



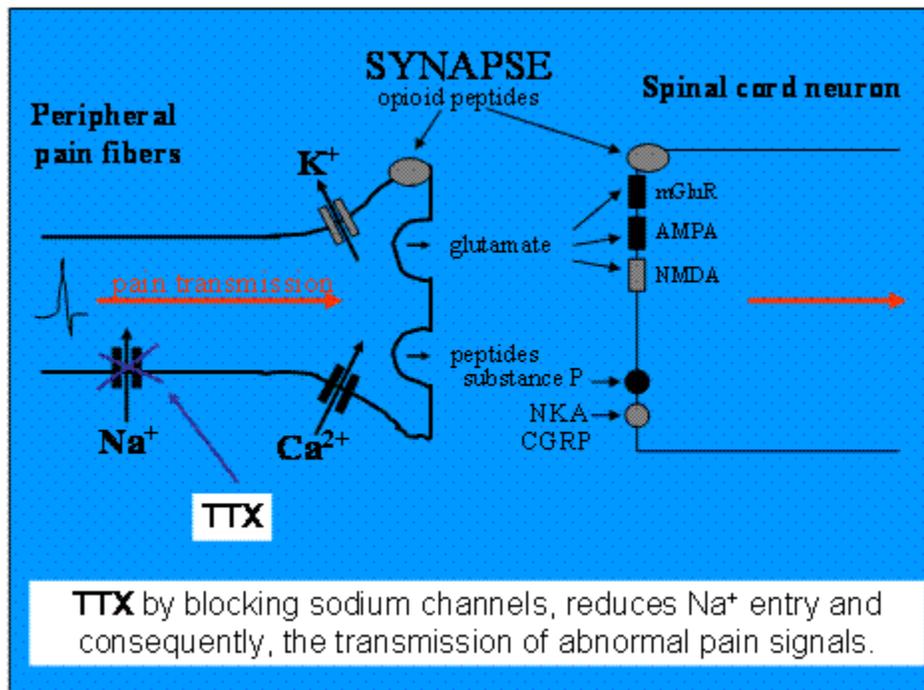
A Clinician's Guide to TTX

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Tetrodotoxin: Mechanism of action

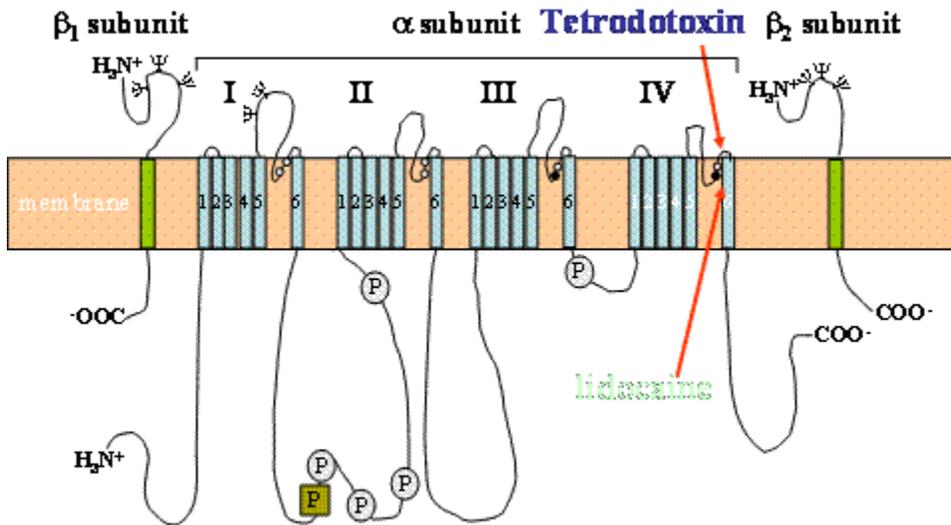
Tetrodotoxin (TTX) is a neurotoxin found in puffer fish and other marine animals. This compound has been used for decades by neuroscientists as a pharmacological probe. It is a non-peptide, guanidinium toxin demonstrating strong analgesic properties and an adequate safety profile, as indicated by early clinical reports. The compound is known to block the sodium (Na^+) channels found on nociceptive pain fibres in a highly selective manner. Its mechanism of action is thought to be related to its ability to stabilize neuronal membranes by inhibiting the Na^+ ionic fluxes required for the initiation and conduction of impulses.



The voltage-gated sodium channels (VGSCs) are responsible for the initiation and transmission of signals in excitable cells by allowing the influx of Na^+ ions, thereby producing the upstroke of the action potential. Nine sodium channel isoforms have been functionally identified and characterized in mammalian tissues. These isoforms differ with respect to their tissue localization, activation/inactivation threshold and rates, and sensitivity to TTX. Tetrodotoxin binds selectively to the alpha subunit of VGSC subtypes Nav 1.1, 1.2, 1.3, 1.4, 1.6 and 1.7. Only nanomolar concentrations of the compound are required to inhibit nerve and skeletal muscle transmission. Other subtypes are relatively insensitive to TTX. In particular, the cardiac Na^+ channel subtype is insensitive to the binding of TTX compared to the neuronal and skeletal muscle subtypes.

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Voltage-gated Na⁺ channel



Tetrodotoxin blocks the Na⁺ channel binding at the outer mouth of the IVth domain of the α subunit of the channel.

Open-label Phase IIa Study

An open-label, multi-dose efficacy and safety study of intramuscular tetrodotoxin in patients with severe cancer-related pain (Study WEX-003)¹

Trial type: Phase IIa study to assess the effects of intramuscular TTX in patients with severe cancer-related pain.

