Pharmacovigilance:**

TDM is essential in avoiding toxicity of drugs with narrow therapeutic range (Fig.1). TDM for drug monitoring holds promise when the drug toxicity simulates the flaring of underlying disease. The classic example being, digoxin toxicity that may mimic certain symptoms of heart disease and measuring the plasma concentration may prove beneficial. Similarly, nephrotoxicity of aminoglycoside antibiotics is difficult to distinguish clinically from that caused by a severe generalized infection which could be clarified with TDM assays.[5]

TDM is also of great value to obtain plasma digoxin concentration in patients with borderline renal function, in aged subjects, and in patients with rapid atrial fibrillation who require higher digitalis doses for heart rate control.[7]

On the other hand, for drugs like phenytoin it is relatively easy to recognize its acute toxicity and measuring the plasma concentration may not be necessary for diagnosis. TDM may still be helpful in adjusting the dosage subsequently.[5]

**Figure 1:** Therapeutic range.[5]




Drug monitoring may guide in subsequent dosage changes when drug interaction is suspected as in case of concomitant administration of thiazide diuretic to patient taking lithium where measuring the plasma lithium concentrations is helpful to avoid toxicity.[5,8]

As pharmacokinetic disposition of drugs differs widely in varied age groups, therapeutic drug monitoring in the newborn infant is necessary as they differ in kinetic disposition when compared to the older children. Similarly, the small size of these patients may make them vulnerable to medication errors which could lead to morbidity and even mortality.[9] TDM could prove as a valuable asset in preventing toxicity and aid in pharmacovigilance.

In addition to above illustrated examples TDM could be important in pharmacovigilance of some other drugs like:

**Anti-epileptic drugs (AED):**

In patients with epilepsy who are on polytherapy and exhibit signs of overdosage, measuring the concentration of the individual AEDs can aid in determining which drug is more likely to be responsible for the toxicity. During overdose, sampling should be undertaken as soon as the patient presents at an emergency department but repeated sampling might be necessary, depending on the timing of the overdose.[6]

**Psychiatric medications:**

Therapeutic drug monitoring of antidepressants allows us to take into account the influence of factors such as comedications, diet, smoking habit, impaired organ function, and compliance.[10]

TDM can help in optimizing regimes of lithium, imipramine, desipramine, nortriptyline, haloperidol and clozapine as relationship between serum concentration and efficacy or toxicity is well established.[1]

**Antimicrobials:**

TDM of aminoglycosides and vancomycin leads to a reduction in incidence of nephrotoxicity.[11] In case of antifungal like flucytosine TDM is necessary for monitoring toxicity but for Triazoles it is much important for judging the efficacy & concomitant drug interactions.[12]

**Immunosupressants:**

TDM of immunosuppressants is required because of wide inter-individual pharmacokinetic variability and risk of drug-drug interactions. Performing TDM assays is also important as there is shortage of donor organs and costs associated with rejection of a transplant is high.[4]

**Antitubercular drugs:**

Some patients are slow to respond to treatment, have drug-resistant TB, are at risk of drug-drug interactions or have concurrent disease states that significantly complicate the clinical situation. Such patients may benefit from TDM and early interventions may preclude the development of further drug resistance.[13]

**Antiretrovirals:**

Patients with HIV are at particular risk for drug-drug interactions. Published guidelines typically reflect interactions only between two drugs and do not hold true when the patient is treated with three or more interacting drugs. Under such complicated circumstances, TDM often is the best available tool for sorting out these interactions and placing the patient on necessary doses that they require.[13]

**Anticancer:**

Cancer patients are especially prone to drug-drug interactions due to significant co medication, impaired liver and kidney function and hypoalbuminemia with altered drug binding.[14] TDM is not routinely used for monitoring anti-cancer therapy except in case of methotrexate. Additional factor in antimetabolite therapy is pharmacogenetic enzymes which play a major role in drug metabolism. This is the area where pharmacogenetic oriented TDM could play vital role.[15]

Appropriate sampling time for selected drugs is elaborated in table given in the appendix below.

**TDM of future:**

In contrast to traditional TDM, which cannot be performed until after a drug is administered to the patient; pharmacogenetics-oriented TDM can be conducted even before treatment begins. Other advantages are (i) it does not require the assumption of steady-state conditions (or patient compliance) for the interpretation of results; (ii) it can often be performed less invasively (with saliva, hair root or buccal swab samples); (iii) it can provide predictive value for multiple drugs [e.g. a number of cytochrome P450 (CYP) 2D6, CYP2C 19 or CYP2C9 substrates] rather than

a single drug; (iv) it provides mechanistic, instead of merely descriptive, information; and (v) it is constant over an individual's lifetime (and not influenced by concurrent drug administration, alteration in hormonal levels or disease states.[16]

Physicians should consider TDM as a tool to establish causality of adverse drug reaction and prevent toxicity whenever necessary. Hence TDM can play a pivotal role in designing of tailored medicine.

