# Fatal self-poisoning with lithium carbonate

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**Summary: In a fatal case of self-poisoning with lithium carbonate there was a progressive increase in serum lithium concentration for 48 hours after ingestion of the overdose. It is suggested that the continuous increase in serum lithium concentration reflects prolonged absorption of lithium from relatively insoluble aggregates of lithium carbonate in the gastrointestinal tract. In this case there was an interval of 45 hours between ingestion of the overdose and the onset of central nervous system depression. Simultaneous peritoneal dialysis and hemodialysis were effective in rapidly reducing the serum lithium concentration but there was little concomitant change in the patient's level of consciousness. The terminal event was a respiratory complication of the comatose state.**

**Résumé:** *Un cas fatal d'autointoxication par le carbone de lithium*

**Dans un cas fatal d'autointoxication par le carbonate de lithium nous avons observé une augmentation progressive de la concentration sérique de lithium pendant 48 heures après ingestion de la dose toxique. Nous estimons que cette augmentation continue reflète une absorption prolongée de lithium à partir d'agrégats de carbonate de lithium, relativement insolubles, situés dans le tube digestif. Dans le cas présent nous avons noté un intervalle de 45 heures entre l'ingestion de la dose toxique et le début de la dépression du système nerveux central. Grâce à l'application simultanée d'une dialyse péritonéale et d'une hémodialyse, nous avons pu rapidement réduire la concentration sérique de lithium, mais cette maneuvre n'a pas été suivie d'une amélioration notable du niveau de conscience du malade. Le stade ultime a été une complication respiratoire de l'état comateux.**

Lithium carbonate is used in the control of acute mania and in the prevention of recurrent attacks of depression and mania. The optimum therapeutic serum concentration of lithium 8 to 12 hours after the last dose is between 0.7 and 1.3 meq/l.[1] However, the margin of safety is small, for adverse effects usually occur with serum concentrations of more than 2 meq/l. The most common clinical manifestations of lithium intoxication are gastrointestinal (nausea, vomiting and diarrhea) and neurologic (hand tremor, sedation, ataxia, weakness, convulsions and coma).[1,2] Cardiac arrhythmias[3] and renal dysfunction[4,5] are less common.

Lithium intoxication can result from (a) accidental or deliberate ingestion of a large amount of drug or (b) gradual accumulation of lithium in patients receiving therapeutic doses of lithium carbonate. The accumulation of lithium may result from an increase in dose or a decrease in renal excretion of lithium due to renal dysfunction, reduced sodium intake or diuretic therapy. The majority of reported cases of lithium intoxication fall into the second category,[2,5-11] and in this situation prodromal gastrointestinal and neurologic effects are a prominent feature. There are few case reports[6,12] describing the clinical course after the ingestion of a large overdose of lithium carbonate. The case we report demonstrates certain unusual features and raises many questions regarding the management of acute lithium intoxication.

## Case report

A 29-year-old woman presented to The Montreal General Hospital Apr. 2, 1974, claiming to have ingested, 1 to 2 hours before, about 200 tablets (60 g) of lithium carbonate, 150 tablets (15 g) of chlorpromazine and 30 tablets (0.9 g) of flurazepam hydrochloride. She denied drinking ethanol and before arrival at hospital had vomited twice. She had been hospitalized 4 years before with an intentional drug overdose and since then had been under psychiatric care for a manic-depressive illness. For the 6 months preceding the overdose her treatment consisted of 1500 mg of lithium carbonate and 200 mg of chlorpromazine each day.

She was alert, oriented and in no physical distress. The oral temperature was 36.7°C, the heart rate 80 beats/min, the blood pressure 100/78 mm Hg and the respiratory rate 20/min. There were no abnormal physical findings. Blood urea nitrogen (BUN) and serum electrolyte values (Table I), chest radiograph and electrocardiogram (ECG) were normal. Gastric aspiration and lavage were performed through a wide-bore tube. A moderate amount of particulate matter was recovered. After lavage a slurry of 100 g of activated charcoal (Norit A) was instilled into the stomach. One month before admission the lithium value had been 0.75 meq/l; on admission it was 3.7 meq/l. Because of the history of ingestion of large amounts of three drugs the patient was admitted to the medical intensive care unit (MICU) for observation.

During her first 2 days in the MICU she remained alert and oriented. Oral temperature increased to 37.8°C and a few scattered rhonchi were heard. There were no abnormal neurologic findings. BUN and serum electrolyte values (Table I), chest radiograph and ECG remained normal. Increasing serum lithium values were noted (Fig. 1) but the only adverse effects observed were nausea, vomiting

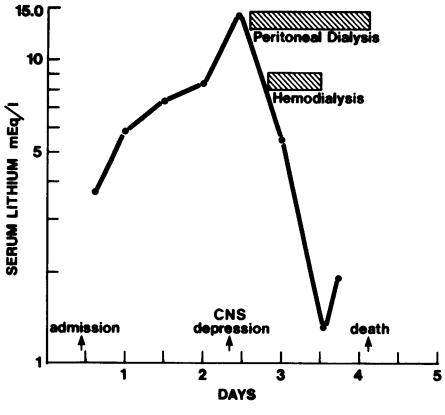


FIG. 1—Log serum lithium concentration and time course.