Trial design: Six ascending dose levels of intramuscular TTX administered over a 4-day treatment period in hospitalized patients. Planned dose groups were to receive 4 consecutive days of: 7.5 mcg b.i.d., 15 mcg b.i.d., 22.5 mcg b.i.d., 30 mcg b.i.d., 30 mcg t.i.d., or 30 mcg q.i.d. of TTX. Each dose level involved 6 patients and was performed sequentially. Patients could re-enrol at a higher dose-level but with a minimum of 6 weeks between treatments.

Patient selection criteria: Patients ≥18 years old with severe unrelieved cancer-related pain (from the cancer or its treatment) for at least 2 weeks, in spite of regular use of strong opioids at high doses. In the presence of neuropathic pain, attempted treatment with maximum doses of at least one adjuvant analgesic. Patients receiving recent chemotherapy, hormonal therapy, bisphosphonates or radiotherapy were excluded. Other exclusions involved specific treatments and conditions potentially interfering with the study.

Assessments: Efficacy was assessed at baseline, during treatment (Days 1-4) and daily post-treatment until Day 15. Evaluation of efficacy was primarily based on changes in pain intensity compared to baseline, as assessed by the short form Brief Pain Inventory (BPI-SF). Safety evaluations included adverse event monitoring, physical/neurological exam, ECG, vital signs, laboratory tests. All safety assessments were completed at screening/ baseline, on Day 5 prior to discharge, Day 8 and at end of study.

Conclusion: TTX administered for 4 days at daily doses ranging from 7.5 mcg b.i.d. to 30 mcg t.i.d. effectively relieved severe, treatment resistant cancer pain in a substantial proportion of patients and often for a prolonged period after treatment. Somatic, visceral and neuropathic pain could all respond. Adverse events were generally mild and transient at doses up to 30 mcg b.i.d. of tetrodotoxin. Further study of this compound is warranted.

Randomized, Double-Blind Phase IIb Study

Tetrodotoxin for moderate to severe cancer pain: A randomized, double-blind, parallel design multicenter study (Study WEX-014)²

Trial type: Phase IIb study to assess the efficacy and safety of TTX in patients with stable but inadequately controlled moderate to severe pain associated with cancer

Trial design: Multicenter, randomized, double-blind placebo-controlled parallel design trial in patients with moderate or severe cancer pain in spite of best available treatment. Patients received 30 mcg b.i.d. subcutaneous TTX or placebo over Days 1-4, with an observation period of 15 days or longer.

Patient selection criteria: Patients ≥ 18 years old with inadequately controlled moderate to severe cancer pain of at least 2 weeks' duration were eligible. Exclusion criteria included planned initiation of chemotherapy, radiotherapy or bisphosphonates within 30 days prior to study; use of systemic local anaesthetics; presence or history of specific medical conditions (eg. heart block, CO₂ retention, hypersensitivity to TTX, pregnancy and lactation).

Assessments: Following a short baseline period, patients were randomized on day 1 to receive study drug or placebo for 4 days. After the treatment period, all patients were seen again on Days 5, 8, and 15 for further safety and efficacy evaluations, and then every 2 weeks until pain returned. The primary endpoint was the proportion of analgesic responders, defined as a patient having a mean reduction in pain intensity $\geq 30\%$ from baseline as assessed by the patient's global pain intensity measure using the Brief Pain Inventory (BPI). Secondary efficacy was assessed using the McGill Pain Questionnaire, the Neuropathic Pain Scale (NPS) and a patient-reported Global impression of pain. Quality of life was assessed using sub-items of the BPI.

Conclusion: This trial suggests that TTX may relieve moderate to severe treatment-resistant cancer pain in a substantial proportion of patients, and often for a prolonged period following treatment. Sensory adverse events, primarily tingling around the mouth were generally mild. Reversible ataxia occurred in one patient and this has been previously described with TTX. Further study of tetrodotoxin is warranted using a composite endpoint.

Ongoing Phase III Studies

Protocol Number: TEC-006

Protocol Title

A Multicentre, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design Trial of the Efficacy and Safety of Subcutaneous Tetrodotoxin (Tectin™) for Moderate to Severe Inadequately Controlled Cancer-Related Pain

Stage

Phase III

Location

Canada

Status

This trial is currently enrolling patients.

Further Information

For further details, please visit ClinicalTrials.gov.

Protocol Number: TEC-006OL

Protocol Title

A Multicentre, Open-Label, Long-Term Efficacy and Safety Continuation Study of Subcutaneous Tetrodotoxin (Tectin™) for Moderate to Severe Cancer-Related Pain

Stage

Phase III

Location

Canada

Status

This trial is currently enrolling patients.

Further Information

This trial is only open to patients enrolled in the TEC-006 trial.

For further details, please visit ClinicalTrials.gov.

References

1. Hagen NA, Fisher KM, Lapointe B, du Souich P, Chary S, Moulin D, et al. An open-label, multi-dose efficacy and safety study of intramuscular tetrodotoxin in patients with severe cancer-related pain. *J Pain Symptom Manage* 2007; 34:171-182.
2. Hagen NA, du Souich P, Lapointe B, Ong-Lam M, Dubuc B, Walde D. Tetrodotoxin for moderate to severe cancer pain: A randomized, double-blind, parallel design multicenter study. *J Pain Symptom Manage* 2008; 35:420-429.

Contact information

Walter Korz
Senior Director Clinical Development
(604) 676-7893
walterk@wexpharma.com