Medical Intelligence

Potential Hazards and Applications of Lithium in Anesthesiology

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The element lithium (Li) is ubiquitous in nature, yet only in the last decade has its use as a therapeutic agent been approved in the United States. Although it is a simple element, Li's pharmacologic mechanism of action remains to be fully understood, and as its therapeutic use becomes more widespread, it poses particular hazards for the anesthesiologist. This short review is meant to inform, as well as to help guide the anesthesiologist in his approach to a patient receiving Li treatment. Moreover, possible new applications for Li in anesthesiology are discussed.

Absorption, Distribution, and Excretion

The presence of Li in the normal diet is so small as to yield undetectable plasma levels. Therapeutically, Li is available for oral administration as its carbonate salt. The intestinal absorption of Li is virtually complete, and its rapid absorption leads to peak plasma levels one to three hours after ingestion.1 When in blood, Li is not bound to plasma proteins and is free to enter various organs. The rate of entry varies with each particular organ, entry into the brain being the slowest due to the blood–brain barrier.2 Li is most highly concentrated by the thyroid gland and by bone, where it is deposited in phosphate salt form, with lesser concentrations of Li occurring in kidney, muscle, and brain.3 The high concentration of Li in the thyroid gland is due to the fact that Li is distributed both intracellularly and extracellularly (i.e., follicular lumen) in this gland.4 The elimination of Li occurs almost exclusively via the kidneys, with less than 1 percent of Li found in the feces.5 The half-life for the renal excretion of an ingested dose of Li is 24 hours. Unlike sodium, Li is reabsorbed by the kidney only in the proximal tubule6; therefore, diuretics with actions distal to this site, such as furosemide, do not affect Li excretion. In contrast, increasing the sodium load to the kidneys produces a prompt increase in Li clearance. Moreover, reduction in sodium intake will decrease Li excretion by the kidney, and may ultimately lead to the accumulation of toxic levels of Li.

Ionic Action

Lithium is an alkali metal, as are sodium and potassium, and thus shares many properties with these ions. Additionally, due to its smaller ionic radius, large sphere of hydration, and high charge density, it functionally resembles calcium and magnesium. The initial administration of Li (300 mg or more) produces a slight natriuresis; however, Li treatment does not alter serum sodium levels7; similarly, Li fails to affect serum levels of potassium.8 Lithium produces an acute increase in serum calcium and hypocalcemia, whereas it has been reported to both increase and decrease serum magnesium.8,9 Therapeutic levels of plasma Li appear to interfere with cellular magnesium-dependent sodium-potassium-activated ATPase,10 and magnesium's actions upon thyroid adenylate cyclase and DNA polymerase.11,12 These ionic actions of therapeutic levels of plasma Li produce only subclinical effects, and their possible relationship to Li's therapeutic actions remains a moot point.

Physiologic Actions

As mentioned above, Li administration initially results in a short-lived natriuresis, often accompanied by slight polyuria and polydipsia. In contrast, long-term administration of Li may rarely result in gross polyuria and polydipsia, resembling a diabetes insipidus-like state. This toxic phenomenon is resistant to treatment with vasopressin, as Li apparently exerts its actions...
via the inhibition of vasopressin-sensitive adenylate cyclase.\textsuperscript{13} Cessation of Li treatment promptly terminates the diabetes insipidus-like state. Lithium administration also exerts a direct action on inhibiting the release of thyroid hormone from the thyroid gland.\textsuperscript{14} This action of Li has been successfully used to treat thyrotoxicosis, and offers the advantage of not interfering with diagnostic tests, as do iodide-containing agents.\textsuperscript{15} Secondary to this effect, chronic Li administration may result in goiter formation, and rarely, in clinical hypothyroidism.\textsuperscript{14} The cardiovascular system is not significantly affected by Li, with the possible exception of T-wave flattening that is of only subclinical interest.\textsuperscript{16} There is no known interaction between Li and the respiratory system. Lithium may also produce leukocytosis, almost always neutrophilic, with leukocyte counts in the range of 10,000 to 14,000/mm\textsuperscript{3}; this action is reversible and does not involve permanent changes in either production or destruction of leukocytes.\textsuperscript{17} This action of Li may prove of future importance in neutropenic states often induced by cancer chemotherapeutic agents. Finally, Li may produce electroencephalographic changes consisting of increased amplitude and decreased frequency, which are not dose-dependent.\textsuperscript{18}

**Therapeutics**

Currently, Li is approved for use in the United States only in the treatment of manic-depressive illness. Lithium has a remarkable effect in calming manic excitement; however, it does not appear as effective in normalizing mood during a depressive episode.\textsuperscript{19} The chronic administration of Li exerts prophylactic actions in decreasing the number of future manic and depressive episodes; therefore, many psychiatric outpatients are currently receiving Li treatment. The mechanism by which Li exerts its psychiatric actions is controversial, but two major theories have been proposed. One theory states that Li exerts antimanic actions by its ability to increase the presynaptic reuptake and metabolism of brain norepinephrine, as mania is suggested to result from an excess in brain norepinephrine activity.\textsuperscript{20} This theory fails to explain the antidepressant actions of Li. The alternative hypothesis states that mania is due to an increased pool of intracellular sodium, and that Li decreases the size of this pool.\textsuperscript{21} The observation that Li produces natriuresis without affecting plasma sodium levels would support this theory; however, the inability to measure this sequestered sodium pool directly, and the lack of evidence of a direct involvement of sodium in depression, would argue against this view. Notwithstanding its application in psychiatry, Li is now receiving therapeutic trials for the relief of premenstrual tension, and a number of neurologic entities, including epilepsy, tardive dyskinesia, Huntington's disease, and migraine.\textsuperscript{22}

