ANIL AGGRAWAL'S
Internet Journal of Forensic Medicine and Toxicology
The world's first online journal devoted entirely to forensic medicine and toxicology · Published 1 January and 1 July

VOL. 1, NO. 2
Downloaded from www.anilaggrawal.com · ISSN 0972-8074 (Online) · https://www.anilaggrawal.com/ij/vol_001_no_002/pg001.html

POSTGRADUATE SECTION

CITE THIS ARTICLE
Aggrawal Anil. Lithium Toxicity - A Review. *Anil Aggrawal's Internet Journal of Forensic Medicine and Toxicology, 2000*; Vol. 1, No. 2 (July-Dec 2000): ; Published August 12, 2000,

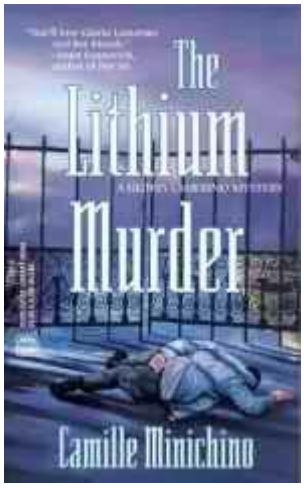
Email Dr. Aggrawal by clicking here

Lithium Toxicity - A Review

-Anil Aggrawal
Department of Forensic Medicine,
Maulana Azad Medical College,
New Delhi-110002,
India

Introduction and History

Click cover to visit Amazon to browse some interesting and useful books on this postgraduate material



Lithium salts have been used in therapeutics for quite sometime. As early as 200 A.D., the Greek physician Galen was prescribing alkaline spring baths for manic patients. Interestingly lithium is

abundant in some alkaline mineral-spring waters. In the 1850s, Lithium salts were used in the treatment of gout. The idea was that since lithium urate is highly water soluble, it would "wash away" the excess uric acid stored in the joints. It however proved worthless. In those days gout was believed to include symptoms of mania and depression, and by extension, it can perhaps be said that these salts were used for treating these symptoms as well. However it was later used "exclusively" for the treatment of psychiatric ailments, when in 1880s, John Aulde and Carl Lange observed that lithium could be used to treat symptoms associated with depression, independent of gout. However its use could never "catch on", because of the serious toxicity associated with it.

In the same era, lithium bromide was used as a sedative and anticonvulsant. In the late 1940s lithium chloride was used as a substitute for sodium chloride in heart patients. However this proved disastrous, as many persons suffered from chronic lithium poisoning, and some even died. Its use as a salt substitute was withdrawn immediately thereafter. It has also been used as a constituent of the soft drink 7-Up, which was once very popular in the US.

In 1949, a little known scientist named J.F.J. Cade in Australia "rediscovered" its use in the treatment of some mental disorders. He was looking for toxic nitrogenous substances in the urine of mental patients. He had to inject these substances in guinea pigs and see the effects. In one of the steps of these experiments, he had to administer lithium salts to guinea pigs. He noticed that the animals became lethargic. Cade immediately saw its use in manic patients, and prescribed it to them. It was met with remarkable success. However in the US, the doctors were so skeptical about it (because of earlier deaths of patients taking lithium chloride as salt substitute), that they did not use it till 1970! A case of over cautiousness undoubtedly.

Chemistry

Lithium was discovered by the Swedish scientist Johan August Arfwedson (1792-1841) in 1817, who believed it to be a new kind of alkali. Fellow scientist Jöns Jakob Berzelius (1779-1848) suggested that this substance be called "lithia" because it was obtained from the mineral petalite, which was stony in nature (Gk *lithos*, stone). Later the British chemist Humphry Davy (1778-1829), changed the name to Lithium, which stuck.

Lithium is the lightest of all metals (group Ia). Its atomic number is 3, and its molecular weight is 6.941 daltons. It is a soft, silver-white metal having a boiling point of 2448^0 F (1342^0 C) and melting point of 358^0 F (181^0 C). Its specific gravity is 0.534. It resembles sodium and potassium quite closely. In fact, it has been conjectured that this is the mechanism of action of lithium. Sodium and potassium are intimately connected with transmission of impulses in nerves, and lithium by "mimicking" these ions, may alter the neuronal membrane stability. Lithium is not known to have any physiologic role in the body, although traces of lithium are found in animal tissues.

