New long-acting local anesthetic derived from algae effectively blocks pain in surgical patients

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A U.S.-Chile collaboration is bringing surgical patients closer to having a long-acting local anesthetic. In a randomized, double-blind trial, patients given neosaxitoxin, a new local anesthetic derived from algae, had significantly less postoperative pain and recovered about two days sooner than those given the commonly used local anesthetic bupivacaine. Based on this finding, Children's Hospital Boston, a co-investigator on the study, has signed a collaboration agreement with biotech start-up company Proteus SA (Santiago, Chile) to move the new anesthetic toward clinical adoption.

Tens of millions of patients have operations requiring local anesthesia each year. Current local anesthetics act for less than 8 hours; when they wear off, patients generally need opioid analgesics, which cause substantial side effects, including nausea, sedation, shallow breathing, sleepiness, constipation and itching. These side effects often delay recovery and can result in prolonged hospitalization.

Neosaxitoxin (neoSTX) provides local anesthesia for more than 24 hours. It is a site 1 sodium-channel blocker, part of a larger class of emerging anesthetics based on molecules derived from aquatic organisms.

"In my opinion, there has not been a truly innovative new local anesthetic medication in the last 40 to 50 years," notes study coauthor

Charles Berde, MD, PhD, chief of the Division of Pain Medicine at Children's Hospital Boston. "Most drugs introduced over that time period have represented only minimal advances. There have been candidate drugs that went in novel directions, but they've had shortcomings, and none have made it to market."

The neoSTX trial, the first of its kind, involved 137 Chilean patients having laparoscopic removal of their gall bladders. As reported in the March-April issue of *Regional Anesthesia and Pain Medicine*, significantly fewer patients randomized to neoSTX reported severe postoperative pain at the incision site at both 12 hours (4 vs. 18 percent) and 24 hours (6 vs. 16 percent). Significantly more neoSTX-treated patients had complete absence of pain at 12 hours, both at rest (88 vs. 69 percent) and with movement (80 vs. 60 percent). Patients in the neoSTX group reported a full functional recovery approximately 2 days earlier. No serious adverse reactions occurred in either group.

The trial was a three-part effort led by first author Alberto Rodríguez-Navarro, MD, at Padre Hurtado Hospital (Santiago, Chile); a clinical-academic team led by Berde; and a pharmaceutical development team led by Luis Novoa, CEO of Proteus SA. "As a surgeon who specializes in abdominal surgery, I think that the future of pain treatment will benefit greatly from this type of multidisciplinary collaboration," says Rodríguez-Navarro.

The Chilean and American investigators met through their scientific publications. Berde and Daniel Kohane, MD, PhD, a clinician-researcher in Critical Care Medicine at Children's, had studied site 1 sodium-channel blockers derived from marine toxins for more than a decade. Their work in rats showed that the compounds lack the side effects of existing anesthetics and opioid analgesics. They are not addictive, have no cardiac toxicity and don't cross the blood-brain barrier, thus avoiding the risk of seizures occasionally seen with existing local anesthetics.

They also cause minimal local tissue reaction, avoiding the nerve and muscle damage seen with high concentrations of existing local anesthetics.

Meanwhile, in Chile, Rodríguez-Navarro had published work examining the anesthetic potential of neoSTX, derived from local algae.

The scientists at Proteus have developed expertise in extracting, culturing and purifying large amounts of neoSTX from freshwater microalgae, and formulating the compound for medical use. The planned clinical studies at Children's, hoped to begin this year, will look for optimal doses that block pain while avoiding toxicity.

Groups of young adult volunteers will receive neoSTX injections under the skin in gradually increasing doses. Although NeoSTX has appeared very safe in over 400 patients in clinical trials so far, the upcoming study will more precisely determine the margin of safety. Subjects will be closely monitored for numbness at the injection sites, as well as whole-body effects.

The team believes that even more prolonged local anesthesia is possible. They have data from animals and exploratory studies in humans showing that combining Site-1 sodium channel blockers with existing local anesthetics can produce nerve blockade for up to 2 to 4 days – with minimal local or systemic side effects.

"We think that the demand for a long-acting local anesthetic will vast," says Novoa of Proteus. "Our initial estimates suggest a market greater than 1 billion dollars."

Children's holds a U.S. patent on site 1 sodium-channel toxins as prolonged-duration local anesthetics. The clinical trial was supported by an Innova Corfo Project.

Provided by Children's Hospital Boston