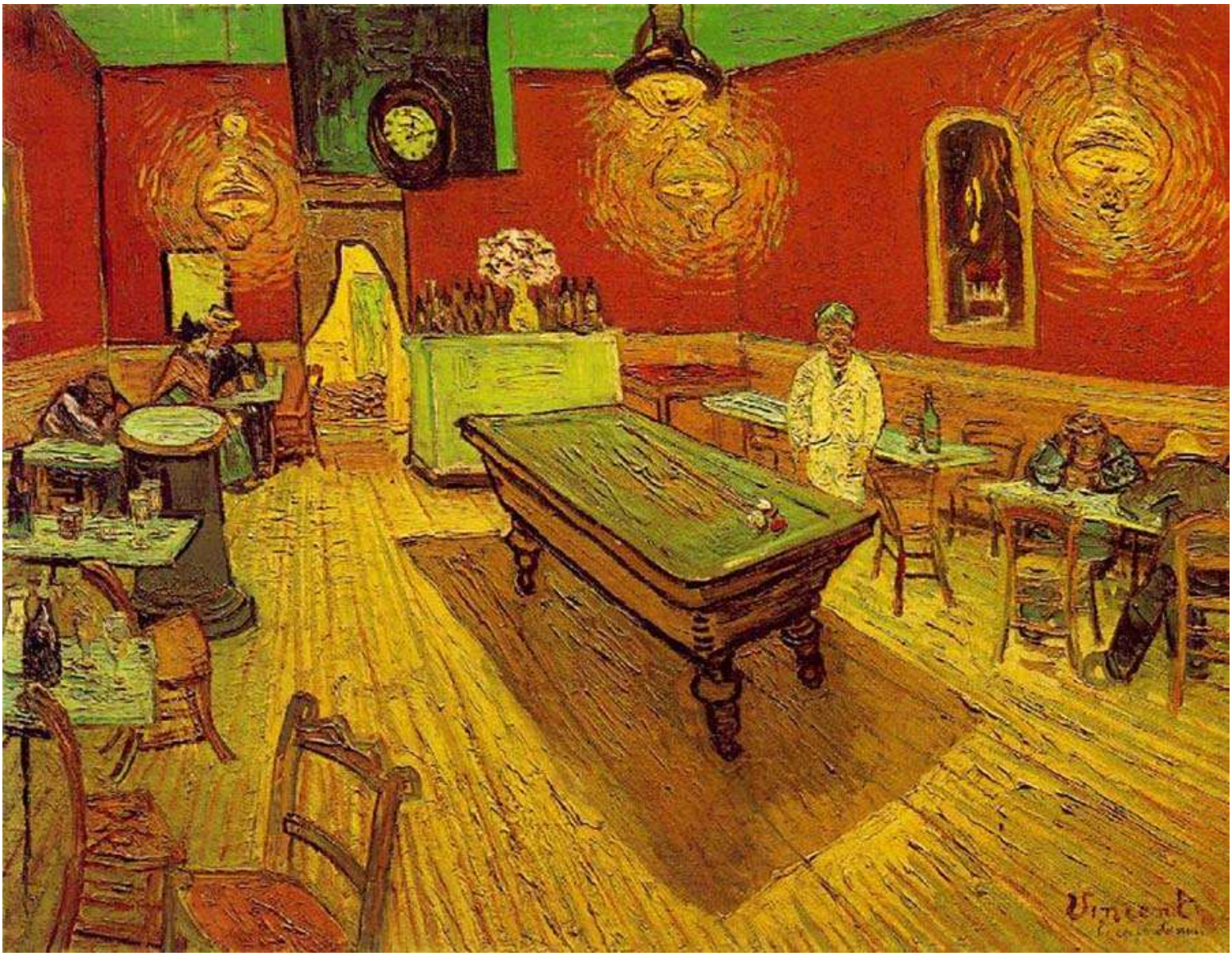
THE NORTHERN HOSPITAL

LITHIUM TOXICITY



"The Night Café", oil on canvas, Vincent van Gogh 1888, Yale University Art Gallery.

"...I have tried to express the terrible passions of humanity by means of reds and greens...a place where one can ruin one's self, go mad, or commit a crime..."

Vincent van Gogh on the "Night Café", 1888.

