

Systemic Tizanidine Hydrochloride (Zanaflex™) Partially Decreases Experimental Postoperative Pain in Rats

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Tizanidine hydrochloride (Zanaflex™; Elan Pharmaceuticals, South San Francisco, CA) is a novel centrally acting α_2 agonist available in oral form for the treatment of muscle spasms. Whereas clonidine may cause hypotension, bradycardia, and sedation (1), tizanidine has an infrequent incidence of clinically significant hemodynamic side effects (2). However, tizanidine does have a moderate incidence of sedation in effective systemic doses. Tizanidine, like clonidine, has analgesic properties related to its α_2 agonist properties in the spinal cord (3). Clonidine reduces postoperative pain in humans when given systemically or epidurally (1). No study has evaluated the effectiveness of the systemic administration of tizanidine for the treatment of postoperative pain.

If systemic tizanidine were shown to be effective in treating postoperative pain, it would be a safe and practical adjunct to systemic opioids or an alternative to clonidine. The objective of this study was to determine whether tizanidine relieves postoperative pain in a rat model.

Methods

The Institutional Animal Care and Use Committee of Emory University approved the study. Male Sprague-Dawley rats (Charles River, Wilmington, MA) weighing 250 to 350 g were housed in groups of two to three and allowed free access to food and water.

A cumulative pain score was used to assess pain behavior (4). The rats were placed on a steel mesh table for 15 min, and the plantar surface of the paw was viewed by using a mirror. Weight bearing was assessed on a scale from 0 to 2. A score of 0 was present if the wound was blanched or distorted by the mesh. A score of 1 was present if the wound rested on the mesh without blanching or distortion. A score of 2 was present if the foot was held completely off the

floor. A sum of 12 scores from 12 consecutive minutes was used for each rat at each time period.

Responses to mechanical stimulation were determined with calibrated von Frey monofilaments applied through openings in a steel mesh floor to an area adjacent to the incision and near the heel as described by Brennan et al. (4). Each monofilament was applied once, starting with 4.08 g and continuing until a paw withdrawal response (PWR) occurred or 6.45 g was reached. The process was repeated every 5 min on both hind paws three times, and the median was considered the withdrawal threshold.

Sixteen rats were acclimated to the environment and underwent baseline testing for pain score and PWR three times before surgery. The rats were anesthetized with inhaled isoflurane and air. After adequate depth of anesthesia was verified by lack of response to tail and toe pinch, a longitudinal 1-cm incision was made in the plantar surface of the left hind paw, starting 0.5 cm from the heel (4). The incision was made through the skin and plantar fascia. The plantaris muscle was elevated and incised longitudinally. The wound was closed with two vertical mattress sutures of 5-0 nylon.

Pain scores and PWRs were obtained on the first postoperative day (POD 1). The rats were treated with tizanidine 1 mg/kg intraperitoneally. Thirty minutes after the dose, they were tested for pain score and PWR. The testing and treatment scheme were repeated on POD 2.

Intragroup and intergroup differences between preoperative and postoperative PWR and pain score values and between Time 0 and subsequent measurement times were analyzed with a nonparametric analysis of variance for repeated measures followed by a Dunn's critical value test for multiple comparisons. Comparisons between the wounded and sham paw at each time point were made by using a Wilcoxon's signed rank test. *P* values <0.05 were considered statistically significant.

Results

There were no differences in right and left hind paws before surgery. Postoperative PWRs on the wounded

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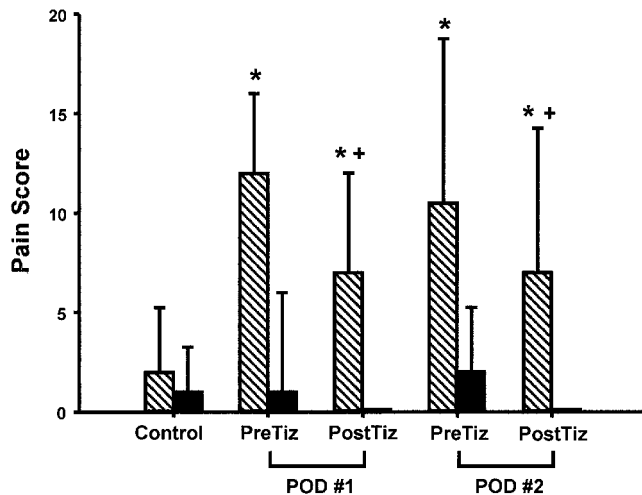


