Compliance with Measurement of Blood Lithium Level during Treatment with Lithium Carbonate

Lithium carbonate is widely used for the treatment of mania and manic states, but it may lead to lithium poisoning if blood lithium level is uncontrolled.

PMDA conducted a survey using medical, dispensing, and Diagnosis Procedure Combination (DPC) claim data\(^1\). The results showed that the serum lithium level might have never been measured\(^2\) in 1200 (52%) of 2309 patients who were prescribed lithium carbonate.

Please pay attention to the following precautions when using lithium carbonate.

1. Data from January 2005 to December 2010 provided by Japan Medical Data Center Co., Ltd.
2. Lithium level measurement was defined as “performed” when the specific drug therapeutic management fee was recorded during the data period.

- Be sure to periodically measure the serum lithium level in accordance with the “Precautions of Dosage and Administration.”
  - Initial phase of administration or in cases of dose-increase
  - Serum lithium level should be measured about **once a week** until the maintenance dose is fixed.
  - Maintenance dose phase (time after starting lithium carbonate at the maintenance dose)
  - Serum lithium level should be measured about **once every 2 to 3 months**.

- A trough level should be assessed based on the results of lithium level measurement, and lithium carbonate should be used at an adjusted dose.

- In addition to periodic measurements, the serum lithium level should be measured in the following cases:
  - **The patient has any factors that may increase the serum lithium level:**
    - Lack of food and water intake
    - Susceptibility to dehydration
    - Start of concomitant use of drugs that may increase the serum lithium level (e.g., nonsteroidal anti-inflammatory drug), etc.
  - Also consider drugs prescribed by another hospital or over-the-counter drugs!
  - **The patient has initial symptoms of lithium poisoning:**
    - Gastrointestinal symptoms such as impaired appetite, nausea, vomiting and diarrhoea
    - Central nerve symptoms such as tremor, somnolence and confusion
    - Motor function symptoms such as movement disorder and ataxia
    - General symptoms such as pyrexia and sweatiness
  - **Patients and their family should be informed of possible lithium poisoning and be instructed to consult their physician if an initial symptom of lithium poisoning occurs.**
  - **The following measures should be taken according to the patient’s serum lithium level:**
    - Serum lithium > 1.5 mEq/L → Dose reduction or drug suspension as necessary
    - Serum lithium > 2.0 mEq/L → Dose reduction or drug suspension

According to the Relief System for Sufferers from Adverse Drug Reactions, the relief benefits are basically not applicable to cases in which a drug was used improperly, for example, in cases where appropriate measurement of serum lithium level was not performed, leading to serious lithium poisoning.
Cases of serious lithium poisoning

**Case 1:** Lithium level increased with poor oral intake

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Primary disease</th>
<th>Complications</th>
<th>Daily dose (Treatment duration)</th>
<th>Clinical course and therapeutic measures</th>
</tr>
</thead>
</table>
| Female | 60s | Bipolar affective disorder | no complications | 800 mg (for approximately 5 years) | Day 1 of administration: 
Day 1 of administration: The patient started receiving 800 mg/day of lithium carbonate. The blood lithium level was within the therapeutic range. 

[7 days before onset]: The patient gradually became unable to eat and drink. The ability to independently urinate and defecate was lost, and she started using diapers. 

[4 days before onset]: The patient had almost no oral intake but her family helped her take drugs. The patient became unable to communicate, with strange noises, swaying and other behaviors. She did not defecate or urinate. 

[day of onset]: The patient was urgently admitted to the hospital. BUN, 35 mg/dL; blood creatinine, 2.3 mg/dL. She had oliguria with urinary output of 350 mL/day. 

Day 3 of onset: The patient took one tablet of the drug after each meal, and needed for treatment of wisdom tooth pain from oral surgery. 

Day 4 of onset (day of discontinuation): Blood lithium level, 4.44 mEq/L; Administration of lithium carbonate was discontinued. 

2 days after discontinuation: Although renal function recovered with transfusion, the patient had complications of disturbed consciousness, aspiration pneumonia, prolonged QT and sinus bradycardia. Blood lithium level, 2.52 mEq/L. An additional transfusion was given. 

