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Effects of perineural tramadol on nerve conduction of sural nerve

Perinöral tramadolün sural sinir iletimi üzerine etkisi

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Summary

Objectives: The aim of this study was to investigate whether tramadol had a dose-dependent blocking effect on nerve conduction when administered perineurally to the sural nerve of healthy volunteers.

Methods: Twenty-four informed healthy subjects were randomized into four equal groups [Saline (placebo), 0.5% tramadol, 1% tramadol and 1.5% tramadol]. The study was designed to be double-blinded. Sensory nerve action potentials were recorded electroneurographically. Two milliliters of study solution was administered to the sural nerve perineurally at the level of the ankle with the guidance of a nerve stimulator. A sensory block was assumed to have developed when the amplitude of the averaged sensory nerve action potentials diminished below 80% of the baseline value in the subsequent recordings.

Results: According to the electroneurographical recordings, none of the volunteers in the saline group had block. However, the block rates with 0.5%, 1% and 1.5% tramadol were 1/6, 4/6 and 6/6, respectively ($p<0.05$). The maximum decrement in the sensory action potential amplitudes with respect to baseline amplitudes (given as median values) were as follows: 7.8% with saline; 12.5% with 0.5% tramadol; 38.5% with 1% tramadol; and 77.5% with 1.5% tramadol ($p<0.05$). While the median duration of sensory block with 0.5% tramadol was 5 minutes, it was 15 minutes with 1% tramadol and 35 minutes with 1.5% tramadol.

Conclusion: Perineurally administered tramadol blocks sensory nerve conduction of the sural nerve in a dose-dependent manner.

Key words: Nerve block; nerve conduction; opioid; peripheral nerve; sural nerve; tramadol.

Özet

Amaç: *Çalışmanın amacı, sağlıklı gönüllülerde sural sinire perinöral olarak uygulanan tramadolün sinir iletimi üzerine doz bağımlı bloke edici etkinliğinin olup olmadığının araştırılmasıdır.*

Gereç ve Yöntem: *Yirmi dört bilgilendirilmiş sağlıklı denek eşit olarak 4 gruba [Salin (plasebo), %0.5 tramadol, %1 tramadol ve %1.5 tramadol] ayrıldı. Çalışma çift kör olarak tasarlandı. Duyusal sinir aksiyon potansiyelleri elektronörografik olarak kaydedildi. 2 ml'lik çalışma solüsyonu sinir stimülatörü yardımı ile ayak bileği düzeyinde sural sinire perinöral olarak enjekte edildi. İzleyen kayıtlamalarda duyu yanıtı amplitüdünün bazal değerin %80'inin altına inmesi durumunda duyusal blok oluştuğu kabul edildi.*

Bulgular: *Elektronörografik kayıtlara göre salin grubundaki hiçbir denekte blok gelişmedi. Bununla birlikte, %0.5, %1 ve %1.5 tramadol ile blok gelişim oranları sırasıyla 1/6, 4/6 ve 6/6'ydı. Başlangıç düzeylerine göre duysal aksiyon potansiyeli amplitüdlerinin ortanca değerlerindeki maksimum azalma salin grubunda %7.8, %0.5 tramadol ile %12.5, %1 tramadol ile %38.5 ve %1.5 tramadol ile %77.5'di ($p<0.05$). %0.5 tramadol ile duysal blok süresi 5 dakika iken, %1 tramadol ile 15 dakika ve % 1.5 tramadol ile 35 dakikaydı.*

Sonuç: *Perinöral olarak sural sinire uygulanan tramadol doz bağımlı olarak duyu sinir iletimini bloke etmektedir.*

Anahtar sözcükler: Sinir bloğu; sinir iletimi; opioid; periferik sinir; sural sinir; tramadol.

