Irish Medication Safety Network

Best Practice Guidelines for Prescribing and Monitoring of Lithium Therapy

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ABOUT THE IMSN

The Irish Medication Safety Network (IMSN) is a voluntary, independent group, comprising hospital pharmacy based specialists actively involved in medication safety and Medication Safety Facilitators/Coordinators which aims to promote patient safety and safe medication practices through collaboration and shared learning within the network and with the wider community.

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INTRODUCTION

Lithium is indicated for the prophylaxis and treatment of mania, in the prophylaxis of bipolar disorder, control of aggressive behaviour or intentional self harm, and as an augmentation strategy for patients with treatment-resistant depression.[1,2] It is a potentially toxic medicine with a narrow therapeutic index and recognised adverse effects on renal and thyroid function.[2,3]

BACKGROUND

There are no national guidelines in place for prescribing or monitoring of lithium therapy in Ireland, and national statistics are not available for adherence with accepted monitoring standards. However, in light of lithium's potential for toxicity and serious adverse effects, it is clear that there is an important potential for harm if accepted procedures are not followed.

EVIDENCE OF HARM

Examples of medication safety incidents which have occurred with lithium.

A 58-year-old woman, with a stable serum lithium level of between 0.5 and 0.9 mmol/L, developed renal impairment associated with severe lithium toxicity, within 5 days of starting to take celecoxib 400mg twice daily. Her lithium level was 4 mmol/L.[4]

A 64-year-old man developed lithium toxicity one week after starting to take indapamide 5mg daily. His serum lithium concentration was 3.93 mmol/L.[4]

Patient referred urgently to psychiatrist by GP for tremor, forgetfulness, unsteady gait, functional decline & unable to hold a glass. Not recognised as potential side-effects of lithium or dealt with urgently. Eventually admitted to hospital with severe lithium toxicity.[5]

Dose equivalence/conversion error: Patient presented to A&E with tremors, nausea & vomiting, dizziness, polyuria, and polydipsia. Lithium level = 2.03mmol/l (severe toxicity). 2 weeks prior, patient switched from liquid to tablets. Psychiatrist wrote to GP to request switch but did not provide dosing details in letter. Patient was initially on lithium citrate liquid 20mls (2080mg) BD. Switched by GP to Lithium carbonate tablets 2g BD (correct equivalent dose should be 1.6g once daily). Lithium stopped on admission. GP & community pharmacy informed of error.[5]

KEY RECOMMENDATIONS

Monitoring

- Prescribers must ensure lithium levels and physical health parameters are monitored at appropriate intervals for each patient.
- Pharmacists, where feasible, should ensure lithium levels are being monitored appropriately, and enquire about side-effects at the point of dispensing.
- If lithium toxicity is suspected, an urgent lithium level is required immediately and seek specialist advice.
- GP and Consultant Psychiatrist must clarify shared responsibility for prescribing and monitoring lithium.[6]

Patient/Carer education

- At initiation patients/carers must be provided with written and verbal information as outlined above. The National Lithium Booklet is available at lithium-therapy-patient-information-booklet.pdf (hse.ie). Information on Lithium may also be found of https://www.choiceandmedication.org/ireland. Hard copies of the National Lithium Booklet are available from the Pharmacy Department, St John of Gods Hospital, Stillorgan.
- It is essential that patients receive this information ongoing throughout their treatment.
- All healthcare professionals involved in the patient's care must remain vigilant and check in with patients recognising when to provide additional information or to refer as appropriate.

Policies & Procedures

- Local policies and procedures should be in place for prescribing and monitoring of lithium therapy, which are audited.
- Arrangements for lithium monitoring and communication of blood test results are explicitly agreed between primary and secondary care.

BEST PRACTICE GUIDANCE

1. INITIAL WORKUP: BEFORE STARTING LITHIUM

- Body weight or Body mass index
- Cardiac function, especially in patients with cardiovascular disease or cardiovascular risk factors may require an ECG
- Estimated glomerular filtration rate, urea and electrolytes
- Serum corrected calcium
- Thyroid function tests - patients should be euthyroid before initiation
- Full blood count
- Pregnancy test for women of childbearing potential[6,7]

Patient Education

Patients should be provided with a copy of the National Lithium Booklet or equivalent and be aware of the following information before commencing lithium.

