Commentary

The Contemporary Use of Lithium

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Lithium, a metallic element, has been known for years to be an effective mood stabilizer. The pioneering studies of Schou et al. in the 1950s[1] brought lithium treatment into the modern era of psychopharmacology. Lithium was the first drug approved in the United States for the treatment of bipolar disorder. By the 1970s, great excitement surrounded this new treatment, which provided much-needed relief for those individuals struggling with the chaos created by the dramatic mood swings associated with manic depressive illness. With the recent advent of newer mood stabilizers, interest in and research related to lithium treatment have waned. However, lithium continues to be prescribed to numerous patients as a highly effective treatment for bipolar disorder and as an adjunct for patients with refractory depression. Some pharmacokinetic features of lithium make it a unique mood-stabilizing modality.

Alan F. Schatzberg, M.D., points out that, over the last several years, our concept of bipolar disorder has been refined and the boundaries of diagnosis expanded to include bipolar I, bipolar II, mixed episodes, rapid cycling, and cyclothymia. Bipolar disorder begins early in life, afflicting approximately 1.3% of the population. In addition to its significant morbidity, it can be a deadly disease, with a suicide rate up to 15% in untreated patients. Patients with bipolar disorder frequently have comorbid substance abuse, which has been demonstrated to result in poorer outcomes. While the diagnosis of classic bipolar disorder is straightforward, it is not uncommon for the clinician to have some difficulty in distinguishing mixed or dysphoric mania from agitated depression, cyclothymia from personality disorder, and attention-deficit/hyperactivity disorder from bipolar disorder. Secondary mania results from physical disease, and it is critical to recognize it and establish its etiology. Common causes of secondary mania include ingestion of stimulant drugs, brain damage, and hyperthyroidism.

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Although lithium was the first mood stabilizer approved for the treatment of bipolar disorder, Charles L. Bowden, M.D., points out that, since 1977, only a few placebo-controlled studies have been conducted. With the advent of other potential therapeutic agents, such as carbamazepine and valproic acid, interest has arisen in assessing the efficacy of these compounds relative to lithium. In a recent study performed by Bowden and colleagues,[2] the efficacy of lithium carbonate was compared with that of divalproex and placebo. Lithium and divalproex were found to be equally effective after 21 days of treatment. In addition, a maintenance study in which drugs were administered over a 1-year period revealed divalproex to be more efficacious and better tolerated than lithium. (Bowden CL, Calabrese JR, McElroy SL, et al. Manuscript submitted). Overall, patients who displayed mixed mania and/or rapid cycling had better outcomes on divalproex. In addition to its role in treating bipolar illness, lithium has been established as important in augmenting responses in patients with partially responsive or refractory major depression. Considerable evidence, including controlled clinical trials,[3] supports this contention.

Lithium carbonate is available in immediate- and sustained-release forms. However, most of what is known regarding the pharmacokinetics of lithium is based on immediate-release preparations. Lithium has unique properties that include minimal protein binding, lack of biotransformation, and exclusively renal elimination. Marked individual variability in the dose-plasma level relation is important to consider, since lithium is potentially toxic, with a small gap between therapeutic and toxic levels, and can have serious adverse effects. Frequently, the side effects of lithium are related to the rate of increase in the plasma concentration. Sustained-release preparations provide for more stable levels over 24 hours than immediate-release preparations and mitigate individual differences in plasma levels. In one of the few studies comparing immediate- with sustained-release lithium, Miller and colleagues[4] demonstrated decreased effects on urine osmolality with Lithobid, a sustained-release preparation. Sustained-release preparations offer the potential advantages of a slower increase rate in plasma concentrations and a greater likelihood of compliance. It is important to monitor lithium plasma levels to maximize the benefit/risk ratio. Clinton D. Kilts, Ph.D., suggested that brain lithium

concentrations may be better predictors of therapeutic response[5] than are serum lithium levels. However, he pointed out that, compared with serum concentrations, brain concentrations respond more slowly to dose changes. In addition, serum levels are only moderately correlated with brain lithium concentrations.

In summary, lithium provides a very effective treatment for bipolar disorder as well as a modality to augment antidepressants in patients with refractory major depression. However, with the advent of interest in the newer anticonvulsant compounds to treat bipolar disorder, the use of lithium, its efficacy, and its unique pharmacokinetic profile have been neglected. The sustained-release preparations should offer further the advantages of diminished side effects and increased patient compliance. Clearly, further research should be performed to understand lithium's mechanism of action and to develop a clearer picture of the patients most likely to benefit from lithium treatment.

Drug names: carbamazepine (Tegretol and others), divalproex (Depakote), sustained-release lithium (Eskalith, Lithobid).

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