Current use

Currently lithium salts are used in the following conditions.

1. ***Treatment of bipolar psychiatric disorders:***

   A primer on bipolar disorders might be useful before we go on further. Mood disorders (earlier known as *affective* disorders), are those disorders of the mind in which the mood swings regularly between mania and depression. Mania is a condition where there is extreme excitation, excessive elation, agitation, over talkativeness, flight of ideas, fleeting attention,

and sometimes violent, destructive or self-destructive behavior. Depression of the other hand is a condition where there is an exaggerated feeling of sadness, melancholy, dejection and worthlessness. Mania and depression are thus two "opposite poles" of the mood.

Unipolar disorders of the mood are those in which the mood remains at "one pole" as in *major depression*. In *bipolar psychiatric disorders*, the mood cyclically switches between these two poles, with the normal symptom free period (*euthymia*) between them, which may last for weeks, months or even years. If the patient is passing through a manic phase, his disorder is diagnosed as *bipolar disorder, manic* and if through a depressed phase, as *bipolar disorder, depressed*. Patients may have depressive and manic features simultaneously. For instance a patient may have extreme fatigue (a symptom of depression), along with racing thoughts (a symptom of mania). Or he may have hypersomnia (a feature of depression) along with increased sexual drive (a symptom of mania). The disorder of these patients is diagnosed as *bipolar disorder, mixed*.

Mood disorders are fairly common. It has been estimated that about 5% of the adult population in the US is suffering from clinically significant mood disorders. Interestingly, disability resulting from mood disorders, even those that are minimally symptomatic, exceeds that of most major chronic medical disorders such as diabetes, arthritis and angina.

A distinction between unipolar and bipolar disorders is important from a clinical standpoint. It has been seen that bipolar disorders respond better to lithium than unipolar disorders. When given to manic patients who characteristically sleep very little, lithium corrects the sleep disorder as the mania abates.

2. ***Treatment of Neutropenic patients:***

   To increase their WBC counts.

3. ***Chronic cluster headache:***

   As a prophylactic agent.

4. ***Thyrotoxicosis:***

   Lithium Carbonate is effective in the treatment of thyrotoxicosis, and provides an alternate therapy when conventional antithyroid regimens are contraindicated by allergies.

Pharmacokinetics of Lithium

The volume of distribution of Lithium (V_d) is 0.7 to 0.9 Liter per kilogram. It approaches that of total body water (in a normal 70 kg man, there is about 42 Liters of total body water. Thus for every kg there is 0.6 L of water in the body). Lithium is completely absorbed from the gut in 8 hours, with peak concentrations in plasma occurring in 2-4 hours after an oral dose.

Approximately 95% of lithium is excreted in urine, 4% in sweat and 1% in faeces. About 80% of the filtered lithium is reabsorbed in the proximal tubules. None is reabsorbed in distal tubules. Elimination half-life is 24 hours, which goes up to 60 hours during chronic lithium treatment.

Lithium is excreted in milk, so mothers taking lithium must not breast-feed their babies.

Mechanism of action

The mechanism of action of lithium salts is not known exactly, but there are some interesting speculations:

1. The major neurotransmitters in the CNS are norepinephrine, serotonin and dopamine. It is believed that depression is due to a decrease of these neurotransmitters at important synaptic sites in the brain, while mania is due to there excess (mnemonic: **D**epression->**D**ecreased; **M**ania->**M**ore). It is proposed that lithium acts by affecting the availability of norepinephrine at central adrenergic terminals.
2. As already mentioned, one of the hypothesis is that lithium acts by chemically "mimicking" sodium and potassium ions, which normally control nerve impulses. Its concentration gradient across the cellular membranes is much smaller than those for sodium and potassium. It may thus alter membrane stability in some way.
3. Lithium may act by altering the activity of cyclic adenine mono phosphate (cAMP)

Lithium toxicity

Lithium is mainly available as lithium carbonate (300 mg tables) and as Lithium citrate syrup. The commonly available tablets are *Licab* (Torrent) 300 mg tablets or capsules, and *Lithocarb* (Merck) 300 mg capsules. The therapeutic index of lithium is very low, approaching almost 2-3). Because of its low therapeutic index, plasma lithium concentrations in patients receiving lithium have to be monitored very carefully. Almost every week the plasma lithium concentration may have to be determined and dosage adjusted accordingly. Optimal concentration is supposed to be between 0.8 and 1.25 mEq per liter. This concentration is achieved by 900-1500 mg of lithium carbonate per day or about 3-5 tablets per day. The following table gives some useful figures regarding lithium toxicity.