- The indication and expected duration of treatment, with at least 6 months treatment recommended to assess efficacy.
- Their target lithium level and the importance of reporting any adverse effects, missed doses and other illnesses.
- The importance of adherence and the risk of relapse with variable compliance/sudden cessation.
- The potential for side effects such as nausea, mild diarrhoea,

1. INITIAL WORKUP: BEFORE STARTING LITHIUM

metallic taste, fatigue, increased thirst or urination, fine tremor, weight gain, reduced libido, skin problems, and renal or thyroid dysfunction which can occur at therapeutic levels.[7]

- Signs of lithium toxicity (see section 3)

Advice to Patients

- Maintain adequate fluid intake and be aware of temperature or exercise changes which may affect hydration.
- Avoid dietary changes which reduce or increase sodium intake.
- Avoid taking over the counter NSAIDs.
- Seek medical advice on taking lithium if they develop diarrhoea or vomiting or become acutely unwell.
- Talk to their doctor as soon as possible if they become pregnant or are planning a pregnancy.[7] Risk and benefits of lithium treatment in relation to childbearing potential must be discussed fully prior to prescribing lithium and advice documented.
- Always inform the Pharmacist that they are taking Lithium before they purchase any OTC medicines or supplements.
- Report signs and symptoms of:
  - lithium toxicity (see section 3)
  - hypothyroidism
  - renal dysfunction (including polyuria and polydipsia)
  - benign intracranial hypertension (persistent headache and visual disturbance)[8]

2. PRESCRIBING LITHIUM

- Usual starting dose is 200mg - 600mg at night, with a usual dose range of 400mg to 1200mg daily[7]. Initial doses from 100mg can be used in the elderly.[1]
- Priadel® 200mg tablets have a break line and may be halved. While halving of the 200mg tablet is outside of Irish licensing, it is stated in the UK SmPC that tablets can be divided accurately to provide a dosage requirement as small as 100mg.[9]
- Preparations vary widely in bioavailability and therefore should be prescribed by brand name and formulation[1]. Switching from one brand to another requires the same precautions as initiation of treatment with weekly monitoring of lithium levels.[9]
- Changing from tablets to liquid formulation is a high-risk process that introduces risk of error. The liquid formulation should be restricted to cases when tablets cannot be taken e.g. swallowing difficulties or enteral feeding tubes.
- Different formulations (e.g., Liquid/tablet) are not interchangeable. If it is necessary to change formulation, lithium levels must be monitored weekly until desired level is established on new regime.

Priadel® tablets (lithium carbonate) and Priadel® liquid (lithium citrate) equivalent doses:

Lithium carbonate 204mg is equivalent to lithium citrate 520mg i.e., one 5mL spoonful of Priadel® 520mg/5mL liquid.[1]

Lithium citrate has an elimination half life of 18-36 hours[11] and is suitable for once daily dosing. [1]

Equivalent doses of Priadel® tablets and Priadel® liquid

Priadel® Tablets	**200 mg daily**	**400 mg daily**	**600 mg daily**	**800 mg daily**	**1 g daily**	**1.2 g daily**	**1.4 g daily**
Priadel® Liquid	5 mL daily	10 mL Daily	15 mL daily	20 mL daily	25 mL daily	30 mL daily	35 mL daily

3. MONITORING LITHIUM LEVELS

- 5-7days after initiation, then weekly until level is stable; then every 3 months for first year.
- After 1 year (if stable): minimum every 6 months, or every 3 months in high-risk patients as listed below.[6]
- On admission to hospital, for established lithium patients.
- Following a dose/formulation change or addition of interacting medications – weekly until stable.
- Take blood sample 12 hours post dose. and if on twice daily dosing, sampling should be done before the morning dose is administered.[8,10.]

High-risk patients[6,8]

- Age 65 years and older.
- Taking meditation that interacts with lithium e.g., Diuretics, ACE inhibitors, ARBs or NSAIDs (not an exhaustive list).
- Risk of impaired renal function: e.g., eGFR declines over two or more tests; or urea and creatinine elevated.
- Impaired thyroid function, raised calcium levels, or other complications.
- Significant change in a patient's sodium or fluid intake.
- Poor symptom control or poor adherence.
- Reporting symptoms of adverse effects or toxicity.
- Last serum-lithium concentration was 0.8 mmol/litre or higher.
- Pregnancy.

Interpreting levels

Optimal therapeutic levels

The optimal maintenance level is the dose at which symptoms are controlled without significant side effects and will vary from patient to patient. Lower levels may be required in the elderly, as they may experience toxicity at standard therapeutic blood levels.[10,12.]

- Bipolar Disorder management
  - 0.6-0.8mmol/L in patients prescribed lithium for the first time.[6]
  - 0.8-1.0 mmol/L in patients who have had a relapse whilst on lithium or who have not had an adequate response.[6]
  - The minimum effective plasma level for prophylaxis is 0.4mmol/L with the optimal range being 0.6-0.8mmol/L.[13]
  - Lower plasma levels of lithium may be effective at preventing relapse of bipolar depression and higher levels to prevent mania.[13]
- Other indications (e.g., augmentation of antidepressant treatment):
  - Determine the dose of lithium according to response and tolerability. Consider range of 0.4-1.0 mmol/L; consider levels 0.4-0.6mmol/L for older adults.[14]

Toxic levels

Lithium toxicity is defined as any plasma level > 1.2 mmol/L but may also occur at lower levels in higher risk groups.[12]

3. MONITORING LITHIUM LEVELS

Signs of lithium toxicity include increasing diarrhoea, vomiting, anorexia, muscle weakness, lethargy, dizziness, ataxia, lack of coordination, tinnitus, blurred vision, coarse tremor of the extremities and lower jaw, muscle hyper-irritability, choreoathetoid movements, dysarthria, and drowsiness.[8]