**Appendix:**

Recommendations for sampling time for selected drugs:[17,18]

| Sr. | Drugs | Time for sample collection |
|---|---|---|
| 1. | Gentamicin | At steady-state (at least four half-lives).<br>Pre sample: within 30 min of the next dose.<br>Post sample: 30 min after 30 min IV infusion, or 30 min to one hour after IV bolus. |
| 2. | Digoxin | At steady-state: eight days (normal renal function).<br>Trough: before next dose.<br>At least 6 h after the last dose. |
| 3. | Carbamazepine | At steady-state: 2-4 weeks after initiation of treatment or 3-5 days after change in dose regimen or 1-2 weeks after addition or discontinuation of a known enzyme inducer.<br>Sampling: trough - within 2 h before next dose.<br>Anytime, if toxicity is suspected. |
| 4. | Phenobarbital | At steady state: 2-3 weeks after initiation of treatment.<br>Sampling: trough - within 2 h before the next dose.<br>At least 3 h after the last dose during the dosing interval.<br>Anytime, if toxicity is suspected. |
| 5. | Phenytoin | Sampling time: trough - within 2 h before next dose.<br>Anytime during the dosing interval.<br>After a loading dose: at least 2 h post loading.<br>Anytime, if toxicity is suspected. |
| 6. | Valproate | At steady state: at least 2-4 days after initiation or change in dose regimen<br>Sampling time: trough - within 2 h before next dose<br>Anytime, if toxicity is suspected. |
| 7. | Lithium | 12 hr sample gives precise guidance for dose adjustment. |

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## SUMMARY OF ADRs IN LTMMC & LTMGH
## (August 2011 to November 2011)

| Sr. No. | Adverse Drug Reaction | Suspected Drugs | Causality Assessment | Literature Documentation |
|---|---|---|---|---|
| 1 | Bleeding | Warfarin, Rosuvastatin | Probable-Warfarin | Well documented |
| 2 | Hepatotoxicity | Isoniazid, Rifampicin, Pyrazinamide, Ethambutol | Possible | Well documented |
| 3 | Per Rectal Bleeding | Warfarin, Aspirin | Possible-Warfarin, Aspirin | Drug Interaction documented |
| 4 | Acute Renal Failure | Rifampicin, Streptomycin | Possible | Well documented |
| 5 | Stevens -Johnson Syndrome | Lamotrigine, Lithium, Armodafinil, Propranolol | Possible | Well documented |
| 6 | Rash | Rifampicin, Streptomycin, Pyrazinamide | Certain-Rifampicin, Pyrazinamide, Possible - Streptomycin | Well documented |
| 7 | Angioedema | Levofloxacin | Probable | Well documented |
| 8 | Rash | Cefixime | Probable | Well documented |
| 9 | Hepatotoxicity | Isoniazid, Rifampicin, Pyrazinamide, Nevirapine | Possible | Well documented |
| 10 | Rash | Isoniazid, Rifampicin, Ethambutol, Pyrazinamide, Nevirapine | Possible | Well documented |
| 11 | Pancreatitis | Stavudine, Lamivudine, Nevirapine | Possible | Well documented |
| 12 | Rash | Ethionamide, Cycloserine, Clofazimine, Kanamycin | Possible | Well documented |
| 13 | Pedal Oedema | Kanamycin | Possible | Well documented |
| 14 | Hypokalemia | Piperacillin-Tazobactam | Probable | Well documented |
| 15 | Peripheral Neuropathy | Stavudine | Possible | Well documented |
| 16 | Leukocytosis with Eosinophilia | Thalidomide | Possible | Well documented |
| 17 | Rash | Amoxicillin | Probable | Well documented |
| 18 | Pancytopenia | Zidovudine | Probable | Well documented |
| 19 | Erythroderma | Phenytoin | Probable | Well documented |
| 20 | Rash | Amikacin, Ceftriaxone | Possible | Well documented |
| 21 | Stevens -Johnson Syndrome | Isoniazid, Rifampicin, Ethambutol, Pyrazinamide | Possible | Well documented |
| 22 | Ataxia & Nystagmus | Phenytoin | Probable | Well documented |

| Sr. No. | Adverse Drug Reaction | Suspected Drugs | Causality Assessment | Literature Documentation |
|---|---|---|---|---|
| 23 | Rash | Cefixime, Metronidazole, Paracetamol | Possible | Well documented |
| 24 | Rash | Clindamycin,Ceftriaxone Artesunate, Ondansetron | Possible | Well documented |
| 25 | Rash | Rifampicin | Probable | Well documented |
| 26 | Hepatotoxicity | Isoniazid, Rifampicin, Pyrazinamide | Possible | Well documented |
| 27 | Rash | Amoxicillin, Clavulanic acid, Artemether, Lumefantrine | Possible | Well documented |
| 28 | Hepatotoxicity | Hydroxychloroquine | Unlikely | Well documented |
| 29 | Urticaria | Diclofenac, Azithromycin, Cefixime | Possible | Well documented |
| 30 | Ecchymosis | Warfarin, Aspirin | Possible | Well documented |
| 31 | Acneiform Eruption | Methylprednisolone, Isoniazid, Rifampicin | Possible | Well documented |
| 32 | Psychosis | Isoniazid, Methylprednisolone | Possible | Well documented |
| 33 | Abnormal Jerky Movements | Bupivacaine | Possible | Well documented |
| 34 | Bradycardia | Bupivacaine | Probable | Well documented |
| 35 | Per rectal bleeding | Warfarin, Amiodarone | Probable | Drug interaction Documented |
| 36 | Urticaria | Clindamycin | Possible | Well documented |
| 37 | Headache,vomiting | Acenocoumarol | Unlikely | Well documented |
| 38 | Urticaria | Sulfadoxine-Pyrimethamine | Possible | Well documented |
| 39 | Diarrhoea | Amoxicillin-Potassium clavulanate | Probable | Well documented |
| 40 | Hypoglycemia | Human Mixtard, Pioglitazone, Metformin | Possible | Well documented |
| 41 | Pseudoallergic Reaction | Iohexol | Probable | Well documented |
| 42 | Toxic Epidermal Necrolysis | Carbamazepine | Probable | Well documented |
| 43 | Stevens-Johnson Syndrome | Nevirapine, Zidovudine, Lamivudine | Possible | Well documented |
| 44 | Hypoglycemia | Gliclazide+metformin, Sitagliptin+metformin, Pioglitazone | Possible | Well documented |
| 45 | Hypotension | Azithromycin, Furosemide | Possible | Well documented |
| 46 | Rash | Amiodarone, Heparin | Possible | Well documented |
| 47 | Rash | Artesunate, Cefotaxime, Clindamycin | Possible | Well documented |
| 48 | Hepatitis | Isoniazid, Rifampicin, Pyrazinamide, Stavudine Lamivudine, Nevirapine | Possible | Well documented |
| 49 | Angioedema | Linezolid, Cefixime | Possible | Well documented |
| 50 | Rash | Cotrimoxazole, Methotrexate, Leviteracetam, 6 -Mercaptopurine | Possible | Well documented |

