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Application of Tetrodotoxin for Anesthetic and Pain Management

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Abstract. Tetrodotoxin (TTX) is a potent neurotoxin that is predominately sourced from marine animals, which serves a dual role as both a fatal toxin and a potential therapeutic compound. TTX functions by selectively binding to voltage-gated sodium channels (VGSCs), preventing sodium ions from entering nerve cells and thereby blocking action potential formation. While its toxicity can lead to severe outcomes like whole-body paralysis and even death, TTX's unique mechanism of action creates possibilities for anesthetic use and pain management. Unlike traditional local anesthetics, TTX offers long-lasting effects with a lower risk of cardiac toxicity due to its selective binding. TTX can effectively manage chronic and neuropathic pain, including cancer-related and chemotherapy-induced pain, with relatively mild side effects when used at controlled doses. Combining TTX with drugs like bupivacaine has shown a synergistic impact, significantly extending pain relief duration while reducing potential toxicity. The lacks of an antidote for TTX necessitates strict dosing controls and further research to ensure safety. This research explores the mechanisms and safety considerations of TTX, and most importantly, its emerging applications will be analyzed.

Keywords: Tetrodotoxin; Pain management; Local anesthetic; Neuropathic pain; Clinical trials.

1. Introduction

The history of consuming pufferfish is long and enchanting across East Asia, especially in Japan. Pufferfish and other marine animals often contain tetrodotoxin (TTX), a potent toxin that can cause severe intoxication and even death if ingested or touched. Moreover, a known antidote does not exist for TTX [1]. Its potent neurotoxicity comes from its unique ability to bind to the receptor on voltage-gated sodium channels (VGSCs) selectively [2]. These channels located on the neuronal membrane are critical for transmitting sensory signals from the nerve cells to the brain [3]. Sodium channels become blocked after TTX binds to it, causing sodium ions to stay out of the neuron. While the chloride ions can still pass through its specialized channel, the membrane loses the depolarization ability required to form an action potential, which is necessary for nerve signal transmission. This blockade becomes a severe neural health issue when muscle cells from all over the body fail to receive signals to move. It leads to paralysis of muscles or suffocation if the muscles from the lung are paralyzed. The worst outcome can be cardiac arrest or even death when the muscles responsible for heartbeats lose their functions.

However, this stunning ability to block VGSCs inspires scientists to utilize TTX for scientific interest. For example, it can be opened to the field of therapeutic application. It has come to a consensus that the current local anesthetics are not perfect due to the possibility of side effects such as cardiac toxicity [4]. Since TTX selectively binds to the VGSCs, problems caused by binding to alternative sites are eluded. Unlike the traditional amide-based local anesthetic, TTX's effect is long-lasting, which means the repeating dosing of local anesthetic can be avoided to ensure the safety of anesthesia [5]. It is still important to consider that TTX has extreme toxicity, so further restrictions must be made to control it. Given its potency and specificity, TTX is a very prospective therapeutic agent for treating pain and providing anesthesia. The biggest challenge to overcome is to reduce its toxicity, and this will be addressed in the last section.

Clinical trials have demonstrated the efficacy of TTX in reducing pain intensity among patients with complex pain conditions. For instance, long-term randomized controlled studies have shown that subcutaneous administration of TTX can provide noticeable pain relief compared to placebo, with a

tolerable degree of side effects [6]. These relative findings greatly suggest that TTX could be a valuable analgesic substitution, especially for patients with special conditions for which opioids are not ideal. This research will discuss the application of the potent neurotoxin TTX in anesthesia and pain management. Specifically, the specific mechanism of action and application performance of TTX will be systematically analyzed.

2. Anesthetic and pain management

2.1. Mechanism

Pathological pain is a severe problem that has bothered a large population in most countries. TTX has gained significant attention in the field of pain management, whether for chronic or neuropathic pain conditions [7]. The possibility of pain relief effects comes from its ability to shut down the VGSCs, including NaV1.7, NaV1.8, and NaV1.9. These sodium channels are upregulated during pathological pain conditions and are mainly responsible for pain conduction [8]. TTX blocks the VGCS by binding to the pore region part of the extracellular side of them. Sodium coming from outside the nerve cells through VGCS is required to depolarize the membrane to produce the action potential [9]. Pain is transmitted by an action potential that passes through a nerve cell. Pain Perception is thus reduced when signals from peripheral nerves to the central nervous system are cut off due to a lack of action potentials. Since TTX has a high specificity for sodium channels, the channels for other ions or other proteins would not be influenced. The cardiac function would also not be affected because NaV1.5 is resistant to TTX and is most relevant to cardiac problems. Almost all applications of TTX are centered around this irreplaceable feature of inhibiting sodium transportation across the cell membrane.

2.2. Clinical trials on pain management

Clinical trials have also proved that TTX can be used safely with minimal adverse effects that can be relieved 29% of the population under this experiment suffered from TTX [10], while the rest of the 71% of patients suffered from the original cancer before treatments. A particular dose relationship exists for tetrodotoxin. Patients dosed with 30 μg show severe nausea, but for patients dosed with less than 30 μg, the most common adverse effects are gastrointestinal disorders, hypesthesia oral, and nervous system disorders. These adverse effects are strongly correlated with the mechanisms of TTX and do not cause severe damage since their intensity is either mild or moderate. Ninety-eight percent of the total adverse effects reported range from mild to moderate. In addition, the tolerance of TTX seems promising. As high as 30 μg twice per day dose for four continuous days is adequate for pain relieving while ensuring the safety of the patients. Building on TTX's use as a cancer pain management solution, it has also shown the potential to reduce chemotherapy-induced neuropathic pain [6]. This severe type of pain can result in a reduction in chemotherapy dose, which strongly affects the patient's life. By injecting TTX subcutaneously, 30 μg BID can reduce up to 30% of the pain score during four weeks.