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Introduction

Tramadol is a synthetic opioid belonging to aminocyclohexanol group which acts by inhibiting the re-uptake of both central and peripheral monoaminergic neurotransmitters (5-hydroxytryptamine and noradrenaline).[1] It may be used as an analgesic via several different routes.[1-3] A local anesthetic efficacy of tramadol was reported following intradermal application.[4] Later, this was confirmed with studies conducted on frog[5,6] and rat[7-9] sciatic nerves. A few clinical studies on human subjects showed conflicting results about the efficacy of tramadol when combined to local anesthetics as an adjunct and the duration of the resulting peripheral nerve block.[10-13] Recently, Ozturk et al.[14] have shown local anesthetic-like effect of perineural 50 mg tramadol on a mixed nerve of the upper extremity. The effects of various opioids other than tramadol have been previously studied on sural nerve.[15,16]

The aim of this study was to investigate the effect of lower doses of perineural tramadol on sural nerve conduction.

Materials and Methods

After approval by the Ethics Committee of our Faculty, 24 male healthy volunteers were enrrolled. The study was explained to the subjects in detail and an informed written consent was obtained from each. They went through a comprehensive interview and a thorough physical examination followed by an electroneurographic assessment. All were healthy and eligible for the study. Subjects were encouraged to report any discomfort or a desire to prompt the termination of the experiment. The subjects were randomized into 4 groups according to the study solutions by means of a computerized random-number generator. Placebo (saline) and tramadol solutions were identically supplied in 2 ml saline. The saline group (Group S) received only saline; the 0.5% tramadol group (Group T10) received 10 mg tramadol; the 1% tramadol group (Group T20) received 20 mg tramadol, and the 1.5% tramadol group (Group T30) received 30 mg tramadol in a double blinded design. The subjects and the investigators who performed the injections or conducted the electroneurographic procedures were blinded to the study solutions.

Electroneurographic procedures were conducted with a DISA Neuromatic 2000 electromyograph (Dantec Electronics, Mileparken 22, DK-2740 Skovlunde, Denmark). Superficial electrodes (TECA NCS disk electrode) were used for recording and stimulation. The skin at the stimulation and recording sites was cleansed with soap and dried with a paper towel. Skin preparatory gel was applied at the contact sites of electrodes which were then secured by using adhesive tape. The active recording electrode was placed on sural nerve behind the lateral malleolus and the reference electrode 3 cm distal to the recording electrode. The stimulating electrode (NM-420S, 5-pin male connector) was placed 14 cm proximally to the active recording electrode with the cathode placed distally. Responses to 50 stimuli of square waves with 200 ms duration and 1 Hz frequency (at an intensity that did not produce muscular artifacts) were averaged.[17] The amplitude of averaged sensory nerve action potentials recorded prior to injection was accepted as the baseline value. A sensory block was assumed to have developed when the amplitude of the averaged sensory nerve action potentials diminished below 80% of the baseline value in the subsequent recordings. If no block was observed within the first 30 minutes the study was terminated. In cases where a block developed, recordings were continued for every 5 minutes up to 30 minutes following the injection and then every 10 minutes, until the amplitude regained 80% of the baseline value. Sural nerve conduction was reevaluated 24 hours afterwards.

The perineural injections were to the vicinity of sural nerve using a teflon-insulated 25G special needle and a nerve stimulator (Stimuplex® HNS 11, Braun, Germany) through a point 5 cm proximal to the active recording electrode. Perineural injection was performed with the assistance of a neural stimulator to avoid the probable misleading effect of the subcutaneous fat tissue on the results. The current intensity of the nerve stimulator was 2 mA, the duration was 100 ms and the frequency was 2 Hz. The bare area of the needle was placed on various sites over the skin and the subject was questioned for a feeling of an electrical shock spreading to the sural nerve innervation area to determine the optimal insertion point of the needle. The needle was introduced slowly and carefully to the vicinity of the nerve ac-

Table 1. Demographic data (mean±SD)

	Group S	Group T_{10}	Group T_{20}	Group T_{30}
Age (year)	37±7	37±10	41±12	35±10
Weight (kg)	83±12	79±10	70±7*	79±3
Height (cm)	171±8	167±5	166±6	180±4†

*: p<0.05, as compared to group S; †: p<0.05, as compared to groups T10 ve T20.
(S: Saline; T_{10}: 0.5% tramadol; T_{20}: 1% tramadol; T_{30}: 1.5% tramadol)

cording to the sensation expressed by the subject in response to an electrical current of less than 1 mA. The study solution was injected when the sensory response could be elicited with a current of 0.5 mA verifying that the location was sufficiently close to the nerve.