# EVALUATION OF A CASE FROM LTMMC AND LTMGH

## Case of Lithium toxicity

Dr. Sachin Ambirwar*, Dr. Sangeeta Pednekar**, Dr. Deepa Korivi***,
Dr. Sonal Thakur****, Dr. N. Moulick*****

** 2nd yr resident, Dept of Pharmacology; ** Professor, Dept of Medicine; *** Asst.Professor, Dept of Medicine; **** 2nd yr resident, Dept of Medicine; ***** Professor & Head, Dept of Medicine.*

### Case report

A 57 year old female was a known case of bipolar disorder since 9 years and was receiving Tab. Lithium carbonate 800 mg/day, Tab. Divalproate 1000mg/day, Tab. Topiramate 50 mg/day and Tab. Quetiapine 50 mg/day. She was also suffering from hypertension since 5 years and was receiving Tab. Enalapril 5 mg twice a day. Patient consulted private hospital and was diagnosed for acute gastroenteritis 8 days prior to her admission to our hospital where she was put on a fixed dose oral combination of Ornidazole 500 mg and Ofloxacin 200 mg twice a day and Tab. Paracetamol 500 mg as and when required her. Her diarrhoea was not relieved and she also developed coarse tremors, altered sensorium, disorientation, confusion and nausea on 4 days after taking these medications.

She was then referred to our medical unit. On admission, temperature was 37.8°C, blood pressure 146/70 mm Hg, pulse rate 98 beats/min and respiratory rate 18 breaths/min. On physical examination, pallor and bilateral pedal edema were noticed. On CNS examination, she was drowsy and disoriented but responding to stimuli, moving all four limbs, pupils were 3 mm dilated, bilaterally equal and reacting to light. On the day of admission laboratory investigations were as follows: Sr. $Na^+$ 151 mEq/L (N:135-145 mEq/L), Sr. $K^+$ 5.4 mEq/L(N: 3.5-5 mEq/L), Sr. creatinine: 2.4 mg/dl(N:0.7-1.2), and TSH: 4.83 IU/ml ( N: 0.5 to 5.0 IU/ml). Her hypernatremia was corrected with free water. Patient continued to be drowsy and had altered sensorium. Therapeutic drug monitoring of Lithium was done and found to be 2.82 mmol/L (N: 0.6-1.2 mmol/L) which was above therapeutic range. Immediately Lithium and all previous medications were stopped. She was diagnosed with "Lithium overdose". She was put on Inj. Ceftriaxone, Inj. Pantoprazole, Inj. Ondansetron, Tab. Olanzapine, Tab. Folic acid and Ferrous sulfate, Tab. Calcium lactate. As Lithium is dialyzable, she received 2 cycles of haemodialysis each for 3 hours for 2 consecutive days and showed dramatic response to it.

On 5$^{th}$ day of admission, Sr. Lithium level came down to 0.2 mmol/L, Sr. Creatinine: 1.9 mg/dl, Free T3:1.85 pg/ml (N:1.4 to 4.4 pg/dl), Free T4: 0.89 ng/dl (N: 0.8 to 1.8 ng/dl) and TSH: 2.43IU/ml. Patient improved clinically, became conscious and was fully oriented, she had no loose motions. She was discharged on 8$^{th}$ day of admission. At the time of discharge blood

pressure was 140/90 mm/Hg and pulse rate 98 beats/ min. On discharge she was prescribed, Tab. Lithium 400 mg once a day after taking psychiatry opinion along with Tab. Valproate 500 mg once a day, Tab. Quetiapine 25 mg once a day and Tab. Amlodipine 5 mg twice a day for hypertension. On follow up after 15 days, patient was symptomatically well.