2.3. Animal studies

Animal studies have also shown that TTX has considerable antinociceptive effects, specifically the ability to reduce neurasthenic pain significantly [11]. When rodents are put under several pain tests, including formalin test and mechanical allodynia, TTX injection is performed and functioned in every test. In the formalin test, the injection of 3 μg/kg to 6 μg/kg reduces the pain score similar to the value that morphine results in. TTX performs better for acute pain in this test, which is more determined by blocking the nociceptor. Similarly, for the allodynia test, which is associated with nerve damage and can last a very long time, 3 μg/kg to 6 μg/kg dosing TTX relieved the stimulus from the tiny filament returns to a level before the surgery. This stimulus was meant to activate Aβ systems to create a feeling of pain that was initially the tactile sense if it was not neuropathic. TTX is an adequate non-opioid alternative for neuropathic pain. Surprisingly, none of the observed adverse effects from TTX were observed, but morphine has caused unwanted sedation.

2.4. Anesthetic

On the other hand, the possibility of using TTX as a local anesthetic is very promising. A local anesthetic shares similarity with TTX's painkiller aspect, which both inhibit the transmission of pain signals from neurons. The difference is that, being a local anesthetic, TTX can also cancel other feelings except for pain. The research was done on the TTX's analgesia ability by assessing the time required for rodents to withdraw their legs from the hot plate after subcutaneous injection [12]. The response of the leg contralateral to the injection was used to measure the adverse effects of TTX Injection. The duration of thermal nociceptive block for 50 μM TTX is equivalent to 0.5% bupivacaine, a potent opioid local anesthetic. The injection of 30 μM TTX works best because higher concentrations result in overt blockade on the contralateral leg, which is not desirable for precise local anesthesia. The practical block lasts around 39 minutes, and the blockade on the other side is less than 5 minutes. In addition, the coadministration with other drugs, such as bupivacaine, can improve both the efficiency and safety of the injection. A combination of 30 μM and 0.5% bupivacaine results in an average of 556 min of blockade, which is far beyond the sum effect of the two drugs (161 min when bupivacine alone). The toxicity of adding a second drug is less than using TTX alone, which can be shown by a significant decrease in the contraction of the contralateral leg (Table 1). Based on the current result, the safety of using tetrodotoxin in clinical trials needs further proof.

Table 1. Side effects of coadministered drugs [12].

TTX (μM)	Coadministered drugs	Duration of effective block of thermal nociception	n	P Value
40	-	45±34	11	-
	Epinephrine	0	10	0.003
	Bupivacaine 15.4 mM	6.4±23	13	0.005
	Bupivacaine 11.6 mM	0	4	0.003
	Bupivacaine 1.93 mM	0	4	0.003
50	-	112±27	12	-
	Epinephrine	2.27±7.5	11	5.6×10^{-9}
	Bupivacaine 15.4 mM	0	10	52×10^{-8}

2.5. Drug delivery

TTX's high therapeutic efficiency is accompanied by its extreme toxicity. Both the high toxicity and narrow therapeutic window pose serious challenges to drug delivery safety and effectiveness. Developing an optimal delivery system for TTX solves these problems straightforwardly. TTX is primarily administered through subcutaneous injection for its precise dosing and effects. Improvement around this can done to limit the toxicity of TTX. Liposome encapsulating is a method that has been commonly used in clinical trials to preserve the drug. Impressive results have been achieved by a recent study to deliver the TTX through aromatized liposomes [13]. The aromatization process is to add additional stabilizing aromatic groups between the lipid bilayers of the liposome. These aromatic groups enhance the stability and control the release rate of TTX. The advantage of aromatized liposomes compared to normal ones is proved when the drug loading of multiple drugs, including TTX, bupivacaine hydrochloride, and doxorubicin hydrochloride, experienced up to 60% increase by aromatization liposomes. This drug delivery methodology is also tested by an in vivo experiment where 300 μL liposome encapsulated sample to the rats' sciatic nerve and then checking the duration of the block based on the time required for rats to withdraw their paws from the hot plate.

The adverse effects of the drug are shown by the block of the contralateral leg (not injected). The TTX injected through aromatized liposome turns out to have significantly low toxicity with an even higher dose. At 30 μg dosing, mortality for usual liposome encapsulated TTX and free TTX is 100%, while the mortality for aromatized liposome TTX is zero. Aromatized liposome encapsulated TTX can have a 0 contralateral block at the same dosing. Most importantly, the duration of the effective block of aromatized liposome is more than double that of the normal liposome. It not only prolongs the effect of anesthesia but also decreases systemic toxicity.

3. Conclusion

In summary, TTX presents a fascinating opportunity in the medical field, especially in pain management. Its ability to block VGSCs so precisely makes it stand out from traditional painkillers and anesthetics, which often come with side effects like cardiac toxicity. Studies on both humans and animals have demonstrated that TTX can provide long-lasting pain relief with relatively mild adverse effects, particularly when compared to opioids or other anesthetics. The combination of TTX with other drugs, like bupivacaine, also shows great potential for extending its effects while maintaining safety. From the studies, the ideal subcutaneous dose of TTX should be below 30 μg. However, careful control and further research are essential, given its extreme toxicity. Unfortunately, there is no antidote for TTX. To reduce its toxicity, a new drug delivery system has been developed to deliver TTX through aromatized liposomes. It greatly boosts the adverse effect dose of TTX. In addition, activated charcoal can likely absorb part of the toxin, and mechanical ventilation can support breathing in case the respiratory muscles are paralyzed. Despite the risks, the therapeutic possibilities of TTX are vast, and it could pave the way for more efficient and safer alternatives in pain treatment.

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