Title : THE CLINICAL POTENTIAL OF TETRODOTOXIN

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Introduction. Tetrodotoxin (TTX) is one of the most potent local anesthetics. It blocks axonal conduction at nanomolar concentrations[1]. But TTX's clinical usefulness has remained questionable because of its low penetrance and high systemic toxicity. The relative influence of these parameters will, of course, vary with site of application. We evaluated the therapeutic to toxic ratio for TTX with a new in vivo peripheral nerve preparation and compared the results with those of a standard clinical local anesthetic, in order to assess TTX's clinical potential.

Material and Methods. Male Sprague-Dawley rats weighing 300-400 g were injected with 10 mgm of sodium pentobarbital, I.P., after a light ether induction. Additional pentobarbital was given, if necessary, until the righting reflex was lost. TTX, 0.4 ug, and/or 1 mg bupivacaine were prepared in 0.2 ml with 1 ug of epinephrine and infused onto the maxillary nerve through a 30g needle guided to the nerve by a metal jig positioned on the roof of the mouth (as described by Fink, et al[2]) The contralateral maxillary nerve was used as a control. Anesthesia was tested by stimulating the lip/whisker area innervated by the maxillary nerve on experimental and control sides and observing whether the stimulus produced a reflex contraction of abdominal muscles. Stimulation consisted of 1-10V 6 msec square wave pulse trains (2 pulses/sec for 5 sec) produced by a Grass S48 stimulator triggering a stimulus isolation unit (DS-2, Digitimer Ltd.), and were delivered through bipolar electrodes (two 30g needles 2 mm apart). The muscle twitch reflex was quantitated by recording the EMG from muscles of the abdominal wall, and displaying it on a Tektronic 5111 oscilloscope after amplification (Tektronic AM502 differential amplifier). Comparison of the EMG response produced by stimulating the control and treated side allowed an accurate determination of the duration of maxillary nerve block.

Results. Table 1 summarizes the results obtained in this study. Blocks were achieved with nearly every attempt. The onset of bupivacaine and bupivacaine/TTX was faster than TTX. This was expected, as TTX exists primarily in the charged form at physiologic pH and would therefore not penetrate biological membranes as easily as bupivacaine. In this preparation, TTX has twice the duration of bupivacaine and the combination has three times the duration of bupivacaine alone.

Discussion. On desheathed frog sciatic nerve, Staiman and Seeman found TTX to be 50,000 times more potent than lidocaine[3]. In mice the intravenous LD_{50} of lidocaine is 20 mgm/kg, whereas it is 10 ug/kg for TTX. If this data can be extrapolated to other species, then TTX has a therapeutic to toxic ratio 25 times better lidocaine. But in Staiman and Seeman's preparation, penetrance is not taken into consideration. In the model we used, which closely approximates a clinical situation, we found that TTX has twice the duration of bupivacaine with only 1/2500 the dose. This figures to be a therapeutic to toxic ratio of at least 2.5 times better than bupivacaine.

In a similar study, using the same dose and concentration of TTX, Adams was unable to block the rat sciatic nerve in 90 percent of the attempts and, when he did, the block lasted only 60 percent as long as ours[4]. This disparity in results is probably due to at least three factors: (1) Adams'[4] preparation had a less precise method for locating the nerve (block onset was three times longer), (2) he did not use epinephrine to retard absorption, and (3) he observed motor rather than sensory block.

This study indicates that TTX should be very useful clinically and may even be safer than conventional local anesthetics. Its low penetrance and high toxicity are more than offset by a high receptor binding energy. Further, since the sites of toxicity of TTX and conventional local anesthetics are different, their toxicity should not be additive and full advantage could be taken of the combination to obtain ultra-long blocks.

References.

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TABLE 1: RAT MAXILLARY NERVE BLOCK WITH TTX AND BUPIVACAINE

	Onset of Block*	Duration of Block
Bupivacaine (1 mg)+ Epinephrine (1 ug)	2	140 ± 15(4)**
TTX (0.4 ug)+ Epinephrine (1 ug)	4.5	252 ± 10(4)
Bupivacaine (1 mg) TTX (0.4 ug)+ Epinephrine (1 ug)	2	396 ± 50(5)

*Mean onset and duration with SD given in minutes
**Number of animals