The therapeutic range of Li is reached when plasma levels are between 0.8 and 1.3 mEq/l, with plasma levels of more than 1.5 mEq/l being associated with toxicity. It should be noted that during an acute manic episode, patients may safely tolerate levels of Li in plasma that would ordinarily be toxic.\textsuperscript{23} Li is usually administered on a t.i.d. or q.i.d. basis, and dosage must be adjusted individually to maintain therapeutic plasma levels. Plasma Li concentrations are easily measured by flame photometry or atomic absorption spectrophotometry, thus providing a rapid means by which Li concentration may be monitored, this being more appropriate six to eight hours after the last dose of Li, at which time the steady-state distribution of Li is complete.

**Toxicities**

The possible hazards of Li in pregnancy are still undetermined. An international register for babies born to mothers receiving Li therapy has begun, and preliminary evidence suggests that Li administration during the first trimester may increase the rate of cardiovascular abnormalities in live-births.\textsuperscript{24} As Li is almost entirely eliminated by the kidneys, the use of Li in individuals with renal disease and Addison's disease, as well as patients receiving salt-restricted diets, must be approached cautiously, with frequent evaluations of Li plasma concentration. The various toxic side effects associated with Li administration are directly correlated with plasma concentration. Mild to moderate intoxication usually manifests itself by nausea, vomiting, diarrhea, muscle weakness, tremor, slurred speech, somnolence, confusion, and electrocardiographic changes involving T-wave depression and widening of the QRS complex. Severe intoxication results in possible epileptiform seizures, stupor, or coma. The treatment of Li intoxication is best handled by discontinuation of Li, institution of supportive measures, and administration of sodium via intravenous infusions (administration of 2 liters of physiologic saline solution over the first six hours is recommended). Diuretics may be employed to hasten Li excretion, but only those with sites of action on the proximal tubule are effective (e.g., mannitol, aminophylline, urea). Other diuretic agents, such as furosemide or thiazides, will not increase Li renal clearance, and by their natriuretic actions will actually exacerbate Li toxicity. Total Li clearance may also be potentiated by peritoneal dialysis or hemodialysis;
however, after hemodialysis there is a rebound increase in Li plasma levels as Li moves out of the tissues. Accordingly, Li plasma concentration must be closely monitored after the termination of hemodialysis to ascertain whether repeat hemodialysis may again become necessary.

**Lithium in Anesthesia**

The anesthesiologist most often encounters a patient receiving Li when administering anesthesia for electroconvulsive-shock treatments (ECT). There have been very few reports of Li interactions with anesthetics, but they are all significant. It has been reported that Li potentiated the actions of both depolarizing and nondepolarizing muscle relaxants in man, while not affecting the actions of nondepolarizing agents in experiments conducted in dogs. There is also the report of a case where Li potentiated the actions of barbiturate anesthesia in a woman receiving ECT; however, her plasma Li levels were in the toxic range at that time. Furthermore, animal studies have shown that Li prolongs the duration of ethanol-induced narcosis. As the use of Li becomes more widespread, it is expected that more case reports of Li interactions will appear in the literature. All of the reports to date indicate that Li potentiates the actions of anesthetics and muscle relaxants; therefore, smaller dosages should be initially administered and their effects evaluated. We suggest that when anesthetics are to be electively administered to patients receiving Li, the last two doses of Li prior to the procedure be withheld. This step will not interfere with Li’s therapeutic action, and will allow plasma concentrations to fall to a level where anesthetic interactions should not occur. Moreover, Li treatment can then be reinstated without significant loss of therapeutic efficacy.

**New Applications**

We previously carried out animal studies comparing Li (45 mg/kg) with droperidol (1.35 mg/kg) as an anesthetic premedicant. We found that when compared with droperidol or saline control, Li was *per se* analgesic, decreased the latency to and increased the duration of pentobarbital-induced narcosis, and produced a synergistic effect with pentobarbital in protecting animals from maximal electroshock-induced seizures. In unpublished work, we have observed that administration of Li (45 mg/kg) to mice (which produces a plasma level of 1.4 mEq/l) produced a greater than twofold potentiation in the efficacy of morphine (5 mg/kg) as measured by the hot-plate analgesia test. Moreover, in mice that were addicted to morphine by twice-daily injections over a four-day period, the concurrent administration of Li reduced the number of naloxone-precipitated jumps by a third.

These facts, and that in comparison with other anesthetic premedicants Li produces no dysphoria, dystonia, or respiratory depression, and that blood levels are easily monitored, lead us to suggest that Li may be used as a safe and effective anesthetic premedicant. Administration of Li *t.t.d.*, beginning with a total daily dosage of 900 or 1,200 mg, and titrating the dosage higher or lower according to blood levels 24 hours after the initial administration, should provide an adequate regimen for surgical premedication. Moreover, due to its action on the thyroid gland, Li not only may help to bring thyrotoxic patients to operation sooner, but also may be the preanesthetic agent of choice for these patients.

**References**

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