TABLE SHOWING SOME IMPORTANT FIGURES RELATED TO LITHIUM TOXICITY

Severity of symptoms	**Toxic Stage**	**Serum lithium concentration (mEq/L)**	**Tablets of *Lithocarb* required to achieve this concentration**
No toxicity (therapeutic)	0	0.4-1.3	3-5
Mild toxicity	I	1.5-2.5	6-10
Serious toxicity	II	2.5-3.5	9-15
Life threatening toxicity	III	>3.5	20

Adapted and Modified from "Clinical Management of Poisoning and Drug Overdose, 2nd Edition 1990. Edited by Lester M. Haddad and James F. Winchester. *W.B. Saunders Company*, Page 658 .

Thus a total of 20 tables taken at a time may be sufficient to kill a person.

Lithium may begin its own vicious cycle of toxicity in a very interesting way. It is known to antagonize the effects of antidiuretic hormone (ADH). Thus the urine output may increase and the

patient may be dehydrated. To compensate for this, there may be more tubular reabsorption of water in the proximal tubules, with associated increased reabsorption of lithium, and consequent toxicity.

Symptoms and signs of Lithium toxicity

Lithium toxicity can occur as a result of acute ingestion of several tablets together (generally more than 20), or it may be a side effect that occurs when a person's lithium level is too high. It can be caused by an abrupt change to a low salt diet, prolonged vomiting or diarrhea, taking too much lithium at once, or fasting. Symptoms can include mental confusion, slurred speech, vomiting, poor coordination, muscle twitching, severe tremors, severe diarrhea, trouble walking or severe drowsiness.

Fatal dose

There is no direct data. But extrapolation from the available clinical data would indicate that about 20 tablets of a lithium salt, or about 6 g should be the fatal dose.

Fatal period

Variable. May vary from one to several days

Post-mortem findings

No characteristic findings are visible. About the only important finding is a high serum lithium concentration, which should be above 3.5 mEq/L

Medicolegal importance

1. ***Homicide:***

   Lithium has never been used for homicidal purposes. At least the available literature does not show a single case of homicide by lithium. But the fact that its taste is salty (not an abnormal taste), and that its fatal dose is not very high, the possibility of homicide by lithium can not be ruled out. When the history of the patient shows the symptoms mentioned above, lithium toxicity should be suspected, and a serum lithium examination should be ordered.

2. ***Suicide:***

   Cases of suicide due to lithium are on record. This is a very real possibility and should be kept in mind by a forensic pathologist conducting post-mortems on suspicious deaths.

3. ***Accident:***

   Accidental poisoning by lithium tablets is not very common, but can occur.

4. ***Liability of a doctor:***

   A doctor should ensure that the stock of lithium tablets is never with the patient, who can take the tablets together in an attempt to kill himself. Or a misguided attempt by him to take several tablets together in a vain attempt to "get well quick" may cause accidental poisoning. The doctor may be held liable for this. He should give specific instructions to the relatives of the manic patient to keep the tablets with him, and give the tablets to him as advised. It

would be advisable if the doctor gives these instructions to the patient's relatives in writing and keeps a duplicate record with himself.

Conclusion

Lithium is a little talked about poison, which is surprising as serious toxicity can occur because of this poison. The current review highlights the medicolegal importance of lithium.

References

The reader is well advised to visit the following sites for additional information on lithium toxicity.

1. DISEASE OF THE MONTH - Lithium Intoxication
2. About Lithium NDI
3. Lithium I
4. Lithium II
5. Lithium III
6. Lithium IV
7. Fact sheet - Lithium
8. Lithium - A practical guide
9. Lithium Toxicity

View this book on Amazon View this book on Amazon View this book on Amazon View this book on Amazon View this book on Amazon

Click covers to purchase these excellent books on Lithium and Lithium toxicity at Amazon.com at a discount from this site.

Please the linked page (pg) to visit the cumulative index of postgraduate material appearing in this journal.