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Combination of Foot Stimulation and Tramadol Treatment Reverses Irritation Induced Bladder Overactivity in Cats

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Abstract

Purpose—We determined whether transcutaneous electrical foot stimulation combined with a low dose of tramadol (Sigma-Aldrich®) could completely suppress bladder overactivity.

Materials and Methods—Repeat cystometrograms were performed in 18 α -chloralose anesthetized cats by infusing the bladder with saline or 0.25% acetic acid. Transcutaneous electrical stimulation (5 Hz) of the cat hind foot at 2 to 4 times the threshold intensity needed to induce observable toe movement was applied to suppress acetic acid induced bladder overactivity. Tramadol (1 to 3 mg/kg intravenously) was administered to enhance foot inhibition.

Results—Acetic acid irritated the bladder, induced bladder overactivity and significantly decreased bladder capacity to a mean $\pm$ SE of $26\% \pm 5\%$ of saline control capacity ($p < 0.01$). Without tramadol, foot stimulation at 2 and 4 threshold intensity applied during acetic acid cystometrograms significantly increased bladder capacity to a mean of $47\% \pm 5\%$ and $62\% \pm 6\%$ of saline control capacity, respectively ($p < 0.05$). Without foot stimulation, tramadol (1 mg/kg) only slightly changed bladder capacity to a mean of $39\% \pm 2\%$ of saline control capacity ($p > 0.05$), while 3 mg/kg significantly increased capacity to $85\% \pm 14\%$ that of control ($p < 0.05$). However, 1 mg/kg tramadol combined with foot stimulation increased bladder capacity to a mean of $71\% \pm 18\%$ (2 threshold intensity) and $84\% \pm 14\%$ (4 threshold intensity), respectively, which did not significantly differ from saline control capacity. In addition, long lasting (greater than 1.5 to 2 hours) post-stimulation inhibition was induced by foot stimulation combined with 3 mg/kg tramadol treatment.

Conclusions—This study suggests a new treatment strategy for overactive bladder by combining foot stimulation with a low dose of tramadol, which is noninvasive and has potentially high efficacy and fewer adverse effects.

Keywords

urinary bladder; overactive; tramadol; foot; electric stimulation; cats

Overactive bladder symptoms, including urgency, frequency and incontinence, are difficult to manage by medication.¹ Electrical stimulation of the tibial^{2,3} or pudendal^{4,5} nerve, or sacral spinal roots^{6,7} is clinically effective for treating OAB. However, sacral and pudendal

neuromodulation is invasive, requiring surgery to implant an Inter-Stim® stimulator and electrodes.⁴⁻⁷ Tibial neuromodulation, which requires a medically trained staff to percutaneously insert an Urgent® PC needle electrode cephalad to the medial malleolus,⁸ stimulates the tibial nerve for 30 minutes each week for 12 consecutive weeks. If the initial 12-week treatment is successful, further neuromodulation is used once every 2 to 3 weeks to maintain efficacy.^{3,8} Although tibial neuromodulation is minimally invasive with a long lasting post-stimulation effect, its efficacy is the same as that of anticholinergic drugs³ that can decrease but not completely eliminate OAB symptoms.¹ Thus, a noninvasive neuromodulation method with higher efficacy is needed.

Tramadol, which is clinically used as an analgesic, stimulates opioid receptors and inhibits serotonin and noradrenaline reuptake.⁹ Animal studies in rats showed that tramadol can inhibit bladder overactivity.¹⁰⁻¹³ A clinical study revealed that tramadol at a dose of 100 mg twice per day effectively treated OAB but with significant adverse effects, including nausea, vomiting, dizziness and constipation.¹⁴

Our previous studies in cats identified a new approach to suppress bladder overactivity by activating somatic afferent nerves in the foot using skin surface electrodes.^{15,16} Similar to tibial neuromodulation,³ foot stimulation in cats can also induce long lasting post-stimulation inhibition¹⁶ but does not completely suppress experimentally induced bladder overactivity.¹⁵ Our recent study in cats indicated that opioid receptors might be involved in foot inhibition of bladder overactivity.¹⁷ Therefore, we hypothesized that foot inhibition of bladder overactivity might be enhanced by low level pharmacological activation of opioid receptors.

