Massive Overdoses with Sustained-Release Lithium Carbonate Preparations: Pharmacokinetic Model Based on Two Case Studies

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Clinically significant delayed absorption after lithium overdose has been reported previously without adequate explanation. We have studied two patients after they took massive intentional lithium overdoses. The first patient presented shortly after ingesting 74 g of lithium carbonate. Pharmacokinetic analysis with a multicompartmental model of 29 serum lithium concentrations during 300 h (including hemodialysis) established absorption and elimination kinetics. Lithium absorption was both slow (peak concentration 33 h after the initial overdose) and delayed (a second peak occurred at 148 h, 30 h after initiation of oral tube feedings). The delayed absorption of a large fraction of lithium implicated a gastrointestinal drug reservoir. Study of the pharmacokinetics in a second patient, who ingested 98 g of lithium carbonate, provided additional evidence of an endogenous reservoir. This patient's medical management was guided by experience gained from the initial case. Appropriate management for a predicted endogenous drug reservoir may have shortened intensive care and hospitalization. In treating overdoses of sustained-release drug preparations, clinically significant delayed absorption triggered by enteral fluids must be considered as a contributor to delayed absorption.

Additional Keyphrases: toxicology · enteral fluids

Lithium salts are prescribed routinely for prophylactic control of manic-depressive episodes (bipolar affective disorders) and treatment of acute mania. Lithium pharmacokinetics are subject to considerable interindividual differences that, given a narrow therapeutic window, dictate close monitoring of serum concentrations (1). At typical therapeutic doses of 600–1800 mg per day, almost 100% of orally administered lithium is absorbed from the stomach and proximal small intestine, with no absorption in the large intestine (2–4). At therapeutic doses of lithium carbonate, peak concentrations in serum are typically attained in 1–2 h, with absorption being complete by 4 h (3). Available sustained-release preparations delay gastrointestinal absorption but generally do not diminish net absorption. Numerous instances of clinically significant delayed absorption in overdose situations have been reported, yet no realistic mechanisms have been put forth to account for these observations (5, 6).

In vivo, lithium is distributed in total body water with minimal protein binding (2). The initial distribution is in extracellular fluids, with equilibration into intracellular compartments in 5–10 days. Plasma half-life typically ranges from 14 to 24 h (7). Elimination is predominantly renal, because lithium undergoes no hepatic metabolism. The kinetics of elimination may be altered markedly by overdosage, lithium and disposition, or co-administration of diuretics or tricyclic antidepressants (7).

Lithium has a narrow therapeutic window. Therapeutic concentrations are 0.6–1.2 mmol/L for prophylactic control of mania and 1.0–1.5 mmol/L for treatment of acute mania. Symptoms of toxicity may present at 1.5 mmol/L, but vary with the individual and the time course of exposure (8, 9). Initial treatment of acute lithium overdose involves emesis or gastric lavage to remove undissolved pills (2, 10). Activated charcoal is not of direct benefit, though it is indicated to adsorb co-administered medications, especially in intentional overdose (suicide) situations (2). As a low-molecular-mass monovalent cation that is not metabolized and not protein-bound, lithium is ideally suited to removal by hemodialysis (11). Clinically, hemodialysis is indicated if the lithium concentration in serum is (a) >4.0 mmol/L, regardless of patient presentation; (b) >2.5 mmol/L in markedly symptomatic patients; or (c) not anticipated to be <0.6 mmol/L within 36 h (10). Theoretically, hemodialysis is most effective when instituted early, before equilibration with extravascular and intracellular compartments has taken place, thereby removing the lithium more rapidly. Early extensive hemodialysis may also reduce toxicity by minimizing tissue concentrations and by limiting the postdialysis rebound inherent with re-equilibration (11, 12). On the basis of a two-compartment model of lithium absorption, we propose a mechanism for the observed delay in absorption, with consequent implications for the role of hemodialysis in the management of acute lithium intoxication.

Materials and Methods

In addition to samples sent specifically for serum lithium determination, serum aliquots sent for other chemistry tests were analyzed for lithium by flame emission photometry with an IL 343 digital flame photometer (Instrumentation Laboratory, Inc., Lexington, MA). Serum lithium concentrations were fit to a two-compartment model of lithium absorption and elimina-
tion. Model parameters were determined by using standard nonlinear least-squares fitting methods (13).