The element Lithium in the form of one of its salts was officially discovered by a little known Swedish chemist, Johan August Arfvedson in 1817. Its name was derived from the Greek word "lithos", meaning stone. The first isolation of elemental lithium was achieved later by the great chemist Sir Humphrey Davy, by the electrolysis of lithium oxide. C.G. Gmelin observed in 1818

that lithium salts when heated would produce a brilliant fiery red flame, a suitably symbolic discovery in view of the subsequent history of one of nature's most fascinating elements.

The history of lithium since the time of C.G. Gmelin has continued to be fiery to say the least. Its explosive reactiveness with water or oxygen was recognized early on, resulting in numerous minor explosions, but nothing in comparison to the explosive potential it was discovered to have by a Hungarian born, American physicist of the 20th century by the name of Edward Teller. Having worked on the Manhattan project during the Second World War that produced the world's first atomic or fission bomb, he foresaw a way to develop an even more destructive weapon, the fusion bomb otherwise known as the hydrogen bomb. The hydrogen bomb works by the fusion of two isotopes of hydrogen, deuterium and tritium, to form helium with the subsequent release of vast amounts of energy, an imitation of the awesome processes that power the stars. The only way this nuclear reaction can be achieved however is at temperatures approaching that of the stars themselves. Teller realized that while deuterium could be provided by the compound lithium-6 deuteride, a source of tritium could also be provided by it so long as it could be bombarded by enough neutrons. There was only one way to do this, by using the original atomic bomb as the trigger the neutrons were provided in abundance as were the temperatures required to fuse the deuterium and tritium. On the first of November 1952 at Enewetak Atoll in the Pacific Ocean the United States exploded the world's first hydrogen bomb. From that day the yield of nuclear weapons would no longer be measured in terms of kilotons, now they would be measured in terms of megatons.

In the 21st century more peaceful and beneficial uses for the fiery element have been discovered, even within the field of nuclear energy. Lithium has the highest heat - capacity of any element and more than twice that of water. This means that it can absorb large amounts of heat with only a slight increase in its own temperature. This property makes lithium an ideal heat transfer material and so is used in many nuclear reactors to absorb excessive heat produced by the fissioning of uranium. In the field of medicine an Australian psychiatrist Dr John Cade discovered in 1947 the mood stabilizing effects of lithium carbonate in patients suffering from bipolar (or manic-depressive) disorder. This was a significant medical breakthrough in an age when this disorder included primitive forms of electroconvulsive therapy and lobotomy as standard treatment in severe cases.

Vincent van Gogh probably suffered a form of bipolar disorder. He was tormented throughout his life by mental illness which reflected in many of his works. In his startling "Night-Café" he depicts his inner turmoil that appears to scream out at us from the blinding lights. He depicts not only his own inner anguish, however but also that of the "terrible passions" of the human condition in general. The blood red walls remind us of C.G. Gmelin's lithium flame. John Cade's discovery unfortunately came too late to save Vincent from his most famous moment of mania when he cut off part of his own ear.

Today however our patients with manic or bipolar disorders can hope for a less tormented life by utilizing the benefits of lithium medication. It must be remembered however that whilst there are benefits from the agent, the margin for error is small. It is important to keep blood levels within the narrow therapeutic range to contain the "terrible passions" of some of our patients. Whilst the blood levels remain therapeutic the lithium will, like the lithium in a 21st century nuclear reactor, "absorb" most of the "heat" of these passions, however, should they be exceeded, the darker side of the fiery element will become apparent with an ever increasing "chain reaction" of complications the further this range is exceeded.

LITHIUM TOXICITY

ACUTE LITHIUM TOXICITY

Introduction

Lithium (Li) is a monovalent cation with no known biological role.

Its medical indications include:

1. Acute mania.

2. Prevention of recurrent episodes of manic-depressive illness.

The exact therapeutic mechanism of action however is unclear, but effects on biological membranes are suspected.

In acute overdose, **GIT upset** is common, however providing adequate urinary lithium excretion is maintained and presentation is not late, significant **neurotoxicity** as is seen with **chronic toxicity** is unlikely to occur.

Most patients with normal renal function can be treated with IV normal saline infusions.

Hemodialysis may be required in patients with renal impairment, especially if they present late with symptoms of neurotoxicity.

History

The Swedish chemist. **Johan August Arfwedson** (1792 -1841) is credited with the discovery of lithium in 1817.

The Australian psychiatrist **John Cade** (1912 - 1980) established the therapeutic usefulness of **lithium carbonate** in the treatment of mania in 1949.

Until this time standard treatments for psychosis included liberal uses of electroconvulsive therapy and the horrific procedure of frontal lobotomy. Lithium carbonate was the first genuinely effective medication in history developed to treat mental illness.