Statistical analyses were performed with the "SPSS 9.0 for Windows" computer software. The demographic characteristics and maximum amplitude decrement rates were evaluated with one-way analysis of variance, the block development rate with the chi-square test, and the change in sensory response amplitude with repeated measurements analysis of variance. A two-sided p<0.05 was accepted as significant.

Results

All the subjects tolerated the procedures well throughout the study. Table 1 presents the general characteristics of the subjects. Mean ages of the subjects were similar among the groups. However, the mean body weights of subjects in group T10 was lower than group S, while the mean height for group T30 was higher than groups T10 and T20 (p<0.05). However, height and weight differences between the groups are not expected to affect the results of this study since baseline values of each subject were used for comparisons with subsequent recordings.

Figure 1 shows the rate of block occurence among the subjects. None of the subjects in Group S displayed a block. Only one subject in group T10 and four subjects in group T20 but all of the subjects in group T30 developed a block. There was a significant difference between group T30 and groups S and T10 and also between group T20 and group S in relation to block occurence rate (p<0.05). Block occurence rate was dose-related (Spearman rho=0.785 and p<0.01). Figure 2 shows the recordings of the

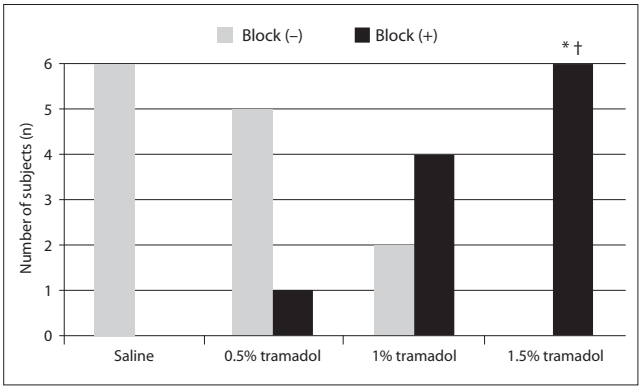

Fig. 1. Number of subjects with/without sensory block. *: p<0.05, as compared to group S, †: p<0.05, as compared to group 0.5%.

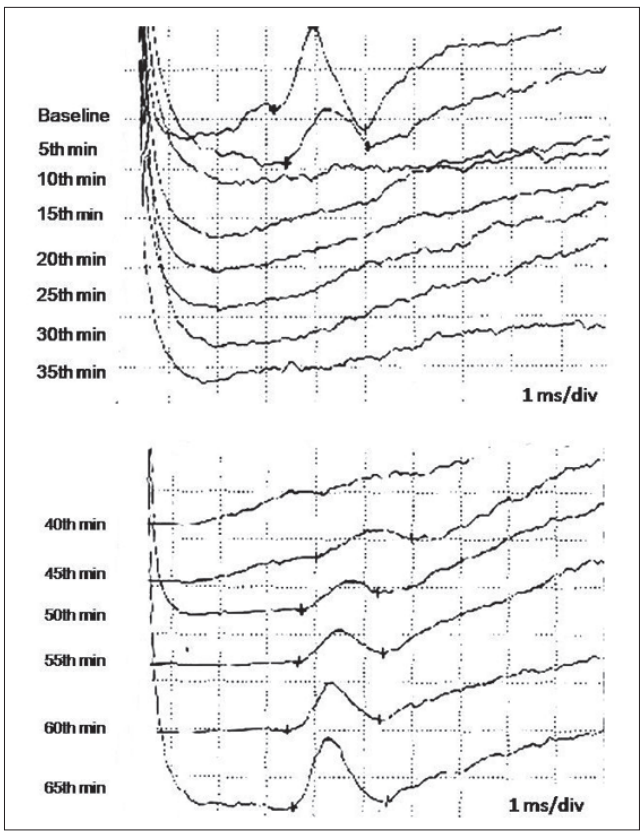

Fig. 2. Temporary difference in amplitude of sensory nerve action potential in a subject who was administered 1.5% of tramadol.

