2001
VOLUME 3
NUMBER 4

Utox Update

UPCC A PUBLICATION OF THE UTAH POISON CONTROL CENTER FOR HEALTH PROFESSIONALS

Lithium

Case

A 57-year-old man was brought to the emergency department with a one-week history of weakness. His past medical history was significant for schizophrenia and a cerebral vascular accident. His medications included haloperidol, olanzapine, lithium and levothyroxine. Significant laboratory results on arrival to the emergency department were a lithium concentration of 4.0 mmol/L, BUN 47 mg/dL and a serum creatinine of 4.3 mg/dL. The patient underwent hemodialysis several times until his lithium concentration was less than 1.0 mmol/L. While hospitalized his urine output increased dramatically, his serum sodium increased and his urine specific gravity decreased. He was diagnosed with nephrogenic diabetes insipidus secondary to lithium intoxication. He required up to one liter of fluids per hour at times to prevent dehydration. His urine output slowly decreased over the next 10 days and he was discharged to a psychiatric institution.

Overview

Lithium is a naturally occurring alkali metal. Lithium salts have been used therapeutically for a wide variety of uses for nearly 150 years. Indications have ranged from cluster headache prophylaxis to cell stimulation in neutropenic patients. In 1970, lithium emerged as the treatment of choice for manic-depressive affective disorder (or bipolar disorder). Lithium continues to play a major role in the treatment of psychoactive diseases today.

Pharmacology & Physiology

Lithium's mechanism of action is not well understood. Lithium substitutes and competes with other ions (sodium, potassium, magnesium, calcium), modifies neurotransmitter function and also effects secondary messenger systems (cAMP, cGMP).[1] It is unknown how these mechanisms contribute to lithium's antimanic and antidepressant effects. A summary of the available forms of lithium and its pharmacokinetic properties can be found in Table 1.

Lithium is distributed in total body water and does not bind to plasma proteins. Lithium is unevenly distributed into body compartments. Higher concentrations of lithium are found in the brain, bone, saliva and thyroid than in the plasma.1 Lithium has a biphasic distribution. The final distribution space is larger than the initial distribution space. This suggests that lithium is bound in the body, although not to plasma proteins. The initial distribution half-life is approximately 5 hours with a terminal half-life ranging from 18-36 hours. Elimination of lithium may be prolonged in the elderly, in patients taking lithium chronically or in patients with renal insufficiency.[1,2]

Adverse events occur in 35-93% of lithium-treated patients.3 Common side effects include excessive thirst, polyuria, memory problems, tremor, weight gain, drowsiness and diarrhea.[3] Lithium has been implicated in the development of a neuroleptic malignant like-syndrome and serotonin syndrome.[4,5]

Drug Interactions

Lithium interacts primarily with drugs that affect renal clearance. Non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors and thiazide diuretics are examples of drugs that alter the clearance of lithium.[2] Serious drug interactions with angiotensin-1 receptor antagonists and levofloxacin also have been reported.[6,7]

Toxicity

Lithium has a narrow therapeutic-index. The therapeutic concentration for bipolar depression is 0.6-1.2 mEq/L. Toxicity can occur at concentrations >1.5 mEq/L.[2] Most poisonings are a result of altered kinetics (change in dosing or elimination) in patients taking lithium chronically.[2] The clinical presentation of lithium toxicity is loosely correlated with serum drug concentrations in patients who develop toxicity after chronic administration. Management of lithium toxicity should be dictated primarily by patient presentation and not serum concentrations.

Acute vs. Chronic Lithium Intoxication

Before treating lithium intoxication, it is important to distinguish whether it is an acute exposure or a chronic exposure. Signs and symptoms may vary between these two types. Table 2 compares and contrasts the clinical symptoms associated with lithium poisoning in the acute and chronic overdose.