In this study the opioid receptor agonist tramadol was administered in combination with foot stimulation to determine whether simultaneous pharmacological and electrical therapy would elicit a synergistic effect to inhibit irritation induced bladder overactivity in cats. A synergistic interaction between tramadol and foot stimulation, which is non-invasive and convenient, might lead to the development of a highly efficacious treatment for OAB with fewer adverse effects.

MATERIALS AND METHODS

The University of Pittsburgh animal care and use committee approved all protocols involving the use of animals in this study. Our experiments were performed in 10 female and 8 male normal cats weighing 2.7 to 4.0 kg under α -chloralose anesthesia (65 mg/kg intravenously, supplemented as necessary) after induction with isoflurane (2% to 3% in O₂). Systemic blood pressure was monitored throughout the experiment via a catheter inserted in the right carotid artery. Tracheotomy was performed and a tube was inserted to keep the airway patent. A catheter for intravenous infusion was introduced in the right cephalic vein. The ureters were cut and drained externally to eliminate distention of the bladder with urine, while preserving kidney function.

A double lumen catheter was inserted through the urethra into the bladder and secured by a ligature around the urethra. One lumen of the catheter was connected to a pump to infuse the bladder with saline or 0.25% AA at the rate of 1 to 2 ml per minute. The other lumen was connected to a pressure transducer to measure bladder pressure. After removing the fur, FE10ND self-adhesive pad electrodes (Grass Technologies, West Warwick, Rhode Island) with a diameter of 1 cm were attached to the skin surface on the left hind foot to apply electrical stimulation (fig. 1).

Uniphasic rectangular pulses (0.2-millisecond pulse width and 5 Hz frequency) were delivered to the foot via the skin electrodes. T was determined by gradually increasing

stimulation intensity. Since our previous study indicated that stimulation intensity greater than 2T was required to inhibit reflex bladder contractions,¹⁵ an intensity of 2T and 4T was used in this study to suppress the bladder overactivity induced by 0.25% AA irritation.

In the first experimental group of 10 cats, foot stimulation was applied during repeat CMGs, which consisted of slow infusion of saline or AA starting with an empty bladder. Bladder capacity was defined as the threshold bladder volume to induce the first large amplitude (greater than 30 cm H₂O) bladder contraction during CMG using saline (fig. 2, A). Initially, 3 to 5 saline CMGs were performed without stimulation to determine control bladder capacity and evaluate reproducibility. Another 3 to 5 CMGs were then done during 30 to 50 minutes with infusion of 0.25% AA to irritate the bladder, activate nociceptive bladder C-fiber afferents and induce bladder overactivity.

After the capacity of the irritated bladder stabilized, 4 CMGs were performed during AA infusion, including 1) prestimulation control CMG, 2) CMG during 2T stimulation, 3) CMG during 4T stimulation and 4) control CMG without stimulation to examine any post-stimulation effect (fig. 2, A). Cumulative doses of tramadol (1 and 3 mg/kg intravenously) were then administered. Ten minutes after administering each dose of tramadol, the 4 CMGs (control, 2T, 4T and control, as in figure 2, A) were repeated during AA infusion. A 5-minute rest period was inserted between repeat CMGs to allow for recovery of the micturition reflex.

A similar protocol was used in the second experimental group of 8 cats, except that the same volume of vehicle solution, ie saline, was administered instead of tramadol before performing the 4 CMGs (control, 2T, 4T and control, as in figure 2, A) to evaluate the effect of repeat foot stimulation alone. Following the vehicle tests, cumulative doses of tramadol (1 and 3 mg/kg intravenously) were given. Control CMG (no stimulation) was performed 10 minutes after each dose to determine the effect of tramadol alone on bladder capacity. Finally, the 4 CMGs (control, 2T, 4T and control, as in figure 2, A) were repeated again to examine any post-stimulation inhibitory effect, ie any increase in bladder capacity during control CMG after 2T and 4T stimulation. After stimulation, an additional 5 CMGs were done during 1.5 to 2 hours without stimulation to determine the duration of the post-stimulation effect.

Bladder capacity was measured during repeat CMG recordings. Bladder capacity measured during the first saline control CMG in each cat served as the baseline value, ie 100%, to normalize other capacity measurements in the same cat. However, in the second experimental group, bladder capacity measured during the last 5 consecutive CMGs after foot stimulation were normalized to the CMG performed after 3 mg/kg tramadol.