**Table I—Fluid intake, urine output and BUN and serum electrolyte values during hospital stay**

| Variable | Hospital day 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Fluid intake (ml) | 610 | 2970 | 4850 | 5000 |
| Urine output (ml) | 500* | 1950* | 210 | 650 |
| BUN (mg/dl) | 6 | 7 | 10 | 5 |
| Serum Na (meq/l) | 137 | 135 | 136 | 139 |
| Serum K (meq/l) | 4.2 | 5.9 | 4.1 | 3.9 |

*Underestimates: several specimens were lost in the watery feces.

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(two episodes/day) and diarrhea (three episodes/day). Intravenous fluids were given to supplement the oral intake.

The first change in consciousness was seen on the morning of day 3, about 45 hours after admission. At 8 am she was drowsy but rousable. By noon she was comatose, with minimal response to maximally painful stimuli and without lateralizing neurologic signs. There was no clinical change in cardiac or pulmonary function. The diarrhea had decreased but because pills had been seen in the feces the previous evening, magnesium sulfate was administered through a nasogastric tube to hasten elimination of any drug that was still in the gastrointestinal tract. Because her clinical condition rapidly deteriorated, peritoneal dialysis was started at 2 pm and hemodialysis at 8 pm that day. Because of the magnesium-sulfate-induced diarrhea and the fluid loss due to dialysis, intravenous fluids were increased to 5 l per 24 hours to maintain fluid balance. Urine output decreased during dialysis but BUN and serum electrolyte values remained normal (Table I). During dialysis the serum lithium value rapidly decreased (Fig. 1) but there was no concomitant change in the patient's level of consciousness.

On day 4 she remained comatose but was more responsive to painful stimuli. Her serum lithium value had decreased to less than 2 meq/l (Fig. 1) and hemodialysis was discontinued at noon. Peritoneal dialysis was continued because she was still oliguric (Table I). Later that day she became more responsive to painful stimuli, and involuntary, jerking movements of her head were observed for the first time. Respiratory distress developed. Rectal temperature was then 38.9°C. Oropharyngeal suction yielded viscid, creamy-white secretions. Chest radiograph revealed mild, subsegmental atelectasis. Arterial blood values were as follows: $Po_2$, 70.8 mm Hg; $Pco_2$, 36.5 mm Hg; pH, 7.42; total $CO_2$, 24.5 meq/l. To facilitate suctioning and to improve oxygenation, an endotracheal tube was inserted after the patient had been sedated with intravenous diazepam. Ventilation with 30% $O_2$ by a volume-cycled respirator was started. Her condition remained stable until respiratory distress suddenly developed at 1 am on day 5. It was believed that the endotracheal tube was blocked by secretions and, as the tube was being replaced, ventricular fibrillation supervened. Cardiac asystole followed. Direct-current countershock and resuscitative measures were unsuccessful. Autopsy was not performed.

## Discussion

In self-poisoning by means of a single overdose the actual amount of any drug ingested is open to question. In this case, particularly because she had been apparently well for 45 hours, we doubted whether the patient had ingested the large amounts of the various drugs claimed. Any ingested chlorpromazine and flurazepam probably did not have a major influence on her clinical course, for one would expect the onset of central nervous system depression within 6 to 12 hours after an overdose of the phenothiazines (e.g. chlorpromazine) or benzodiazepines (e.g. flurazepam).[13]

The most unusual feature of this case was the progressive increase in serum lithium concentration for 48 hours after admission. There are three possible explanations for this phenomenon: (a) impaired excretion, (b) altered distribution or (c) continued absorption of lithium. Lithium is excreted almost entirely by the kidneys,[14] and the patient's renal function, as judged by the BUN values, was always normal (Table I). Her urine output was adequate during the phase of progressively increasing serum lithium concentration (Table I) but she became oliguric after dialysis was started. The oliguria probably resulted from a negative fluid balance during dialysis but it is possible that it reflects lithium-induced renal dysfunction. The claim by Almy and Taylor[15] that manic patients retain more orally administered lithium during the active manic phase than normals is not supported by the work of other investigators.[16] Inhibition of renal excretion of lithium by chlorpromazine seems unlikely because chlorpromazine induces a very small increase in lithium excretion.[17] There is nothing to suggest that flurazepam may influence lithium excretion by the kidney.