- In patients with suspected or symptoms of lithium toxicity (e.g. diarrhoea, vomiting, tremor, mental state changes, or falls):
  - o withhold lithium
  - o take urgent serum lithium level and U&Es
  - o seek specialist advice[8]

Stopping Lithium

Lithium should be stopped gradually over at least 4 weeks and preferably over up to three months unless toxicity is suspected or proven. During dose reduction and for 3 months after lithium is stopped monitor the person closely for signs of mania and depression.[6]

Avoid large dose reductions which may result in plasma level reductions > 0.2mmol/L.[10]

4. MONITORING OF PHYSICAL HEALTH

- Plasma levels of lithium are dependent on renal function and lithium treatment can lead to reduced GFR and increases the risk of hypothyroidism.[10] Lithium also causes weight gain, further increasing the risk of physical comorbidity and mortality, which is significantly higher for patients with enduring mental illness than the general population.[15]
- Monitor the patient at every appointment for symptoms of neurotoxicity including paresthesia, ataxia tremor and cognitive impairment which can occur at therapeutic levels of lithium.[6]
- Patients with diabetes insipidus (nephrogenic diabetes insipidus can occur in up to 40% of patients with lithium induced renal impairment[16]) who are unable to maintain adequate fluid intake due to nausea and sickness are at increased risk of hypernatremia and may require hospitalisation.[17]

Recommended six monthly monitoring[6]

- Body weight or Body mass index
- Estimated glomerular filtration rate, urea and electrolytes, serum corrected calcium
- Thyroid function tests

Monitor more often if there is evidence of impaired renal or thyroid function, raised calcium levels or an increase in mood symptoms that might be related to impaired thyroid function.[6]

Refer to a renal physician if eGFR drops to < 45ml/min[12]; there is a consistent decline in eGFR>5 ml/minute within one year or >10 ml/minute within five years[18]; or any clinical concerns. In some populations the eGFR may overestimate renal function and therefore calculation of creatinine clearance is more appropriate.[12]

5. LITHIUM AND SURGERY

Risks associated with the use of lithium in the perioperative period include:

- Exacerbating symptoms of mania, bipolar disorder, or recurrent depression if lithium is omitted.
- Potential for lithium toxicity secondary to dehydration if lithium is continued.

Advice in the perioperative period

- Elective surgery
  - o Check urea and electrolytes, thyroid function and ECG pre-operatively unless recently checked.
  - o Minor surgery-continue lithium.
  - o Major surgery- stop lithium 24 hours before operation.
- Emergency surgery

  If there is insufficient time, follow the advice for elective surgery. Ensure adequate hydration and monitor renal function closely.
- Post-operative advice

  Restart lithium post-operatively when next dose is due providing renal function is stable. Monitor electrolytes closely and ensure adequate hydration[19] especially in patients with diabetes insipidus[16]. In these patients regular monitoring of urine output and twice daily U&Es are recommended due to higher risk of developing hypernatremia.[17]

6. LITHIUM IN BREASTFEEDING AND PREGNANCY

Lithium is potentially teratogenic, however the risk of Ebstein's Anomaly (a rare heart defect caused by lithium) has been shown to be lower then originally thought.[20]

Women who become pregnant while on lithium, should not stop treatment abruptly and should be advised to seek specialist advice where the risks and benefits of continuing treatment or discontinuation should be discussed.[12] Lithium levels need to be checked monthly during pregnancy and dose increases may be required, especially in the second and third trimester due to fluid volume changes.[20] If the dose is increased during pregnancy, this must be reviewed post partum. Provide patients with the necessary information to support shared decision making. The recommended websites are listed below.

Lithium is not generally recommended in breastfeeding but may be used in rare cases under specialist Perinatal Team supervision and with strict infant monitoring conditions.[21, 22]

https://www.choiceandmedication.org/ireland/

https://www.medicinesinpregnancy.org/

ACTIONS / IMPLEMENTATION

The following safety strategies address the key recommendations:

- Local clinical policies and procedures should include a requirement to follow current monitoring guidelines for lithium therapy, as described in section 3 above.
- Plans or systems should be put in place to effectively communicate blood test results between laboratory services and prescribers.
- Local policies and procedures should specify the requirement to issue and support the use of a lithium booklet.
- Local policies and procedures should direct prescribers, pharmacists, and nurses to check the scheduling of blood tests, and to reassure themselves where feasible before prescribing, dispensing or administering that, given the test results, no patient harm will result.
- Local policies and procedures should direct healthcare practitioners to communicate and take account of possible changes in lithium levels when interacting medicines are identified.
- Active promotion of key recommendations should be undertaken at suitable educational opportunities e.g., nursing in-services, intern orientation, junior doctor education sessions.
- Passive promotion of recommendations should be undertaken by means of in-house publications, where available, e.g., Prescribers' Guides, medication safety bulletins, medication safety intranet sites.

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