Figure 1. The effect of tizanidine on pain scores. Pain scores (0–24; see Methods) for both the wounded (left; hatched bars) and contralateral (right; black bars) paws are plotted on the ordinate versus treatment on the abscissa. Data are presented as median \pm interquartile difference ($Q_{75} - Q_{25}$). Scores for the wounded and contralateral paws were not significantly different in the control period. Pain scores for the contralateral paw were not significantly different from control at any time. Pain scores for the wounded paw were significantly higher than control ($P < 0.001$) and the contralateral paw ($P < 0.001$) at all postoperative measurement times, demonstrating a behavioral pain response to the paw incision (*). Tizanidine (Tiz) 1 mg/kg resulted in a significant decrease in pain score for the wounded paw ($P < 0.01$) on both postoperative days (PODs) (+). No attendant changes were noted in pain scores for the contralateral paw.

paw were significantly lower than the contralateral paw, whereas pain scores were significantly higher on the wounded side before treatment with tizanidine (Figs. 1 and 2), indicating the presence of postoperative pain after paw incision. Tizanidine 1 mg/kg significantly improved PWRs and pain scores on POD 1, but it improved only pain scores on POD 2. Pain scores remained much higher on the wounded paw than the contralateral paw after tizanidine treatment. PWRs were not significantly different from preoperative values after tizanidine treatment on POD 1. However, PWRs were not significantly improved after tizanidine on POD 2.

Discussion

Many drugs are analgesic only for specific types of pain. We would not expect anticonvulsants or α_1 antagonists to relieve somatic postoperative pain, although they are effective in some types of neuropathic pain (5,6). Even potent opioids are often not as effective with neuropathic pain as they are when used for postoperative pain (7). However, clonidine, which is an α_2 agonist like tizanidine, is effective both systemically and epidurally for postoperative pain (1). Tizanidine has significant antinociceptive effects without

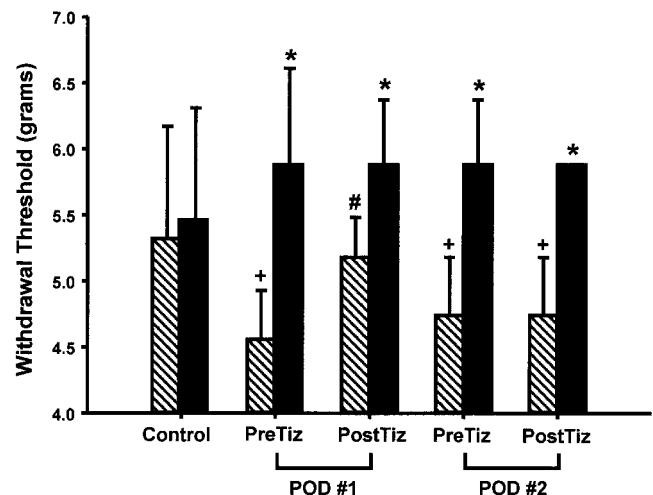


Figure 2. The effect of tizanidine on mechanical allodynia. Withdrawal thresholds in grams (measured by using Von Frey filaments as described in Methods) for both the wounded (left; hatched bars) and contralateral (right; black bars) paws are plotted on the ordinate versus treatment on the abscissa. Data are presented as median \pm interquartile difference ($Q_{75} - Q_{25}$). Values for the wounded and contralateral paws were not significantly different in the control period. Values for the contralateral paw were not significantly different from control at any time. However, values for the contralateral paw were significantly greater than the wounded paw at all postoperative measurement times (*). Values for the wounded paw were also significantly less than control at all postoperative times except after treatment with tizanidine on postoperative day (POD) 1 (+ $P < 0.01$). On POD 1, tizanidine resulted in a significant improvement in mechanical allodynia compared with the preinjection value (# $P < 0.025$). This value was not significantly different from control.

hypotension in rats when it is given subcutaneously (8). Tizanidine has analgesic properties in nonneuropathic pain in humans, such as tension headaches and back pain (9,10). We have shown an analgesic effect of systemic tizanidine on thermal hyperalgesia in a model of neuropathic pain (11). In that study, there was a slight nonspecific effect on the sham side. Given the available information on tizanidine and clonidine, we believed it would be effective in a postoperative pain model.

Our data show that systemic tizanidine improves mechanical allodynia in an experimental model of postoperative pain but does not completely relieve it. Pain scores were still much higher than in the preoperative control, and we do not believe that the analgesic effect of systemic tizanidine for postoperative pain is clinically significant. Larger doses of tizanidine may have an increased analgesic effect in this model. However, systemic doses of tizanidine larger than 1 mg/kg are significantly sedating in the rat (11). Given that systemic tizanidine does not completely relieve postoperative pain in a nonsedating dose, we are not encouraged to perform further animal or human investigations of systemic tizanidine for postoperative pain. However, it is possible that the intraspinal administration of tizanidine could achieve spinal

cord concentrations that are large enough to relieve postoperative pain without causing sedation.

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