Redistribution of lithium from storage sites to the vascular space is another consideration. Recent work suggests that bone may be an important storage site[18] and intermittent urinary excretion of lithium has been observed for several months after discontinuation of the drug.[19] In several case reports of lithium intoxication[20-22] the serum lithium value continued to increase for 2 to 3 days after discontinuation of the drug. This feature remains unexplained, for the reports all concerned the ingestion of the usual formulations of lithium and not sustained-release preparations.

The most plausible explanation for the progressive increase in serum lithium concentration in this patient is continued absorption from the gastrointestinal tract. Surreptitious intake of the drug was not possible because the patient was closely observed in an intensive care unit and no drug was available at her bedside. With therapeutic doses of lithium carbonate, peak serum lithium concentrations are attained in 1 to 2 hours[23] and absorption is complete in 4 hours.[24] However, lithium carbonate is the least soluble of the lithium salts[25] and, with the ingestion of a large amount of the drug, it is possible that relatively insoluble aggregates of lithium carbonate could be formed in the gastrointestinal tract. A comparable situation may be salicylate self-poisoning; Matthew *et al*[26] have recovered large quantities of salicylate in gastric lavage fluid as long as 9 hours after ingestion of the overdose. The slow release of lithium into solution from insoluble aggregates of lithium carbonate could account for continued lithium absorption long after the ingestion of the overdose. The only support for this hypothesis is that pills of an unknown nature were seen in the feces about 36 hours after admission. Activated charcoal binds mainly to the un-ionized moiety of lipid-soluble drugs,[27] so one would not expect activated charcoal to bind lithium ions and thereby reduce the amount of lithium available for absorption. In this case, activated charcoal was administered for its possible benefit in binding any chlorpromazine or flurazepam in the gastrointestinal tract.

Another unusual feature of this case was the very high serum lithium concentration; a peak of 14 meq/l was recorded (Fig. 1). The highest serum lithium value recorded in previously reported cases of lithium intoxication was about 7 meq/l.[9] The lack of correlation between both the increasing and decreasing serum lithium concentration and the patient's level of consciousness is not surprising because presumably it is the brain content of lithium that is important in producing the neurologic effects. Slow equilibration between lithium in blood and that in the brain is well documented in animal experiments.[18]

A controversial aspect of this patient's management was the timing of dialysis. Despite increasing serum lithium values in the toxic range, we chose to initiate dialysis only when there was a change in consciousness. Our rationale was that the main aim of dialysis is to accelerate removal of lithium from the body in an attempt to shorten the duration of coma and its attendant complications. In our patient there was no evidence of renal impairment and no neurologic effects of lithium intoxication were observed in her initial 45 hours in hospital. Dialysis was very effective in rapidly decreasing the serum lithium concentration (Fig. 1) but the patient's mental state improved only slightly. Furthermore, death[8] and persistent neurologic sequelae[28] despite rapid reduction of serum lithium concentration by dialysis have been reported. The terminal event was a respiratory complication of the comatose state. Similar complications have been prominent in other cases of lithium intoxication.

Based on other case reports and our present experience, we make the fol-

lowing suggestions concerning the management of severe lithium intoxication:

*Investigations*

1. Assessment of renal function by measurement of BUN, serum creatinine and creatinine clearance (since the kidney is the major site of elimination of lithium).

2. Continuous ECG monitoring for cardiac arrhythmias.

3. Serial determinations of serum lithium concentration during the first few days after ingestion of the overdose to exclude the possibility of progressive increase in concentration.

*Treatment*

1. Institution of supportive measures to prevent dehydration, to maintain blood pressure and urine output with intravenous fluids, to ensure adequate oxygenation, and to correct electrolyte and acid-base imbalance.

2. Prevention of further drug absorption by means of gastric aspiration and lavage through a wide-bore nasogastric tube in all cases provided the gag reflex is present. Activated charcoal does not bind lithium, so its use as a gastrointestinal adsorbent is not indicated unless one suspects a multiple drug intoxication.

3. Augmentation of drug elimination, providing renal function is normal, by administration of mannitol to produce an osmotic diuresis. This is worth a trial in cases of lithium intoxication because mannitol hastens the renal elimination of lithium;[14,30] on the other hand, administration of furosemide, thiazides or ethacrynic acid does not promote lithium excretion.[14] The most efficient way of expediting the removal of lithium from the body is hemodialysis.[7] We do not believe it is useful to set any arbitrary value for serum lithium above which hemodialysis is to be initiated, but dialysis should be started promptly if the clinical condition deteriorates despite adequate supportive therapy or if there is major impairment of renal function. Permanent neurologic sequelae have been observed in patients exposed to toxic serum lithium concentrations for several days,[29] so hemodialysis should also be started if there is a progressive increase in serum lithium concentration, even though the patient may be asymptomatic at this stage. Dialysis may have to be continued for several hours after the serum lithium value has returned to the therapeutic range because there is often a rebound increase in serum lithium concentration on discontinuation of the dialysis.[7,8] Presumably this rebound effect is due to redistribution of lithium from the tissues.

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