It was not until 1970, however, that the US Food and Drug Administration approved lithium for clinical use in the treatment of mania. In 1974 it was approved as a preventative treatment for manic-depressive illness.

Preparation

Lithium carbonate as:

Standard release tablets:

- 250 mg.

Slow release tablets:

- 450 mg.

Toxicology

Lithium, unlike Na and K has a relatively small gradient of distribution across biological membranes.

It can replace Na in supporting a single action potential in a nerve cell, but is not an adequate substitute for the Na pump and cannot therefore maintain a biological membrane potential.

Like most metal salts lithium carbonate acts as a direct irritant to the GIT.

Once absorbed lithium ions substitute for sodium and potassium ions and are thought to modulate intracellular second messengers

They may also affect neurotransmitter (including serotonin) production and release.

Pharmacokinetics

Absorption:

- Almost complete oral absorption will have occurred by 6 hours with standard preparations.
- Peak levels occur within 4 hours with standard preparations.
- **Absorption may be significantly delayed however in large acute overdose and/ or with sustained release preparations. Delayed peak absorption may occur up to 12 hours post ingestion in these cases.**

Distribution:

- Vd is equal to the total body water of approximately 0.7 - 0.9 L/Kg.
- It crosses membranes slowly, which accounts for a biphasic type distribution with slow onset of action and slow redistribution into cells, (diffuses quickly into liver and kidney, but takes up to 8-10 days to reach equilibrium with the brain.)

Metabolism / Excretion:

- Lithium is not metabolized.
- It is excreted by the kidney (with 60-70% reabsorbed by the proximal tubule the rest excreted in the urine).
- Clearance is dependent on the GFR.

Lithium is handled by the body like sodium, ie. it is retained if sodium intake is low and is excreted (along with sodium) if sodium intake is high. Its clearance therefore will be reduced in cases of body water or sodium depletion.

The elimination half-life is around 24 hours once steady state is reached.

Risk Assessment

Dose Ingested related risk:

In the setting of **normal renal** function an ingestion of **< 25 grams** of **standard preparation** is relatively benign causing only GIT upset.

In the setting of normal renal function an ingestion of **> 25 grams** is more problematic, however with good supportive care and providing the patient is **not** water or sodium depleted and has normal renal function, neurotoxicity is uncommon.

Factors influencing toxicity:

The following 3 factors significantly enhance lithium toxicity:

1. **Renal impairment**
2. **Dehydration**
3. **Sodium depletion**

Under these conditions lithium will be preferentially distributed to tissues, including the CNS, rather than be excreted. There will be enhanced probability of delayed neurotoxicity.

Late presentations:

Patients who present **late** following acute overdose and who have **clinical symptoms of neurotoxicity** have a risk assessment similar to that of **chronic toxicity**, i.e altered conscious state or seizure activity indicate severe toxicity and the risk of permanent sequelae.

Clinical Features

Note that **slow-release** preparations will **significantly delay peak levels.**

Clinical effects are related to:

1. Lithium level.
2. The **duration** of exposure to the increased level.

Toxicity can be **acute** or **chronic.**

Single acute overdoses may produce *less severe* toxicity than chronic intoxication at the same serum level. In the chronic setting there can be **rapid** absorption, but **slow** distribution

The earliest signs of toxicity will generally be GIT upset.

This will be followed *late*, by increasingly severe neurological signs of toxicity.

Cardiac complications have been documented but are much less common.

Clinical effects may include:

1. GIT upset:

    - The earliest signs of toxicity will generally be GIT upset.
    - Nausea, vomiting, diarrhea.
        - ♥ Significant fluid losses can occur, aggravating toxicity.
    - GIT upset is much more prominent in **acute** overdose compared with chronic toxicity.

2. Neurological:

    Neurological symptoms are the most serious toxic effects and may include:

    Tremor

    - **This is the earliest and most frequent neurological sign.**
    - Neurological features uncommonly progress beyond tremor provided adequate lithium excretion is maintained.

    *In more severe and **chronic** cases:*

    Encephalopathies:

    - Confusion
    - **Seizures**
    - **Coma and death.**

    Extrapyramidal effects:

    - A Parkinsonian syndrome (tremor & cogwheel rigidity)
    - Movement disorders (myoclonus chareoathetosis)

    Pyramidal effects:

    - Hyperreflexia

Cerebellar effects:

- Permanent cerebellar degeneration has been documented after acute overdose.