Case Reports

Case 1. A 34-year-old 70-kg man, with long-term bipolar manic depressive disorder, was found unconscious (t = 0 h) covered with vomitus laden with pill fragments. He had been seen 2 h earlier in no apparent distress. Two bottles of Lithobid (maximum of 300 tablets of 300 mg each, i.e., 90 g) were found empty along with a suicide note. Thirty minutes after discovery, the rescue squad delivered the patient to the University of Virginia Health Sciences Center Emergency Room. He was responsive only to deep painful stimuli; his Glasgow Coma Scale score was 4. His pupils were equal at 2 mm, round, and initially nonreactive. His temperature was 38.7 °C, blood pressure 119/94 mmHg, and respirations shallow at 20. Electrocardiogram demonstrated slightly irregular sinus rhythm at 90 with a mildly prolonged QTc. Results for arterial blood gas and portable chest roentgenogram were unremarkable. Reflexes were mildly increased yet symmetric; we noted no focal neurologic abnormalities. Results of initial routine electrolytes and complete blood counts were unremarkable. A toxicology screen (thin-layer and gas chromatography) and Abbott TDx tests (Abbott Labs., North Chicago, IL) gave negative results for the presence of phenytoin, acetaminophen, ethanol, salicylates, or phenobarbital. The lithium concentration in serum was 4.13 mmol/L. Gastric lavage with a large-bore Edlich tube and 2000 mL of isotonic saline followed by tap water until clear (2000 mL) retrieved noticeable amounts of pill fragments. One liter of charcoal–sorbitol slurry was instilled and the Edlich tube removed.

The patient was admitted to the medical intensive care unit, intubated, and given 24-h nursing care. The nursing staff noted a charcoal stool 20 h after administration of the slurry. During the subsequent four days, the patient underwent four daily hemodialysis procedures of 3–6 h each. His neurological status improved as the serum lithium returned to nontoxic concentrations. On the fifth day, he was extubated and enteral tube feedings were initiated via nasogastric tube. During the next 12 to 24 h, however, the patient again became comatose as the serum lithium concentration returned to toxic concentrations, necessitating resumption of hemodialysis. By the tenth day, his condition had stabilized enough to permit transfer from the intensive care unit, though he remained hospitalized for nephrogenic diabetes insipidus secondary to lithium intoxication.

Case 2. A 25-year-old 110-kg man with chronic paranoid schizophrenia ingested >300 pills in an intentional suicide attempt (t = 0 h), including as much as 98 g of lithium carbonate, 45 g of carbamazepine, 75 g of chlorpromazine, 960 mg of perphenazine, 15 mg of benztpine, and ethanol. Within 1 h, he was taken to the local hospital emergency room. His temperature was 35.7 °C, pulse 108, respirations 20, and blood pressure 123/79 mmHg. Bowel sounds were noted in all four quadrants. Spontaneous emesis demonstrated food particles without discernible pill fragments. A nasogastric tube was inserted to lavage the patient with isotonic saline and activated charcoal. Serum lithium concentration at t = 1 h was 1.40 mmol/L, carbamazepine 11.0 μmol/L, and ethanol 42.3 mmol/L. At t = 3.5 h, lithium increased to 2.80 mmol/L, carbamazepine to 17.6 μmol/L, and ethanol decreased to 26 mmol/L. By t = 5.5 h, serum lithium increased to 3.30 mmol/L and carbamazepine to 19.0 μmol/L. He was subsequently transferred to the University of Virginia Health Sciences Center for emergency hemodialysis.