**Discussion**

Lithium remains a mainstay of treatment for bipolar disorder but dose individualization, measurement of serum drug concentrations and monitoring for adverse reactions are vital in order to maximize therapeutic response. Lithium however has a narrow therapeutic index (therapeutic level 0.6-1.2 mEq/L).[1] Lithium functions as a mood stabilizer in patients with bipolar disorders. Approximately 80% of manic patients respond to acute Lithium treatment. It affects ion transport and cell membrane potential by competing with sodium and potassium. These effects may alter neuronal function. Lithium inhibits inositol metabolism, and prevents the accumulation of cyclic adenosine 5'-monophosphate. These secondary messengers (inositol and cyclic adenosine 5'-monophosphate) work through the G protein system, and alterations in their metabolism and intracellular levels probably influence neurotransmitter activity. Lithium also enhances the effect of serotonin and acetylcholine, reduces the effect of dopamine and has variable effects on norepinephrine activity in brain. Side effects of Lithium generally correlate with the patient's serum level and often present as central nervous system (CNS) manifestations. Severe neurologic sequelae may occur in patients who take overdoses.[2]

Drug interactions, changes in diet and fluid intake, illness and compliance can all markedly affect serum drug concentration reducing therapeutic response or causing toxicity.[1] Drug interactions between Lithium and Angiotensin Converting Enzyme (ACE) inhibitors as well as with Topiramate have been documented. Finley and colleagues conducted a longitudinal case-controlled study in 20 psychiatric patients to study potential interaction between Lithium and ACE inhibitors initiated for the treatment of hypertension. The authors reported an average increase of 36.1% in serum Lithium concentrations, with four patients presenting with presumed Lithium toxicity. Despite the paucity of research, the interaction of Lithium and ACE inhibitors has clinically relevant consequences. Captopril, Enalapril, and Lisinopril have all been implicated in this interaction. The precise mechanism of this interaction has yet to be determined, but varying theories are proposed, including sodium depletion and ACE inhibitor-induced renal insufficiency.[3]

On the other hand coadministration with Topiramate may increase the serum concentrations of Lithium. The exact mechanism of interaction is unknown, but may involve reduced Lithium elimination due to competition by Topiramate for renal excretion and/or sodium depletion secondary to the inhibitory effect of Topiramate on carbonic anhydrase. There have been isolated

case reports of patients treated with Lithium who developed symptoms of toxicity (e.g., impaired concentration, confusion, memory loss, lethargy, tremor, bradycardia, nystagmus) in association with elevated serum Lithium levels following the addition or increase in dosage of Topiramate.[4]

In our case, these interactions are less likely. The patient was taking both the above mentioned drugs concomitantly since 5 years and 9 years respectively. In spite of these interactions, Lithium toxicity never surfaced.

The most frequent side effect of Lithium is nephrogenic diabetes insipidus, with an estimated prevalence of 20 to 70%. Patients present with polyuria, polydipsia, and an inability to concentrate urine. Chronic treatment with Lithium results in a marked reduction in the vasopressin-regulated water channel aquaporin-2 in the apical plasma membrane of principal cells in the collecting duct and a marked inhibition of water reabsorption, even when serum Lithium levels are therapeutic. This side effect is very important clinically since patients with Lithium-induced diabetes insipidus must maintain their oral fluid intake to keep up with their urinary losses to avoid becoming volume-depleted.

Lithium toxicity typically occurs in 1 of the following 3 scenarios: 1) acute overdose in a patient who does not usually take Lithium; 2) acute overdose in a patient chronically on Lithium; and 3) chronic toxicity resulting from drug accumulation during therapeutic use.

Volume depletion increases proximal reabsorption of Lithium along with Na thus placing the patient at risk for acute on chronic Lithium toxicity.

In our case toxicity precipitated following the episodes of diarrhea which might have resulted in decrease in circulating volume, which stimulated proximal tubule sodium reabsorption resulting in increased serum Lithium level. Measurement of blood electrolytes can reveal a high sodium level (hypernatremia) as dehydration develops, which probably also explains the hypernatremia seen in our case also.[2]

Thus though certain drug interactions are well known, attention should also be paid to trivial factors which might precipitate severe reactions.

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# PUBLISHED CASE REPORTS ON LITHIUM TOXICITY

## Ataxia from Lithium toxicity successfully treated with high-dose buspirone: a single-case experimental design

*Arch Phys Med Rehabil. 2001 Aug;82(8):1145-8.*
*Megna J, O'dell M*

Injury to the cerebellum commonly results in clumsiness or uncoordinated movement, which is referred to as ataxia. The severity of ataxia varies according to the extent of the lesion. Severe ataxia usually restricts activities of daily living, impairs mobility, and increases level of disability.

Recent studies investigating use of serotonin agonists in the treatment of ataxia have produced mixed results; however, buspirone with an affinity specific to the 5-hydroxytryptamine (1A) subreceptors has shown promise.

In this brief report, we use a prospective, open, single-case experimental design to describe substantial subjective and objective dose-dependent improvement of ataxia after unusually high doses of buspirone taken by a patient whose severe ataxia was due to Lithium toxicity.

## Alert: inaccurate Lithium assay results

*Aust N Z J Psychiatry. 2008 Jul;42(7):643-5.*

*Parker G.*

**OBJECTIVES:** A patient who had experienced bipolar disorder for over 20 years and who had been euthymic for most of that period while highly compliant with Lithium, had falsely low Lithium levels reported over two periods, 6 years apart, and was actually Lithium toxic on the most recent occasion. At that latter time the spuriously low Lithium levels reported on the assay risked dispelling any clinical suspicion of Lithium toxicity, although toxicity was later confirmed.

**METHOD:** Case report.

**RESULTS:** The latter incident identified a serious problem, whereby it is likely that the particular assay risks generating spuriously low values when high serum levels of Lithium are present--a so-called 'hook phenomenon' that has been described for some quantitative immunoassays.