3. CVS:

- Non-specific ST-T wave changes may occur.
- Conduction problems, rarely.

Investigations

1. FBE
2. U&Es / glucose
   - Detect and monitor hyponatremia
   - Detect and monitor renal impairment.
3. Consider the possibility of co-ingestion:
   - Blood alcohol
   - Paracetamol levels
4. Lithium levels

   Serum lithium levels are useful to:

   - Confirm that ingestion has occurred.
   - Monitoring of progress
   - Determine the safety of medical discharge.

   The normal therapeutic range of lithium is 0.6 - 1.00 mmol / L

   Peak levels > 5 mmol / L may be seen at 4 -5 hours post acute overdose.

   It is important to note that the therapeutic index of lithium is low and peak levels may be **delayed i**n certain situations, including:

   - **Large acute overdoses.**
   - **Sustained release preparations.**

   It is further important to note that lithium clearance may be significantly delayed in:

- The elderly
- Renal impairment/ failure.
- Acute on chronic ingestions, (as mentioned above this is due to rapid absorption, but slow distribution in the chronic setting).

Serum levels should therefore be checked regularly.

5. ECG:

- Minor ST-T wave changes may be seen but serious arrhythmias are not usually seen with lithium overdose.
- Consider also the possibility of cardiotoxic coingestants

Management

1. ABC as clinically indicated.

- IV access, take blood tests to urgently check renal function and lithium levels.

2. Monitoring:

- ECG monitoring is not necessary when the initial ECG is normal and in the absence of any other co-ingestants.
- Consider IDC to monitor urine output in those with established toxicity
    - ♥ Urine output is ideally > 1 ml / /kg / hour.

3. Charcoal

- This is **not** effective for lithium ingestion.

4. Normal saline:

- Is given primarily to correct any **dehydration** and to **enhance loss** of lithium.
- It is especially important in late presentations where there has been significant GIT fluid loss.
- Forced saline diuresis is *not* recommended and is inferior to dialysis.

5. Whole bowel irrigation:

- This has been advocated following overdose of sustained release preparations, however, the benefit of this intervention is unproven and provides no theoretical benefit over meticulous supportive care in patients with normal renal function. It is not useful if toxicity is chronic.

6. Hemodialysis:

- Elimination of lithium can be enhanced with hemodialysis, however in patients with normal renal function whose hydration and sodium repletion are ensured, the additional elimination is not usually required.

- Hemodialysis is reserved for patients with **established renal failure**, and particularly those who **present late** with **clinical features of lithium neurotoxicity**.

If doubt exists about the need for dialysis, consult a clinical toxicologist.

Disposition

All patients with toxic levels must be admitted for a period of ongoing observation and lithium level monitoring, even if not symptomatic.

Patients even with "normal" levels, but who have taken **large amounts** of lithium, especially if **sustained release, elderly or who have renal impairment** should be admitted for ongoing observation and lithium level monitoring.

Patients with significant symptoms or very high levels should be referred to ICU

Patients with no clinical evidence of neurotoxicity and a serum lithium level **< 2.5 mmol / L** ***and falling*** may be medically cleared.

CHRONIC LITHIUM TOXICITY

Introduction

Acute lithium overdose and chronic lithium toxicity represent two distinct clinical entities.

Neurological symptoms are more likely to be seen with *chronic* toxicity.

Neurological symptoms develop in patients on lithium therapy when **renal lithium excretion** is impaired for any reason.

Chronic lithium toxicity should be considered in any patient who is taking lithium and presents with neurological symptoms.

Toxicology

Lithium *neurotoxicity* develops in patients on lithium therapy when renal lithium excretion is impaired for any reason.

Certain drugs can impair the excretion of lithium, in particular:

1. NSAIDs.
2. ACE inhibitors.
3. SSRIs
4. Thiazide diuretics.
5. Topiramate

Medical conditions associated with chronic toxicity:

- Nephrogenic diabetes insipidus.
- Hypothyroidism

Both these conditions have been associated with lithium therapy, and both can further aggravate lithium toxicity in their own right.

Risk Assessment

Chronic lithium toxicity should be considered in any patient who is taking lithium and presents with neurological symptoms.

Altered conscious state or seizure activity indicate **severe** toxicity and the risk of **permanent** sequelae.

Serum lithium levels correlate *poorly* with **chronic** toxicity.

Clinical Features

1. GIT upset

    - This is *not* nearly as prominent as in acute overdose.

