Researchers closer to improving safety, effectiveness of lithium therapy

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This shows crystals under the microscope. Credit: © University of South Florida

Lithium, one of the oldest and most widely used drugs to treat neuropsychiatric illnesses, such as bipolar disorder, has a serious drawback – toxicity. In a continued effort to find a safer form of lithium, researchers at the University of South Florida (USF) have discovered that lithium salicylate, an alternative salt form, might be the

answer.

The researchers found that oral lithium salicylate produced steady lithium levels up to 48 hours in rats without the toxic spike associated with the rapid absorption of current FDA-approved lithium carbonate. They concluded that lithium salicylate could be more effective than lithium carbonate, yet without accompanying risks of toxicity, a potentially important development in the next generation of lithium therapeutics.

Their study results appeared in a recent issue of *RSC Advances*, the journal of the Royal Society of Chemistry.

While lithium carbonate has been very effective for the treatment of mania in bipolar disorder, and credited for reducing suicides in depressive phases of the disease, patients who take lithium carbonate are often noncompliant because of adverse effects, including hand tremor, diarrhea, vomiting, weight gain and decreased thyroid function. New drugs that are as effective as lithium carbonate, but without toxicity, have not been forthcoming.

"Despite its narrow therapeutic window and the emergence of proprietary alternatives, U.S. FDA-approved lithium therapeutics are still regarded as the 'gold standard' for the treatment of the manic phase of bipolar disorder," said study lead author Adam J. Smith, PhD, a neuroscientist at the Center of Excellence for Aging and Brain Repair, Department of Neurosurgery, at USF Health.

"Our previous research suggested that re-engineering lithium therapeutics by crystal engineering might produce better performance with reduced toxicities."

Crystal engineering is the design and synthesis of molecular solid crystal

structures with desired properties using intermolecular interactions, Smith said.

For their latest study published in *RSC Advances*, the researchers tested two previously untested salts of lithium—salicylate and lactate—both of which are structurally different from lithium carbonate. In laboratory rats, they found that lithium salicylate and lithium lactate exhibited "profoundly different pharmacokinetics" when compared to the FDA-approved and widely used lithium carbonate. Pharmacokinetics is the way the body absorbs, distributes and gets rid of a drug.

"To our knowledge, this is the first pharmacokinetic study of lithium salicylate and lithium lactate in laboratory animals," Smith said.

The findings support earlier suggestions that an ideal lithium preparation would be one that would both "flatten" high blood level peaks and also slow declining blood concentrations, the researchers report.

"This is exactly the pharmacokinetic profile produced by lithium salicylate in our study," said senior author Doug Shytle, PhD, also of the Center of Excellence for Aging and Brain Repair at USF Health. "Remarkably, lithium salicylate produced elevated levels of lithium in the blood and brain 48 hours after the dose, but without the sharp peaks that contribute to the toxicity problems of lithium in the currently used form."

That 48-hour window, the researchers said, represents a critical difference between lithium salicylate and current FDA-approved lithium therapeutics. If these preclinical results hold true in humans, this would allow for a less frequent dosing regimen and possibly fewer troublesome side effects that plague conventional lithium therapy.

"Psychiatry has long struggled with the fact that, while lithium is highly

effective for treating bipolar disorder, the narrow therapeutic window and side effect profile often makes lithium both difficult and sometimes dangerous to work with clinically," said Todd Gould, MD, of the Department of Psychiatry at the University of Maryland, an expert in the mechanisms of lithium and the neurobiology of bipolar disorder.

"The pharmacokinetic data by Dr. Smith and colleagues suggests that lithium salts other than the commonly used lithium carbonate may have a broader therapeutic window and potentially fewer side effects. Studies in humans will be needed to confirm safety and demonstrate that the pharmacokinetic profile observed in rats is similarly observed in humans."

USF researchers continue to pursue a safer, more effective lithium therapy, and expect to soon conduct the experiments required to support early clinical trials.

More information: Smith, A. J., S. Kim, J. Tan, K. B. Sneed, P. R. Sanberg, C. V. Borlongan and R. D. Shytle (2014). "Plasma and brain pharmacokinetics of previously unexplored lithium salts." RSC Advances 2014, 12362. pubs.rsc.org/en/content/articl … a46962j#!divAbstract

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