**CONCLUSIONS:** It is in situations of high potential gravity--when Lithium toxicity is present--that Lithium quantification is most likely to be compromised and low values generated. Also of grave concern is the fact that there are no regulatory processes in place to communicate this problem to Lithium prescribers.

**Neonatal Lithium toxicity as a result of maternal toxicity**

*Vet Hum Toxicol. 1997 Apr;39(2):92-3.*

*Flaherty B, Krenzelok EP.*

**Abstract**

Lithium carbonate is used for the treatment of bipolar disorder. Because of its widespread use, many women of childbearing age are taking Lithium carbonate, which belongs to the US FDA Category D. Administration during pregnancy can result in fetal toxicity. A 17-y-old female with pre-eclampsia and a history of manic depression gave birth to an infant at 37-w gestational age. Several hours prior to delivery, the mother had a Lithium level of 2.6 mEq/L. The infant's initial Lithium level after birth was 2.1 mEq/L. A subsequent Lithium level on the 3rd day of the child's life was 1.4 mEq/L; the half-life in the infant was > 24 h. During the first 4 day of life, the infant was lethargic and exhibited poor suck-swallow coordination that required supplemental enteral feeding. By the 7th d of life, the infant was alert and tolerating all oral feedings. Lithium carbonate readily crosses the placental barrier and can produce teratogenic effects and toxicity. Neonates exposed in utero should be carefully monitored for symptoms of toxicity. In this case only minor toxic effects occurred.

**Cerebellar syndrome in a patient with pneumonia under Lithium treatment: A case report**

*Prog Neuropsychopharmacol Biol Psychiatry.* 2006;30(8):1532-4. Epub 2006 Jun 23.

*Ozsoy S,* Basturk M, Esel E.

**Abstract**

We report the case of a 31-year-old man with bipolar disorder who was on a combination therapy of Lithium, Lamotrigine and Escitalopram. Serum Lithium level was within therapeutic range. Cerebellar symptoms such as dysarthria, ataxia, and dyskinesia developed in the patient following the pneumonia. Cerebellar syndrome was most likely due to Lithium neurotoxicity, which was associated with additional factors such as acute febrile pneumonia, fever and hyponatremia. The reported case suggests that infections may increase the risk of cerebellar toxicity of Lithium, even in the therapeutic doses.

# PHARMACOGENETIC AND ANTI-EPILEPTIC DRUGS

Dr. James John, *3rd yr resident, Dept of Pharmacology*

Epilepsy is a common chronic neurological disease, of which the worldwide prevalence is estimated to be 0.6-1.0%. There are approximately 15 antiepileptic drugs (AEDs) currently available for the treatment of epilepsy, and several new drugs in the pipeline. All have been shown to be efficacious in trials, but their efficacy and adverse drug reaction (ADR) profiles are generally unpredictable in an individual patient. Pharmacogenetics addresses the genetic component of such patient variability.[1]

Common ADRs to AEDs are given in Table 1.

**Table 1:** Antiepileptic drugs with usual ADRs[2]

| **Antiepileptic drug** | **Common and specific ADRs** |
|---|---|
| Phenobarbital | Sedation, depression |
| Phenytoin | Ataxia, vertigo, gum hypertrophy, hirsutism, megaloblastic anaemia, fetal malformation, hypersensitivity reactions |
| Carbamazepine (CBZ) | Sedation, ataxia, blurred vision, water retention, hypersensitivity reactions, leucopenia, liver failure (rare) |
| Valproic acid | Nausea, hair loss, weight gain, fetal malformations |
| Ethosuximide | Nausea, anorexia, mood changes, headache |
| Lamotrigine | Dizziness, sedation, rashes |
| Felbamate | Aplastic anaemia and liver damage (rare but serious) |
| Vigabatrin | Sedation, behavioural and mood changes,visual field defects |
| Topiramate | Sedation, nephrolithiasis |
| Benzodiazepines, Gabapentin, Tiagabine, Levetiracetam, Zonisamide | Sedation |

**Pharmacogenetics associated with idiosyncratic adverse reactions[3, 4]**

Although relatively rare, idiosyncratic drug reactions are a well known problem with AED treatment and are important because they put the patient at significant and potentially life threatening risks. The best known examples are the hypersensitivity syndrome induced by aromatic AEDs (Phenytoin, Phenobarbital and Carbamazepine) and Lamotrigine and Felbamate-induced aplastic anemia. Although the physiological basis of idiosyncratic drug reactions is yet not entirely elucidated, it is thought that they are immune-mediated, probably involving the formation of reactive metabolites.

It is likely that genetic factors play a role in an individual's predisposition to develop an idiosyncratic drug reaction. Candidate genes are those encoding the enzymes - mainly CYP isoenzymes or microsomal epoxide hydrolase [mEH], and genes encoding components of the immune system. There is evidence supporting the view that such cutaneous adverse reactions involve major histocompatibility complex (MHC)-dependent presentation of its metabolites for T cell activation. The HLA-B allele can elicit immune responses by presenting endogenous antigens to the cytotoxic T cells, resulting in proliferation of the cytotoxic cells.