At t = 7.5 h, the patient arrived somnolent but arousable, with incoherent speech, disconjugate gaze, minimally reactive pupils, and a Glasgow Coma Scale score of 13. Electrocardiogram demonstrated tachycardia at 120 with a moderately prolonged QTc. Respirations were shallow at 16; his blood pressure was 125/80 mmHg and his temperature was 37.2 °C. The neurological exam was nonfocal except for symmetrically diminished deep tendon reflexes. Assay of arterial blood gas (the patient was breathing room air) showed a pH of 7.39. Results for routine determinations of electrolytes, urinalysis, and complete blood counts were essentially within normal limits. Serum lithium concentration was 3.70 mmol/L and carbamazepine was 45.7 μmol/L. A urine drug screen was otherwise negative. Bowel sounds were markedly diminished. He was admitted to the medical intensive care unit, and hemodialysis was begun at t = 9.75 h for 6 h.

Thirty minutes before the end of the initial hemodialysis (t = 15.25 h), 1 L of activated charcoal–sorbitol slurry was administered in an attempt to adsorb any residual anticholinergic medications, because the patient’s gastrointestinal tract had not resumed motility. Within 60 min of discontinuing hemodialysis, serum lithium had increased from 2.37 to 3.68 mmol/L. Hemodialysis was resumed 3 h later (t = 19.75 h) and continued for 12 h more. Serum lithium decreased steadily for the first 8 h (t = 20 to 28 h) of the second hemodialysis until an additional charcoal–sorbitol slurry was administered via nasogastric tube. Over the next 4 h, serum lithium increased despite continuous hemodialysis, and increased more abruptly after discontinuation of hemodialysis. Seven hours later (t = 38.75 h), a third hemodialysis period was initiated for 17 h as serum lithium reached 4.89 mmol/L. Again, serum lithium decreased initially until administration of a third charcoal–sorbitol slurry (t = 40 h) led to another increase in serum lithium despite continued hemodialysis. After discontinuing the third hemodialysis episode (t = 56 h), serum lithium concentrations demonstrated a slight increase consistent with re-equilibration from extravascular sites. He was discharged from the medical intensive care unit to a psychiatric ward on the fourth day after the overdose.

Results

A schematic diagram of the multicompartomt model of lithium pharmacokinetics is shown in Figure 1.
Absorption into the bloodstream (compartment 3) takes place from both the stomach (compartment 1 at rate \( k_3 \)) and the gut (compartment 2 at rate \( k_g \)), with a rate constant of \( k_{	ext{em}} \) for emptying from the stomach into the gut. Bloodstream (compartment 3) lithium equilibrates with the tissues (compartment 4) and is eliminated via urine excretion and hemodialysis. The delayed compartment could represent any quiescent region of the gastrointestinal tract that harbors unabsorbed drug.

Case 1. Serum lithium concentrations were obtained at 29 points during the 300 h after the overdose (see Figure 2). During each of the five separate 3- to 6-h hemodialysis periods, serum lithium concentration decreased by \( \sim 30\% \text{ to } 50\% \). Early in hemodialysis, the dialysate/serum partition coefficient was 0.191 (SD 0.006, \( n = 3 \)); in contrast, at the end of hemodialysis, the coefficient was 0.156 (SD 0.018, \( n = 3 \)). Figure 2 shows the best-fit curve determined from concentrations of serum lithium in the first 100 h after the overdose. The marked rebound after each hemodialysis indicates lithium redistribution from extravascular and intracellular sites. Beyond the initial 100 h, however, a single dose model could not adequately account for the marked increase in lithium concentration from the tissue or gut compartments (dotted line, Figure 2). The patient had not received any lithium or other psychiatric medications since the initial overdose and no new medications had been started. Just before the resurgence in lithium concentration, however, the patient had been started on enteral fluids. Apparently, the patient was mobilizing lithium from previously quiescent stores.

The best-fit curve for the later data \((t > 100 \text{ h})\) made use of kinetic constants from the earlier data. Although it is not possible to determine both the absorption fraction and the volume of distribution \((V_d)\) without data from an intravenous administration, the \( V_d \) is relatively predictable. We assumed a typical \( V_d \) (central) of 0.18 L/kg and calculated the amount of drug absorbed. These data indicate that the patient began absorbing an additional 15–20 g of lithium carbonate sometime shortly after 110 h. Moreover, the delayed dose showed an absorption profile more consistent with an origin in the intestine than with a slower absorption from the stomach. The concentrations were well described by this single-dose linear model for the first 110 h; allowing a second dose at 118 h provided a remarkably good description of the 16 values between 110 and 300 h.