An acute exposure follows the ingestion of an "overdose" of lithium (unintentional or intentional) in patients previously not on lithium or in patients who are on lithium chronically (acute-on-chronic) Patients present with gastrointestinal symptoms and usually mild neurologic abnormalities. Non-specific ST segment changes have been noted on the electrocardiogram in acute

continued on page 2

IN THIS ISSUE

Table 1: Lithium Quick Facts [1]

Protein binding	Minimal (<10%)
Volume of Distribution	0.7 - 1.0 L/kg
Absorption	Rapidly and completely from GI tract
Time to peak	Immediate release preparations = 15 minutes to 3 hours Sustained release preparations = 2 to 6 hours
Terminal half-life	18 - 36 Hours
Excretion	Primarily renal, freely filtered by glomerulus 80% reabsorbed (60% in proximal tubule, 20% between loop of Henle and collecting duct)
Available forms	300 mg (8.1 mEq) lithium carbonate capsules and tablets 300 mg and 450 mg lithium carbonate sustained-release tablets 8 mEq lithium (as citrate)/5 ml syrup

continued from page 1

lithium poisoning. Acute poisonings are generally less severe than chronic intoxications.

Chronic poisoning occurs in patients who are maintained on lithium therapeutically. Generally toxicity occurs after a dosing change or a decrease in lithium excretion due to a drug interaction, renal disease, dehydration, or illness. Toxicity is more severe and predominantly neurologic in nature. Neurological symptoms of mild toxicity include weakness and a fine tremor and are typically associated with lithium concentrations between 1.5 and 2.5 mEq/L. Symptoms worsen to muscle twitching, tinnitus, hyperreflexia, and slurred speech in moderate toxicity. Severe toxicity is characterized by symptoms of confusion, clonus, coma, seizures and muscular irritability. Irreversible neurotoxicity may occur at concentrations greater than 3 to 4 mEq/L and may be fatal. Patients on long-term lithium therapy often experience urinary concentrating impairment. Nephrogenic diabetes insipidus has been described in up to 20% of patients on long-term lithium therapy.

Patients with steady-state lithium concentrations who overdose have an acute-on-chronic poisoning. These patients can present with both acute and chronic poisoning symptoms.

General Management

Initial treatment of a lithium intoxication should include airway, circulation and breathing support along with intravenous fluids. Blood should be drawn to assess an initial lithium concentration, kidney function (BUN and serum creatinine) and serum electrolytes. In addition, an electrocardiogram and urinalysis should be obtained. Serial lithium concentrations should be followed every few hours.

Decontamination

Activated charcoal does not bind well to lithium and has no role when lithium is the sole agent in the overdose. Gastric lavage may be useful early after an acute overdose to remove any remaining pills in the stomach. Whole bowel irrigation (WBI) may be useful to reduce the absorption of sustained-release lithium. WBI, with a polyethylene glycol electrolyte solution, at 1500 to 2000 cc/hour should be considered for adult patients with acute toxic ingestions of lithium, especially if lithium concentrations are rising.[8]

The use of sodium polystyrene sulfonate (SPS) resin to reduce lithium concentrations in both acute and chronic intoxications of lithium in rats has been studied.[9] These studies demonstrated the ability of SPS to lower lithium concentrations after single oral doses and repetitive dosing. Although the studies showed some benefit, the treatment is impractical for humans because the equivalent dose of SPS is too high and would result in hypokalemia.

Fluid and Electrolyte Management

Most patients with lithium intoxication are volume depleted and may require intravenous rehydration. Forced saline diuresis would theoretically increase lithium elimination by increasing glomerular filtration but this has not been documented clinically. Fluid overload and hypernatremia are risks associated with saline diuresis.[8] Urinary alkalinization has little effect on serum lithium concentrations. Sodium bicarbonate is not recommended because of the risk of hypokalemia and fluid overload.