Two associations of immune response genes with severe ADRs in patients on AEDs have been reported. An association was identified between the TNF2 allele of the TNFα gene, resulting in elevated expression of TNFα, and CBZ hypersensitivity. An exceptionally strong association has been found between the HLA-B*1502 allele, among people of Asian origin, and development of Stevens-Johnson syndrome on carbamazepine therapy. The FDA recently issued recommendations for screening of people of Asian origin for the HLA-B*1502 allele before initiating treatment with Carbamazepine. It recommended that those Asians who tested positive for the allele should avoid exposure to Carbamazepine.

The highest frequency of expression of the allele outside India have been reported among Filipinos (from Philippines), Chinese from Taiwan, mainland China and Hong Kong and among the Thai and Malaysians, in whom frequency is in the order of 10-20%. Within India, in the ethnic population from Kandhesh Pawra in Maharashtra, in Western India, the frequency of expression of this allele is as high as 6%. In Mumbai the frequency is 1.9%, while in North Indian populations from Delhi and Punjab, the frequency of expression is about 1%.[4]

The median duration of developing Carbamazepine induced SJS/TEN is 25 to 90 days. Patients who have been taking Carbamazepine for more than 3 months without developing skin reactions are at low risk of Carbamazepine-induced cutaneous reactions. However, it should be noted that patients who are tested positive for HLA-B*1502 may be at increased risk of SJS/TEN from other antiepileptic drugs namely Lamotrigine, Phenytoin and Phenobarbital and so it is probably advisable to avoid other antiepileptic drugs also known to cause SJS/TEN.

**Pharmacogenetics affecting plasma concentration/response for AED**

There are three main categories of candidate genes [5]

- Genes encoding drug transporters of which AEDs are known substrates
- Genes encoding drug-metabolizing enzymes (DMEs) involved in the breakdown of AEDs
- Genes encoding AED targets

**Drug transporters**[3]

Functional polymorphisms in genes encoding drug transporters can be expected to alter AED uptake, cerebral distribution or efflux, and thus result in interindividual differences in AED concentration. The two principal families are the multidrug resistance proteins (MDR or ABCB) and the multidrug resistance associated proteins (MRP or ABCC). They act as active efflux

pumps and may pump AEDs back from the brain into the blood, and perhaps from blood into the gut, thus lowering the concentration of AEDs and contributing to AED resistance. Other multidrug resistance proteins shown to be upregulated in human refractory epileptic tissue are the Cisplatin resistance-associated protein (hCRA-a) and major vault protein (MVP).

### Drug-metabolizing enzymes [1,3,6]

Functional variants in the encoding genes are expected to result in interindividual differences in the rate of AED metabolism. The main candidate genes in this category are those encoding the different enzymes of the CYP superfamily. The most studied in this category is CYP2C9, which accounts for up to 90% of the metabolism of phenytoin.

### AED targets[3]

As several first-line AEDs are known to act through binding to the sodium channel α-subunit, genes encoding sodium channels are the most obvious candidates in this category. Other major AED targets include potassium channels, calcium channels, GABA and glutamate receptors, GABA transporters and GABA transaminase.

The following table summarizes the important pharmacogenetic association of anti-epileptic drugs.

**Table 2 :** Pharmacogenetics and epilepsy [1,3]

| Gene category | Gene | Phenotype | Association |
|---|---|---|---|
| **Transporter** | MDR1 | Drug response | Refractory epilepsy.<br>Higher doses of phenytoin and carbamazepine required. |
| **Drug metabolizing enzyme** | CYP2C9 | Plasma concentration | Phenytoin CNS toxicity.<br>Lower doses required of Phenytoin, Phenobarbital and Carbamazepine |
| | CYP2C19 | Plasma concentration | ↑/↓ dose of Phenobarbital, Valproate, Zonisamide. |
| | mEH | Adverse reactions<br>Plasma conc. | Risk of craniofacial abnormalities with Phenytoin.<br>↑/↓ Carbamazepine maintenance dose. |
| | GST | Adverse reactions | Mild hepatotoxicity with Carbamazepine and valproate |
| | UGT | Plasma conc. | ↑/↓ maintenance dose of Lamotrigine |
| **Drug target** | SCN1A | Drug response | Refractory epilepsy.<br>Higher doses of Phenytoin and Carbamazepine required |
| | SCN1B | Phenytoin sensitivity | Low maximal tolerated dose of Phenytoin |
| | SCN2A, 3A, 8A, 1B, 2B | Drug response | Refractory epilepsy. |
| | CHRNA4 | Carbamazepine sensitivity | Low maximal tolerated dose of Carbamazepine |
| **Immune response** | TNFα | Adverse reaction | Carbamazepine hypersensitivity |
| | HLA-B* 1502 | Adverse reaction | Stevens Johnson syndrome with Carbamazepine |

*MDR - multidrug resistance proteins, CYP - Cytochrome P450, CNS - central nervous system, mEH - microsomal epoxide hydrolase, GST - Glutathione S-transferase, UGT - UDP glucuronosyl transferase, SCN - sodium channel neuronal voltage gated, CHRNA4 - cholinergic receptor, nicotinic, α 4-subunit, TNF - Tumor Necrosis Factor, HLA - Human Leukocyte Antigen.*

To date, the only genetic variation that appears strong enough to warrant clinical application is the association of Carbamazepine hypersensitivity with the HLA-B*1502 allele. At present, genetic factors play no role whatsoever in the choice of AED treatment. The clinician could avail of a set of genetic tests to aid his choice of AED. These tests could, for instance, include genotyping of a few polymorphisms each in one or more drug transporter genes, DMEs, AED target genes and immune-related genes. The outcome of these tests could then be converted into an individualized ranking order of AEDs. Additionally, the results could help predict which dose should be aimed for to control seizures without causing ADRs, and perhaps how quickly the dose can be increased.