Repeat measurements in the same cat were averaged. Normalized data on different cats are presented as the mean $\pm$ SE. ANOVA (assuming normal distribution without the Kolmogorov-Smirnov test) followed by the Dunnett multiple comparison (with reference to the control in each test group) and the Student t test were used to detect statistical significance, which was considered at $p < 0.05$.

RESULTS

Bladder Overactivity

Suppression by foot stimulation—AA irritation significantly decreased bladder capacity to a mean of $26\% \pm 5\%$ of control capacity (mean 9.5 ± 1.2 ml in 18 cats) measured during saline infusion ($p < 0.01$, fig. 2). Without tramadol treatment, foot stimulation at an intensity of 2T and 4T applied during AA CMGs significantly increased bladder capacity to

a mean of $47\% \pm 5\%$ and $62\% \pm 6\%$, respectively, of saline control capacity ($p < 0.05$, fig. 2). However, it failed to completely reverse the effect of AA irritation and restore bladder capacity to the saline control level.

Dose dependent effect of tramadol—Tramadol in the absence of foot stimulation increased bladder capacity during AA CMGs in dose dependent fashion (fig. 3, *A*). The 1 mg/kg dose only slightly changed bladder capacity to a mean of $39\% \pm 2\%$ of saline control capacity but 3 mg/kg significantly increased capacity to a mean of $85\% \pm 14\%$ of saline control capacity ($p > 0.05$ and < 0.05 , respectively, fig. 3, *C*).

Combined effect of tramadol and foot stimulation—Neither foot stimulation nor 1 mg/kg tramadol administered alone during AA CMGs increased bladder capacity to the saline control level (fig. 3, *C*). However, foot stimulation combined with 1 mg/kg tramadol increased bladder capacity to a level (mean $71\% \pm 18\%$ for 2T and $84\% \pm 14\%$ for 4T) equivalent to, ie not significantly different from, saline control capacity ($p > 0.05$, fig. 3, *B* and *C*). Figure 3, *C* shows saline control capacity. After 3 mg/kg tramadol, foot stimulation at 2T and 4T significantly increased bladder capacity to a mean of $132\% \pm 24\%$ and $152\% \pm 24\%$, respectively, of saline control capacity ($p < 0.05$). Compared to tramadol treatment alone, foot stimulation significantly increased bladder capacity at 4T but not at 2T after each tramadol dose ($p < 0.05$, fig. 3, *C*).

Tramadol Treatment Unmasked Post-Stimulation Inhibition

Post-stimulation AA results without tramadol treatment revealed that the inhibition of bladder overactivity induced by foot stimulation was quickly reversible within 5 minutes (fig. 2). However, after tramadol (3 mg/kg) administration foot stimulation induced a significant increase in bladder capacity in 10 cats, which persisted after the termination of stimulation ($p < 0.05$, fig. 4, *A* and *B*). This post-stimulation inhibition did not occur during repeat application of foot stimulation without tramadol or following low dose (1 mg/kg) tramadol treatment (fig. 4, *B* and *C*). After administering 3 mg/kg tramadol, the post-stimulation inhibition induced by applying 2T and 4T foot stimulation during 2 repeat CMGs persisted at least 1.5 to 2 hours on the following 5 consecutive CMGs (fig. 5). The magnitude of the post-stimulation inhibition was equivalent to the transient increase in bladder capacity elicited by foot stimulation during CMG after 3 mg/kg tramadol (fig. 5, *A*).

DISCUSSION

Foot stimulation without tramadol treatment significantly suppressed irritation induced bladder overactivity but its efficacy was low, only reversing AA induced small bladder capacity to 50% to 60% of saline control capacity (fig. 2). Tramadol without foot stimulation significantly suppressed bladder overactivity but its efficacy at 1 mg/kg was also low with reversal to 40% of saline control capacity (fig. 3). However, foot stimulation combined with a low dose of tramadol (1 mg/kg) restored the irritated bladder to a capacity equivalent to the saline control level (fig. 3). Foot stimulation also induced post-stimulation inhibition after 3 mg/kg tramadol that lasted more than 1.5 to 2 hours (figs. 4 and 5). These results indicate a potential new treatment strategy for OAB by combining foot stimulation with a low dose of tramadol.