3-6 days after discontinuation: Polyuria and hypernatraemia occurred. 

7 days after discontinuation: Blood lithium level decreased to 0.25 mEq/L. Prolonged QT and disturbed consciousness were improving. 

14 days after discontinuation: The patient resumed oral intake. Although transfusion and electrolyte correction were performed, it was difficult to control the electrolyte balance, and polyuria and hyposthenuria persisted. 

41 days after discontinuation: The symptoms remitted. |

Concomitant medications: Unknown

**Case 2:** Lithium level increased after addition of a nonsteroidal anti-inflammatory drug

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Primary disease</th>
<th>Complications</th>
<th>Daily dose (Treatment duration)</th>
<th>Clinical course and therapeutic measures</th>
</tr>
</thead>
</table>
| Male | 40s | Bipolar disorder, toothache |  | 400 mg (for approximately 8 months) ↓ 600 mg (for approximately 6 months before onset) | Day 1 of administration: The patient started receiving 400 mg/day of lithium carbonate. The dose of lithium carbonate was increased to 600 mg/day. 

Month 8 of administration [6 months before onset]: Loxoprofen sodium hydrate 60 mg/day was prescribed as needed for treatment of wisdom tooth pain from oral surgery. The patient took one tablet of the drug after each meal, and sometimes took as many as 7 tablets daily. 

Month 14 of administration [11 days before onset]: The patient visited the emergency outpatient department with complaints of staggering gait and inarticulate. General blood tests and head CT showed no significant findings. He received an intramuscular injection of biperiden lactate for suspected drug-induced extrapyramidal symptoms and went home. |

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<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 8 of onset (day of discontinuation)</td>
<td>The patient visited the hospital because of persisted staggering gait and faecal incontinence. Lithium poisoning was suspected and his blood lithium level was measured. As a result, blood lithium level was 2.4 mEq/L and he was admitted to the hospital. Administration of lithium carbonate was discontinued. After fluid replacement was started, his condition improved uneventfully.</td>
</tr>
<tr>
<td>Unknown day</td>
<td>The patient was discharged from the hospital.</td>
</tr>
</tbody>
</table>

Concomitant medications: Loxoprofen sodium hydrate
Lithium carbonate package insert (excerpt)

Dosage and Administration

Administration of lithium carbonate is usually started for adult patients as oral administration of 400 to 600 mg per day in 2 to 3 divided doses, and the dose is gradually increased every 3-7 days up to 1200 mg per day. When the patient improves, the dose should be gradually decreased to the usual maintenance dose of 200 to 800 mg per day in 1 to 3 divided oral doses, while monitoring the symptoms. The dose may be increased or decreased depending on the patient’s age and symptoms.

Precautions of Dosage and Administration

Lithium poisoning may occur as a result of an overdose. Serum lithium level should be measured about once weekly at the initial phase of administration and during the dose-increase phase until the maintenance dose is fixed, and about once every 2 to 3 months during the maintenance dose phase. Lithium carbonate should be used while assessing a trough level based on the results of lithium level measurement. If the patient has any factor that may increase the serum lithium level (e.g., lack of food and water intake, susceptibility to dehydration, concomitant use of drugs that may increase the serum lithium level such as nonsteroidal anti-inflammatory drugs), or any initial symptom of lithium poisoning, serum lithium level should be measured. [See the “Careful Administration,” “Important Precautions (5),” “Drug Interactions” and “Adverse Reactions (1)-1) Lithium poisoning” sections.]

(1) If the serum lithium level exceeds 1.5 mEq/L, the patient should be carefully monitored for clinical symptoms, and appropriate measures such as dose reduction or drug suspension should be taken as necessary.

(2) If the serum lithium level exceeds 2.0 mEq/L, toxicity associated with lithium may occur by overdose. The dose of this drug should be reduced or administration should be discontinued.