Elimination Methods

Lithium is easily dialyzable because of its small size, small volume of distribution and lack of protein binding. Hemodialysis can decrease the half-life of lithium and increase its clearance rate from 10-40ml/minute up to 70-170 ml/minute.[8] Patients receiving hemodialysis will often develop a “rebound” lithium concentration after treatment. Lithium concentrations should be drawn immediately following dialysis and repeated 6 hours later. Indications and endpoints for hemodialysis are quite controversial. Various authors have suggested criteria, none of which have been substantiated in clinical trials. Indications for hemodialysis which will result in the best patient outcomes with the lowest risk should account for the duration of lithium exposure, the possibility of delayed absorption, the serum

continued on page 4

Table 2: Lithium Toxicity

Organ System	Acute Poisoning	Chronic Poisoning
Endocrine	None	Hypothyroidism
Cardiovascular	Prolonged QT interval, ST and T wave changes	Myocarditis
Gastrointestinal	Nausea, vomiting	Minimal
Hematologic	Leukocytosis	Aplastic anemia
Neuromuscular	Myopathy, peripheral neuropathy	Same
Neurologic	*Mild:* fine tremor, lightheadedness, weakness *Moderate:* apathy, drowsiness, hyperreflexia, muscle twitching, slurred speech, tinnitus *Severe:* choreoathetoid movements, clonus, coma, confusion, seizures	*Mild:* same *Moderate:* same *Severe:* Parkinson’s disease, memory deficits, pseudotumor cerebri
Skin	None	Ulcers, localized edema, dermatitis
Renal	Urine concentrating defects	Rapidly and completely from GI tract
Congenital	None	Hypothyroidism

Meet the UPCC Staff

Brad Dahl is a native Californian. He completed a Doctor of Pharmacy degree and a general residency at the University of Utah in 1992 and has been with the Utah Poison Control Center ever since. Brad is the most senior specialist in poison information. He is a great resource for callers as well as other UPCC staff. Brad loves to teach. He is a clinical instructor at the College of Pharmacy and has provided many toxicology related lectures at the College of Pharmacy, for emergency medical technician training and in the community. His lectures are always engaging and informative. His love of toxicology is only matched by his love of his family, his rescued greyhounds and playing the bass in rock n' roll bands.

SPI Corner

Ideas for this section come from the specialists in poison information (SPI) who staff the phones at the Utah Poison Control Center (UPCC). The purpose of this section is to address issues related to the management of poisoned patients that are controversial or where conflicting information is available.

Multiple or Repeat Dose Activated Charcoal

Recently there have been several calls about the role of multiple dose charcoal (MDAC) in poison management. There are two distinct ways multiple dose charcoal may be useful for treatment of poisoned patients, enhanced elimination and prevention of absorption.

Multiple doses of charcoal can cause an 'intestinal dialysis' where medication is actually removed from the circulation across the gut wall. MDAC may work by several mechanisms. Medications in the circulation may diffuse passively from the circulation across the gut wall due to a concentration gradient. Theophylline and phenobarbital are examples of such medications. Other medications may be removed due to the interruption of enterohepatic circulation such as digitoxin.

Another application of MDAC is to prevent absorption. The treatment of drugs with erratic absorption kinetics may require more than one dose of charcoal. For example, carbamazepine, valproic acid and aspirin serum concentrations may increase several hours after ingestion despite receiving a single dose of charcoal. In general, repeat drug concentrations should be obtained for these medications to document a significant decrease and downward trend in serum concentrations. If serum concentrations continue to rise, a second or third dose of charcoal may be indicated. When using more than one dose, it is important to monitor bowel sounds. Obstruction or ileus may occur, particularly with an anticholinergic poison.

There are several formulations of charcoal available on the market. It comes as a powder and premixed forms. The premixed formulations generally are aqueous or contain sorbitol. Sorbitol is used as a sweetener and as a cathartic to decrease gut transit time and limit the amount of drug desorption from the activated charcoal. If more the one dose of activated charcoal is required, the aqueous formulation is preferred for subsequent doses to prevent persistent diarrhea, dehydration and electrolyte disturbances. The typical dose of activated charcoal is 1-2 g per kilogram of patient weight repeated every four to six hours. If the amount of toxin ingested is known it is recommended to administer 10:1 charcoal to toxin ratio.

Studies have shown that repeat doses of charcoal can lower serum drug concentrations although clinical data of improved outcome is lacking. Charcoal is relatively cheap, safe and well tolerated. Occasionally antiemetics are required. Some textbooks have suggested continuous nasogastric infusion of charcoal if multiple doses or large doses are required in a patient with poor tolerance.