A recent clinical study showed that tramadol (100 mg or 1.4 mg/kg for a 70 kg individual twice per day) significantly decreased the number of incontinence episodes and produced a 25% increase in bladder capacity in patients with OAB.¹⁴ However, the adverse effects of tramadol, including nausea, vomiting, dizziness and constipation, prevented using a higher dose to achieve better clinical efficacy. Thus, the tramadol dose necessary to enhance the

effects of foot stimulation in cats is an important consideration when evaluating the clinical implications of the current results.

Relating the tramadol doses in cats to doses in humans is complicated due to species differences and different administration routes. The human oral dose (1.4 mg/kg) effective for decreasing OAB symptoms¹⁴ is approximately half the intravenous dose of tramadol (3 mg/kg or greater) that significantly increased bladder capacity in our current study (fig. 3, C). When tramadol is used clinically as an analgesic, the recommended oral dose is 50 to 100 mg (0.7 to 1.4 mg/kg for a 70 kg individual) every 4 to 6 hours.⁹ That is less than half the recommended oral dose (4 mg/kg every 6 hours) to treat pain in cats.^{18,19} These data indicate that cats are less sensitive to the effects of tramadol.

Although our experiments examined the effects of tramadol administered intravenously, this is not likely to be a major impediment to predicting clinical efficacy because oral tramadol is rapidly and almost completely absorbed in cats, and intravenous and oral tramadol doses produce similar plasma concentrations.¹⁸ Therefore, the effective tramadol dose (1 mg/kg) combined with foot stimulation to fully reverse AA induced bladder overactivity is much less than the analgesic dose (4 mg/kg)^{18,19} and the bladder inhibition dose (3 mg/kg) in cats (fig. 3). This suggests that the clinical dose of tramadol might be significantly decreased when combined with foot stimulation for OAB, significantly reducing or eliminating the adverse effects of tramadol.

Combining foot stimulation with tramadol also has significant advantages over sacral or tibial neuromodulation alone. Sacral neuromodulation is invasive, requiring surgery to implant the stimulator and electrode.^{6,7} Tibial neuromodulation is minimally invasive but has low efficacy for treating OAB.³ Our results show that the efficacy of foot stimulation can be significantly increased to completely inhibit bladder overactivity if combined with a low dose of tramadol (fig. 3). This raises the possibility of a combined clinical treatment strategy that would be noninvasive with high efficacy and fewer adverse effects.

Tibial neuromodulation has a significant post-stimulation inhibitory effect that requires only an initial treatment of 30 minutes of stimulation once per week for 12 weeks, followed by a maintenance treatment of once every 2 to 3 weeks.^{3,8} Our previous studies in cats showed that tibial nerve stimulation can also induce prolonged (greater than 2 hours) post-stimulation inhibition of reflex bladder activity during saline infusion,²⁰ while foot stimulation only induces brief (10 to 15 minutes) post-stimulation inhibition.¹⁶

The current study further shows that foot stimulation alone does not induce post-stimulation inhibition during AA irritation (figs. 1 and 4, C). Without post-stimulation inhibition, foot stimulation would have to be applied continuously to treat OAB. However, our current results indicate that long lasting (greater than 1.5 to 2 hours) post-stimulation inhibition of irritation induced bladder overactivity could be unmasked by an analgesic dose (3 mg/kg) of tramadol (fig. 5). The magnitude of the post-stimulation inhibition was as strong as the acute inhibition induced by foot stimulation during CMG in terms of increasing bladder capacity (fig. 5, A). Therefore, in clinical application foot stimulation might not have to be continuous if combined with an analgesic dose of tramadol.

However, clinical studies are necessary to determine the duration of the post-stimulation inhibition unmasked by tramadol. Because foot stimulation is noninvasive and tramadol is currently used in clinical practice, a clinical trial to test the combined treatment should be feasible.

Although the mechanisms underlying the additive effect of tramadol and foot stimulation are uncertain, the activation of opioid receptors may be important. Tramadol induces analgesia

in part by activating opioid receptors, and tramadol effects in cats and rats are suppressed by the opioid receptor antagonist naloxone.^{11,21,22} Our recent study showed that naloxone also suppressed the foot inhibition of bladder overactivity,¹⁷ suggesting that the synergistic interaction between the 2 treatments to unmask post-stimulation inhibition might be due to the activation of opioid receptors by tramadol.