**References:**

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2. Antiepileptic drugs. In : Rang HP, Dale MM, Ritter JM, Chapter, Flower RJ, Henderson G. editors, Rang and Dale's Pharmacology, 6th edition. Churchill Livingstone, 2010 : 575-588.
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## REGULATORY

### Potential Signals of Serious Risks/New Safety Information Identified by the Adverse Event Reporting System (AERS) between April - June 2011.

Dr Kalpesh Dalvi, *Assistant Professor, Dept of Pharmacology*

The table below lists the names of products and potential signals of serious risks/new safety information that was identified for these products during the period April - June 2011.

The appearance of a drug on this list does not mean that FDA has concluded that the drug has the listed risk. It means that FDA has identified a potential safety issue, but does not mean that FDA has identified a causal relationship between the drug and the listed risk.

FDA wants to emphasize that the listing of a drug and a potential safety issue on this Web site does not mean that FDA is suggesting prescribers should not prescribe the drug or that patients taking the drug should stop taking the medication.

| Product Name : Active Ingredient (Trade) or Product Class | Potential Signal of a Serious Risk / New Safety Information | Additional Information (as of July 31, 2011) |
|---|---|---|
| Anagrelide HCl and Aspirin | Drug interaction resulting in hemorrhagic events | FDA is continuing to evaluate this issue to determine the need for any regulatory action. |
| Asenapine maleate | Oral blistering, Oral ulceration, Oral erosion | FDA is continuing to evaluate these issues to determine the need for any regulatory action. |
| Bevacizumab | Osteonecrosis of jaw | FDA is continuing to evaluate this issue to determine the need for any regulatory action. |
| Colistimethate sodium for injection | Deaths due to dosing confusion and medication errors | FDA is continuing to evaluate this issue to determine the need for any regulatory action. |
| Dronedarone HCl | Pulmonary toxicity | FDA is continuing to evaluate this issue to determine the need for any regulatory action. |
| Everolimus | Acute and chronic pancreatitis, Gallbladder disorder | FDA is continuing to evaluate these issues to determine the need for any regulatory action. |
| Methotrexate sodium and Proton pump inhibitors | Drug interaction resulting in decreased elimination of methotrexate | FDA is continuing to evaluate this issue to determine the need for any regulatory action. |
| Muscarinic receptor antagonist products | Somnolence | FDA is continuing to evaluate this issue to determine the need for any regulatory action. |
| Sodium ferric gluconate complex | Anaphylactic reactions | FDA is continuing to evaluate this issue to determine the need for any regulatory action. |
| Voriconazole | Fluorosis and Periostitis with long-term use | FDA is continuing to evaluate this issue to determine the need for any regulatory action. |

**Reference:**

Potential Signals of Serious Risks/New Safety Information Identified by the Adverse Event Reporting System (AERS) between April - June 2011 [Cited 2011 December 16] Available from: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm270938.htm

## EXAMPLES OF SOUND-ALIKE AND / OR LOOK-ALIKE DRUGS NAMES PAIRS IN INDIA

| Brand Names | Generic Names |
|---|---|
| Tibitol | Ethambutol |
| Tobitil | Tenoxicam |
| Pronim | Nimesulide |
| Pronil | Fluoxetine |
| Farizym | Enzymes |
| Fasigyn | Tinidazole |
| Celib | Celecoxib |
| Celin | Vitamin C |
| Dan | Diclofenac |
| Dax | Cefadroxil |
| Eltocin | Erythromycin |
| Eltroxin | Thyroxine |
| Azod | Azithromycin |
| Azox | Alprazolam |
| Acein | Enalapril |
| Acem | Clarithromycin |
| Clomin | Dicyclomine +Paracetamol |
| Clomine | Clomipramine |
| Vizol | Multivitamin |
| Vizole | Levamisole |
| Adiflox (Ointment) | Ciprofloxacin |
| Adilox (Capsule) | Ampicillin + Cloxacillin |