In conclusion, multiple doses of charcoal may be indicated to enhance elimination or prevent absorption for certain types of medication. Please contact the UPCC for general questions or individual patient management issues regarding the administration of activated charcoal.

Jennifer Grover, PharmD

M-44 Sodium Cyanide Device

The United States Department of Agriculture, Animal and Plant Health Inspection Service, Bureau of Wildlife Services would like us to remind you that the M-44 sodium cyanide device is used in Utah. The device is tubular and is placed in the ground with 1.5 inches sticking out of the ground baited with meat. This device is used in specific situations to control coyotes, redfox, gray fox and wild dogs. The purpose of the device is to protect livestock, poultry, endangered species and to prevent the spread of disease. Although this device is primarily used on private lands, it may also be used on federal land in any county in the state. Areas where it is used are marked with signs. While human exposure to this device would be extremely unlikely, it is important to know that this device contains 91% sodium cyanide. Please report any exposure to this device to the Utah Poison Control Center at (801) 581-7504 or (800) 456-7707. We thank you in advance for your assistance.

The Utah Poison Control Center thanks

McNeil Consumer Healthcare

for their generous contribution which allowed us to produce and distribute this newsletter.

continued from page 2

lithium concentration, and the patient's clinical symptoms.[8,10] In general, patients who present with significant neurologic symptoms (confusion, seizures, coma, myoclonus), or those with elevated lithium concentrations and renal failure should be considered for hemodialysis. Small studies have demonstrated that continuous arteriovenous or continuous venovenous hemodiafiltration (CAVH or CVVH) may be effective in decreasing lithium elimination. Until larger, more conclusive studies are performed, hemodialysis remains the elimination option of choice.[8]

Summary

Lithium has a long history of treating psychotic disorders and remains widely used today. Because of its narrow therapeutic index and risk of serious complications, lithium should be carefully monitored in all patients receiving therapy. Prolonged exposure of the central nervous system to sustained lithium concentrations can cause permanent neurologic sequelae such as memory deficits, Parkinson's disease and personality changes. Fluid resuscitation and hemodialysis are the treatments of choice.

Erica Hermansen, Pharm.D. Student

References

1. Ward ME, Musa MN, Bailey L. Clinical pharmacokinetics of lithium. J Clin Pharmacol 1994;34:280-285.
2. Timmer RT, Sands JM. Lithium intoxication. J Am Soc Nephrol. 1999;10:666-674.
3. Dunner DL. Optimizing lithium treatment. J Clin Psychiatry. 2000;61:76-81.
4. Koehler PJ, Marandolle JF. Neuroleptic malignant-like syndrome and lithium. Lancet 1988;2:1499-1500.
5. Noveske FG, Hahn KR, Flynn RJ. Possible toxicity of combined fluoxetine and lithium. Am JPsychiatry 1989;146:1515.
6. Takahashi H, Higuchi H, Shimizu T. Severe lithium toxicity induced by combined levofloxacin administration. J Clin Psychiatry. 2000;61:949-50.
7. Zwanzger P, Marcuse A, Boerner RJ, Walther A, Rupprecht R. Lithium intoxication after administration of AT! blocker. J Clin Psychiatry. 2001;62:208-209.
8. Scharman EJ. Methods used to decrease lithium absorption or enhance elimination. J Toxicol Clin Toxicol. 1997;35:601-8.
9. Linakis JG, Savitt DL, Wu TY, Lockhart GR, Lacouture PG. Use of sodium polystyrene sulfonate for reduction of plasma lithium concentrations after chronic lithium administration. J Toxicol Clin Toxicol. 1998;36:309-313.
10. Bailey B, McGuigan M. Comparison of patients hemodialyzed for lithium poisoning and for whom dialysis was recommended by PCC but not done: what lesson can we learn. Clin Nephrol. 2000;54:388-392.

Utah Poison Control Center
410 Chipeta Way, Suite 230
Salt Lake City, UT 84108

NON-PROFIT ORG.
U.S. POSTAGE PAID
Salt Lake City, Utah
Permit No. 1529

ADDRESS SERVICE REQUESTED