However, tramadol is also an inhibitor of serotonin and noradrenaline reuptake.⁹ Serotonergic agonists inhibit reflex bladder activity in cats.^{23,24} Therefore, it is possible that the effects of tramadol observed in this study could have been due in part to enhanced central serotonergic inhibitory control of bladder reflexes. More studies are needed to explore the possible neurotransmitter mechanisms underlying the combined treatment strategy.

Notably, this study was done using α -chloralose anesthesia, which could have influenced reflex bladder activity and responses to tramadol or electrical foot stimulation. However, this anesthetic influence was constant throughout the experiment during stimulation and tramadol treatment. The influence of α -chloralose anesthesia on the results should be taken into account when considering the potential clinical applications of the current findings. In addition, foot stimulation at an intensity of 2T to 4T was used in this study. At this intensity range, stimulation probably only activated the large afferent nerve fibers rather than the small A δ and C-fiber afferents that can induce painful sensations.^{25,26} However, the sensations induced by foot stimulation must be explored in clinical studies.

CONCLUSIONS

This study suggests a novel treatment strategy for OAB by combining foot stimulation with a low dose of tramadol. This strategy is noninvasive with potentially high efficacy and fewer adverse effects. If proven to be clinically successful, it could have a significant impact on current treatments for OAB.

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Abbreviations and Acronyms

AA	acetic acid
CMG	cystometrogram
OAB	overactive bladder
T	threshold intensity needed to induce observable toe movement

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Figure 1. Electrode placement for electrical stimulation of cat hind foot. Electrode 1 is at front of foot pad and electrode 2 is at heel.

Figure 2.

Suppression of AA induced bladder overactivity by transcutaneous stimulation of somatic afferent nerves in foot. Stimulation was done at 5 Hz frequency and 0.2-millisecond pulse width. *A*, repeat CMG recordings in cat 5 show decreased bladder capacity after AA irritation and increased capacity during foot stimulation with 2T and 4T. Stimulation was done with T of 6 V and infusion rate of 1 ml per minute. Horizontal black bars indicate stimulation duration. *B*, bladder capacity measured from CMGs under different conditions in 18 cats. Stimulation was done with T of 2.5 to 24 V. Asterisk indicates statistically significant difference.

Figure 3.

Suppression of AA induced bladder overactivity by combined intravenous tramadol and transcutaneous stimulation of somatic afferent nerves in foot. *A*, effect of tramadol alone without foot stimulation on CMG recordings in cat 17. *B*, effect of tramadol combined with foot stimulation on CMG recordings in cat 5. Stimulation was done at 5 Hz frequency and 0.2-millisecond pulse width with T of 6 V and infusion rate of 1 ml per minute. Horizontal black bars indicate stimulation duration. *C*, bladder capacity measured from CMGs at different tramadol doses in 8 cats for tramadol (*TM*) alone group and in 10 in tramadol plus stimulation group. Stimulation was done at 5 Hz frequency and 0.2-millisecond pulse width with T of 2.5 to 20 V. Asterisk indicates statistically significant difference vs control, ie at 0 mg/kg tramadol. # indicates statistically significant difference vs saline capacity (dashed line). @ indicates tramadol alone vs tramadol plus 4T statistically significantly different.

Figure 4.

Post-stimulation inhibition of AA induced bladder overactivity after 3 mg/kg intravenous tramadol. *A*, repeat CMG traces after tramadol administration in cat 5. Stimulation was done at 5 Hz frequency and 0.2-millisecond pulse width with T of 6 V and infusion rate of 1 ml per minute. Vertical dashed lines indicate post-stimulation bladder capacity increase. *B*, summarized results show significant (asterisk) increase in bladder capacity after stimulation at 3 mg/kg tramadol in 10 cats. # indicates significant difference vs saline capacity (dashed line). *C*, control results reveal no increase in capacity after repeat stimulation when tramadol was not administered, ie 0 mg/kg tramadol, in 8 cats.

Figure 5.

Post-stimulation inhibition of AA induced bladder overactivity was long lasting. *A*, repeat CMG traces in cat 11 demonstrate that after 3 mg/kg tramadol with 2T and 4T foot stimulation at 4 V threshold, increased bladder capacity was maintained in following 5 consecutive CMGs. *B*, summarized results show that bladder capacity during 5 consecutive CMGs done during 1.5 to 2 hours after stimulation was significantly (asterisk) increased over capacity on control CMGs (*A*). Stimulation was done at 5 Hz frequency and 0.2-millisecond pulse width with T of 4 to 24 V in 8 cats.