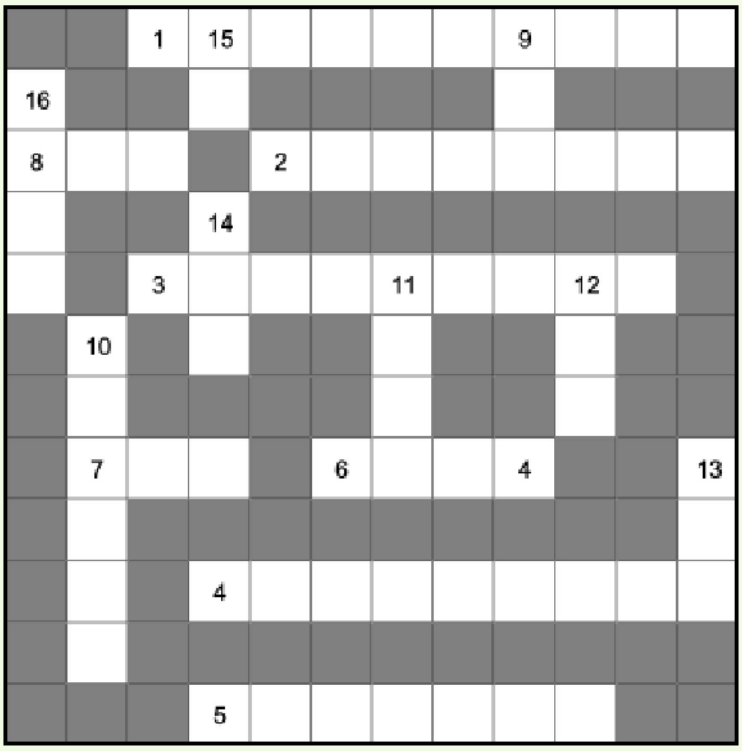
| Brand Names | Generic Names |
|---|---|
| Edegra | Sildenafil |
| Allergra | Fexofenadine |
| Hemsi | Ferrous Fumarate |
| Hemsyl | Ethamsylate |
| Maladine | Mepacrine |
| Mala-D | OCP - |
| Allerzine | Cetirizine |
| Alergin | Ephedrine + Theophylline |
| Xental 400 | Pentoxiphylline |
| Zentel 400 | Albendazole |
| Lyser-D | Diclofenac + Serratiopeptidase |
| Nizer-D | Nimesulide + Pseudoephedrine |
| Oceoh | Cefixime |
| Ocef | Cephalexin |
| Enzide | Enalapril |
| N-Side | Nimesulide |
| Normace | Enalapril |
| Normax | Norfloxacin |
| Betanate (Ointment) | Clobetasol |
| Betanase (Tab.) | Glibenclamide ' |
| Piplar (Drops) | Pipenzolate |
| Ciplar (Tab.) | Propranolol |

**Reference :**

Study of Misbranding And SALA Drugs Responsible For Medication Errors In Maharashtra And Gujarat [Cited 2011 December 16]. Available fromhttp: //www.whoindia.org/Link Files Essential Drugs Study of Misbranding and SALA Drugs Responsible for Medication Errors in Maharashtra & Gujara.pdf

# CROSSWORD

Dr. Sharmada Nerlekar *(Associate Professor Dept. of Pharmacology)*




**Across**

1. This antiepileptic can cause renal stones [10]
2. This is a unique adverse drug reaction seen with ethosuximide [8]
3. Barbiturates are contra indicated in patients with _____. [9]
4. An antiepileptic useful in controlling seizures in Lennox -Gastaut syndrome but causing aplastic anaemia in some patients is ___ [9]
5. TDM is useful for this antimanic drug [7]
6. Hydralazine induced lupus is most common in female patients with the HLA _____ haplotype [4]
7. Water retention due to carbamazepine is due to increase in _____ [3]
8. Over expression of ____ results in tumor resistance to many cancer chemotherapy agents as well as increases the risk of their adverse effects [3]

**Down**

9. TDM is of no value for 'hit and run' drugs like _____ inhibitors [3]
10. Tiagabine produces this CNS adverse drug reaction [6]
11. _____ loss is a cosmetic ADR reported with valproic acid [4]
12. This anti tubercular drug inhibits metabolism of phenytoin, thus increasing its adverse drug reactions [3]
13. In some cases DIC (disseminated intravascular coagulation) and _____ are reported with lamotrigine [3]
14. _____ phenytoin on IV injection is less damaging to the blood vessel intima [3]
15. The advantage of ____ carbazepine is that toxic effects due to epoxide metabolite are avoided [2]
16. ____ deficiency increases risk of severe bone marrow toxicity with azathioprine. [4]

---

**ANSWERS**

1.Topiramate 2. Hiccough 3.Porphyria 4.Felbamate 5.Lithium 6.DRW 4 7.ADH 8.PGP (P Glycoprotein) 9.MAO (Monomine Oxidase) 10.Ataxia 11.Hair 12.INH (Isoniazid) 13.SLE (Systemic Lupus Erythromatosis) 14.FOS (Phenytoin) 15.OX (Carbazepine) 16.TPMT (Thiopurine Methyl Transferase)

# PUZZLE

Dr. Girish Joshi* & Dr. Abhilasha Rashmi**
Associate Professor* & Assistant Professor**, Department Pharmacology.

**Match the columns A & B**

| | Column A | | Column B |
|---|---|---|---|
| 1) | Amoxapine | a) | GIT distress & Miosis |
| 2) | Vigabatrin | b) | Drowsiness, Amnesia & Urolithiasis |
| 3) | Enflurane | c) | Optic neuropathy & Blood dyscrasias |
| 4) | Quetiapine | d) | Hepatotoxicity & Seizures |
| 5) | Zonisamide | e) | Seizures & Extrapyramidal side effects |
| 6) | Buspirone | f) | Chromosomal defects in WBCs |
| 7) | Cannabis | g) | Visual field defects & behavioural changes |
| 8) | Tolcapone | h) | Hypertension & tremors |
| 9) | D-Penicillamine | i) | Cataract & priapism |
| 10) | Modafinil | j) | Hepatotoxicity & Postural hypotension |

**Answers:**

1-e; 2-g; 3-d; 4-i; 5-b; 6-a; 7-f; 8-j; 9-c; 10-h.

# PUZZLE

Dr. Girish Joshi* & Dr. Abhilasha Rashmi**
Associate Professor* & Assistant Professor**, Department Pharmacology.

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**Answers:**

1-e; 2-g; 3-d; 4-i; 5-b; 6-a; 7-f; 8-j; 9-c; 10-h.

We would like to request all the departments to contribute in ADR reporting.

Please feel free to contact us for the same.

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