2. Clinical features may include those of a precipitating dehydration illness.

3. The clinical features will be principally neurological:

    The *Hansen and Amdisen* classification is most commonly used with respect to severity of chronic toxicity: [3]

Grade of Toxicity	Clinical features
Grade I	Tremor, hyper-reflexia, agitation, ataxia, muscle weakness
Grade II	Reduced conscious state, rigidity, hypotension.
Grade III	Coma, convulsions, myoclonus.

Investigations

1. FBE

2. U&Es/ glucose

3. TFTs

4. Lithium levels:

    - Serum lithium levels are essential to help confirm the diagnosis, but concentrations do not correlate well clinical features of chronic toxicity.

    - Serial levels are useful for monitoring the response to treatment.

5. ECG

Management

Possible cases should be discussed with a clinical toxicologist.

1. ABC as clinically indicated.

2. Monitoring:

- Consider IDC to monitor urine output.
- ECG monitoring is not necessary when the initial ECG is normal and in the absence of any other co-ingestants.

3. Charcoal
   - This is **not** effective.
4. Commence IV normal saline fluid resuscitation.
   - This is very important in order to correct any underlying dehydration.
5. Cease any other drugs which may be impairing the excretion of lithium.
6. Hemodialysis:

   The exact indications are not well defined in the chronic toxicity setting.

   The need for hemodialysis should be discussed with a clinical toxicologist.

   In general terms:

   - **It should be considered in any patient with a lithium level of > 2.5 mmol/L and neurological symptoms.**
   - It is most useful in those with established renal impairment.

   Dialysis may need to be prolonged and repeated to eliminate the lithium.

   Resolution of neurological symptoms may be slow (weeks) because of slow redistribution from the CNS and it may be incomplete.

   Lithium neurotoxicity may persist even after serum levels have returned to normal therapeutic ranges.

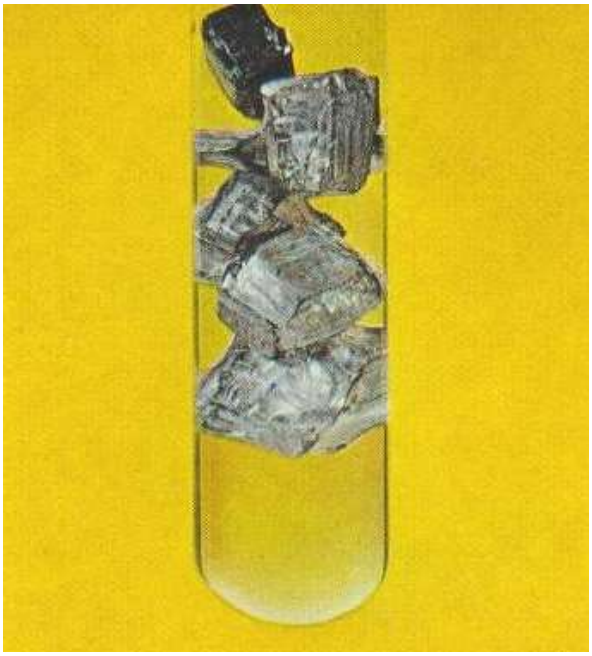
   Continuous arteriovenous or venovenous haemofiltration achieve lower clearances than haemodialysis, but may be used in situations where haemodialysis is not available.

Disposition

Any patient with **chronic** lithium toxicity requires hospital admission.

Appendix 1

Chemistry of Lithium:



Lithium (Time-Life, "The Elements", 1963)

The element lithium, the lightest of the solid elements was discovered in 1817 by the Swedish chemist, Johan August Arfvedson. It is a soft metal that can be cut by a knife and an extremely reactive one, reacting explosively with water to produce hydrogen and with oxygen to produce a black lithium oxide, (seen above the level of the inert oil in the picture). It is ever found naturally in its free or pure form because of its extreme chemical reactivity.

Physical Properties:

Elemental symbol	**Li**: from the Greek "lithos" meaning stone.
Atomic number	3
Atomic weight	6.941
Boiling point	180.54 Celsius.
Classification	Metal
Physical Appearance	Silvery-White-Grey

References:

1. Acute Lithium Overdose in: Murray L et al. Toxicology Handbook 3rd ed 2015.

2. Chronic Lithium Overdose in: Murray L et al. Toxicology Handbook 3rd ed 2015.

3. Hansen HE, Amdisen A. Lithium intoxication. Quarterly Journal of Medicine, 1978: 123 - 144.

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