Tetrodotoxin Is Safe and Effective for Severe, Refractory Cancer Pain

Researchers affiliated with the Canadian Tetrodotoxin Study Group reported recently that short-term intramuscular administration of International Wex Technologies' Tectin brand of tetrodotoxin, a neurotoxin derived from the puffer fish, can safely relieve refractory pain suffered by cancer patients for more than 2 weeks.

The treatment of cancer pain is complicated by the unpredictability of patient response to different types of analgesia. Studies in animal models have shown that differences in the expression of sodium channels, which are found on nociceptive pain fibers, have an important role in persistent pain.

In preliminary testing, scientists discovered that tetrodotoxin blocks the transmission of sodium along neural pathways in a highly selective manner. The compound is believed to be one of the most deadly nerve toxins found in Nature, since just a small amount can completely paralyze a human being. However, investigators believe that carefully titrated, tiny doses of the nonnarcotic substance can relieve pain effectively in cancer patients—without the adverse reactions, drug interactions, and addictive potential associated with other pain relievers.

At the 18th annual meeting of the International Society for Biological Therapy of Cancer, held in Bethesda, Maryland, Dr. Edward Sellers, a senior medical consultant to International Wex Technologies, presented an interim analysis of the results of a phase IIa trial, the first open-label, multicenter, dose-escalation clinical investigation of tetrodotoxin in patients with refractory cancer pain.

Twenty-two subjects were injected intramuscularly with 15, 30, 45, or 60 μg of tetrodotoxin over 4 consecutive days. All subjects suffered from severe pain caused by their malignancy or cancer treatment; none of them had received any benefit from currently established analgesic regimens.

The team reported that 17 (68%) of the 25 tetrodotoxin treatments administered elicited a full or partial analgesic response, based on the primary endpoint of a reduction in pain intensity of $\geq$ 33% on the Brief Pain Inventory. The investigators noted that patients exhibited a cumulative onset of pain relief that began on about the third day of therapy and that often lasted for many days after the final treatment. In some cases, patients enjoyed pain relief for 15 days or longer.

No serious adverse events occurred. Among the responses described as "striking" was reduced allodynia. The investigators noted that some patients became drowsy, apparently from the lingering effects of a relative overdose of opioids that were present when sudden improvement in pain occurred.

On the basis of these findings, the researchers concluded that intramuscular administration of tetrodotoxin for 4 days at carefully titrated doses can safely relieve the refractory pain suffered by cancer patients. The researchers urged that use of higher tetrodotoxin doses be studied in relieving cancer pain and that a larger, multicenter, controlled trial of the compound be conducted. Toward that end, representatives for International Wex Technologies are filing for a pivotal phase IIb/III clinical trial with Health Canada that will replace intramuscular administration of the drug with subcutaneous injection to achieve better tolerance in the target population. Phase II studies also are planned to begin in China.

Tetrodotoxin also is being tested for alleviation of withdrawal symptoms in opioid-dependent patients and as a dental anesthetic. The Vancouver, BC, manufacturer anticipates that the drug will be approved in Canada for its analgesic application in late-2005 and will be launched in 2006.