Figure 3 shows the model fit for an assumed initial dose of 46 g of lithium carbonate absorbed from the stomach and a delayed dose of 19 g absorbed from the gut, beginning at 118 h. The concentration of lithium in the stomach compartment initially diminishes as the concentration in the gut and bloodstream compartments increases. The delayed dose can be described by an enteral lithium-containing drug reservoir that is not available for absorption until enteral fluids are initiated. The delayed compartment empties directly into the gut at about 118 h, leading to abrupt increases in lithium concentrations. By pharmacokinetic analysis, we estimate that 70\% of the ingested lithium was absorbed during the initial phase and the remaining 30\% during the delayed phase. Interestingly, at \( t = 173 \text{ h} \), the concentration of lithium in cerebrospinal fluid was 1.2 mmol/L; in serum, it was 3.4 mmol/L.
Case 2. Figure 4 shows the best-fit model for the serum lithium concentrations, and demonstrates the effects of hemodialysis and gastric lavage. Allowing additional doses directly into the gut compartment at times of gastric lavage provided a remarkably good description of serum lithium concentrations throughout the time course studied. By pharmacokinetic analysis, we estimate that 44% of the ingested lithium was absorbed during the initial phase, 6% after the first enteral fluids, 26% after the second fluids, and 24% after the last lavage.

Discussion

For the first four to five days in case 1, serum lithium concentration was well described by this model, based on a single oral dose. The abrupt increase in serum lithium that began after the initiation of gastrointestinal tube feedings on the fifth day, however, implicated an unexpected process. The drug formulation may provide a rationale for the 100- to 120-h delay in the absorption of 30% of the ingested dose. Lithium carbonate is the least soluble of the common lithium salts. The specific formulation taken by this patient (Lithobid, a sustained-release preparation of lithium carbonate) included carnauba wax and compounds to delay absorption (14). As has been reported for massive overdoses of drugs such as meprobamate (Milltown), gastric drug bezoars have been found at autopsy (15) and removed by gastrotomy (16). In this first patient, initiation of tube feedings may have stimulated the gastrointestinal tract, leading to secretion of hydrochloric acid from parietal cells; this in turn would hasten dissolution of the drug mass and result in deposition of a delayed lithium bolus directly into the duodenum.

The second patient was given fluids via a nasogastric tube only three times during hemodialysis; each was temporally associated with subsequent increases in serum lithium despite concurrent hemodialysis. He did not receive any other enteral fluids during the 120 h in the intensive care unit nor did he receive any psychiatric medications during that period. The nursing staff noted the first charcoal stool at 36.5 h, indicating reduced gastrointestinal motility during the initial 120-h period. The value 120 h was used to estimate the compartmental model parameters.

Lithium overdoses of these magnitudes or with these blood concentrations are rare. This number of observations permits separation of the absorption and redistribution contributions to postdialysis rebound. For the index case, only 30% of the absorption was delayed, whereas for the second case, 57% of ingested lithium was absorbed in the delayed phase. The difference may be due in part to co-ingestion of anticholinergic medication in the second patient. In both patients, delayed absorption appears to have been the major contributor to the rebound effect. The quantity of lithium absorbed in each of these patients after instillation of fluid directly into the gastrointestinal tract implicates an intestinal drug depot.

These data emphasize the value of early extensive hemodialysis in the treatment of lithium overdose to minimize tissue concentration and postdialysis rebound. Whole-bowel irrigation is reportedly superior to activated charcoal–sorbitol decontamination of patients after ingestion of sustained-release pharmaceuticals (14); however, this procedure needs more evaluation before it can be recommended in the treatment for overdose of sustained-release lithium compounds. Lithium carbonate is the least soluble of the common lithium salts, and enteral fluids may substantially hasten absorption and increase already dangerous serum lithium concentrations. Consequently, oral fluids should be restricted until concentrations of serum lithium are in the nontoxic range, and consideration should be given to concomitant hemodialysis and monitoring of serum lithium in anticipation of delayed absorption of intra-intestinal lithium.

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References

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