Careful Administration (lithium carbonate should be administered carefully to the following patients)

(3) Patients who may have lithium retention [Lithium poisoning may occur]

1) Patients with a history of renal disorder; 2) patients who do not consume sufficient food and drink; 3) elderly patients [See the “Use in the Elderly” section]

(6) Patients highly reactive to lithium [Symptoms of poisoning may occur even if the serum lithium level is under 1.5 mEq/L]

Important Precautions

(5) Patients and their family should be thoroughly informed that lithium poisoning may occur during treatment with lithium carbonate in case of lack of food and water intake, susceptibility to dehydration and concomitant use of nonsteroidal anti-inflammatory drug, etc., and be instructed to consult their physician if an initial symptom of lithium poisoning occurs. [See the “Precautions of Dosage and Administration,” “Careful Administration,” “Drug Interactions” and “Adverse Reactions (1)-1) Lithium poisoning” sections.]

Clinically Significant Adverse Reactions

1) Lithium poisoning

Gastrointestinal symptoms such as impaired appetite, queasy, vomiting, and diarrhoea, central nervous symptoms such as tremor, somnolence, and confusion, motor dysfunction symptoms such as movement disorder and ataxia, and general symptoms such as pyrexia and sweating may occur as the initial symptoms of lithium poisoning. If such symptoms are observed, appropriate measures such as dose reduction and discontinuing administration should be taken. If poisoning progresses, electrolyte abnormality associated with acute renal failure may occur, leading to generalised convulsion and myoclonus, etc.

Treatment: No specific antidote is available for lithium poisoning. If lithium poisoning is observed, administration of this drug should be discontinued. Prevention of infection and maintenance of the cardiac and respiratory functions should be performed, and the acceleration of excretion of this drug and restoration of electrolyte balance should be attempted by fluid replacement and diuretics (e.g., mannitol and aminophylline). If the patient is not responsive to diuretics or develops renal dysfunction, hemodialysis should be performed. Since the decreased serum lithium level may reelevate after hemodialysis, the measurement of serum lithium level should be repeated. If the serum lithium level is increased after hemodialysis, appropriate measures such as additional hemodialysis should be taken.

Precautions for concomitant use (drugs which are reported to possibly cause lithium poisoning when used concomitantly with lithium carbonate)

Diuretics (thiazide diuretics, loop diuretics, etc.), angiotensin converting enzyme inhibitors (enalapril maleate etc.), angiotensin II receptor blockers (losartan potassium etc.), nonsteroidal anti-inflammatory drugs (loxoprofen sodium hydrate etc.), metronidazole

Use in the Elderly

Since elderly patients have generally decreased physiological functions, this drug should be carefully administered by monitoring the patient’s condition. [Since elderly patients often have impaired renal function, serum lithium level may be elevated.]

See information on the precautions related lithium carbonate, at the Pharmaceuticals and Medical Devices Information website http://www.info.pmda.go.jp/psearch/html/menu_tenpu_base.html (In Japanese)

Product names of lithium carbonate (Name of Marketing Authorization Holder)

LIMAS tab. 100, 200 (Taisho Pharmaceutical Co., Ltd.)
LITHIOMAL Tablet 100 mg, 200 mg (Fujinaga Pharm Co., Ltd.)
Lithium Carbonate Tab. 100 mg “AMEL”, Lithium Carbonate Tab. 200 mg “AMEL” (Kyowa Pharmaceutical Industry)
Lithium Carbonate TABLETS 100 “YOSHITOMI”, Lithium Carbonate TABLETS 200 “YOSHITOMI” (Zensei Pharmaceutical Industries Co., Ltd.)

About this information

* “PMDA Alert for Proper Use of Drugs” communicates to healthcare providers with clear information from the perspective of promoting the proper use of drugs. The information presented here includes such cases where the reporting frequencies of similar reports have not decreased despite relevant alerts provided in package inserts, among Adverse Drug Reaction/Infection cases reported in accordance with the Pharmaceutical Affairs Law.
* We have tried to ensure the accuracy of this information at the time of its compilation but do not guarantee its accuracy in the future.
* This information is not intended to impose constraints on the discretion of healthcare professionals or to impose obligations and responsibilities on them, but is provided to promote the proper use of drugs.

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