Table 2. Electroneurographic features of sensory block [median (25–75%)]

	Group S	Group T_{10}	Group T_{20}	Group T_{30}
Maximum decrement in sensory nerve conduction amplitude (%)	7.8 (3.2-14.6) (n: 6)	12.5 (8.6-17.0) (n: 6)	38.5 (15.0-57.3)* (n: 6)	68.3 (53.8-100)* (n: 6)
Time of maximum sensory block (min)	–	5.0 (n: 1)	12.5 (6.3-15.0) (n: 4)	10.0 (5.0-11.3) (n: 6)
Initial time of block (min)	–	5.0 (n: 1)	8.8±4.8 (n: 4)	7.5±2.7 (n: 6)
Duration of sensory block (min)	–	5.0 (n: 1)	25.0±20.0 (n: 4)	51.7±38.6 (n: 6)

*: $p<0.05$, as compared to group S; (S: Saline; T_{10}: 0.5% tramadol; T_{20}: 1% tramadol; T_{30}: 1.5% tramadol).

consecutive sensory responses of a subject in the T30 group during the study.

Median values of maximum amplitude reduction rates were 7.8% for group S, 12.5% for group T10, 38.5% for group T20 and 68.3% for group T30. There was no significant difference between group S and group T10 but the reduction in groups T20 and T30 were significant when compared with the other groups ($p<0.05$) (Table 2).

Mean values for maximum sensory block occurrence time was 12.5 minutes for group T20 and 10 minutes for group T30. The mean interval until block development was 8.8 min for group T20 and 7.5 minutes for group T30. The block duration was approximately 25 minutes in group T20 and 51.7 minutes in group T30.

The clinical examination and electrophysiological assessments 24th hours after the study were normal in all subjects.

Discussion

This placebo-controlled, double-blind study indicated that perineurally administered tramadol produces a decrement in the sensory response amplitude of sural nerve in a dose-related manner and produces a brief sensory conduction block.

The identification of opioid receptors in the spinal cord and peripheral nerves have led to studies with the hope of achieving fewer side effects, but longer periods of analgesia with lower doses of opioids solely or in combination with local anesthetics.[18] Pang et al.[4] were the first to point out that tramadol may have a local anesthetic-like effect after their study where they administered 1.66% tramadol intradermally. Later, Tsai et al.[7] reported that tramadol, when applied directly to the rat sciatic nerve (at concentrations of 1.25%, 2.5% and 5%), reduced spinal somatosensorial evoked potential amplitudes in a dose-related manner and that the block recovery duration was 180 minutes on average when 1.25% and 2.5% concentrations were used. We also have observed that the block-inducing effect of tramadol on human peripheral nerves was dose/concentration dependent similar to the results of Tsai et al.'s study. However, we noted a much briefer conduction block in humans compared to the 180-minute duration reported by Tsai et al.[7] Sensory block following perineural administration of tramadol to the human sural nerve developes only after a concentration of 1-1.5% is used. A sensory block for only 5 minutes occured in one out of six subjects with 0.5% tramadol.

Clinical assessment and follow-up of sensory block may sometimes be difficult. Electroneurography provides quantitative and objective information to support the clinical findings. Sural nerve was preferred as a sensory nerve which is relatively easy to assess electroneurographically.[17]

Nerve conduction blocking effect of perineural opioids in human peripheral nerves has been shown for meperidine[15,16] and tramadol.[10-14] A local anesthetic-like effect was observed with 50 mg of tramadol on ulnar nerve which have both motor and sensory

fibers. Sensory block duration was longer and the maximal amplitude decrement was found to be more pronounced in sensory rather than the motor nerve action potentials. In this study, we aimed to investigate the effectiveness of various doses of tramadol selectively on sural nerve which purely consists of sensory fibers and whether it is effective with lower doses. Therefore, we selected 3 different doses of tramadol which were all lower than Ozturk et al's study.[14] The median duration of the sensory block that they achieved was 25 minutes while we have observed a longer period of sensory block (51.7 minutes with 30 mg tramadol) with lesser dose. This may be due to the smaller diameter of sural nerve in comparison to the ulnar nerve.

Our observation is consistent with Acalovski et al.'s[19] who have clinically demonstrated that tramadol used solely at a concentration of 0.25% for IVRA does not generate a block. It may be postulated from our results that a block with tramadol during IVRA may develop at concentrations around 1-1.5%. A study on the frog sciatic nerve has shown 6.6 mM of tramadol is required to produce a block similar to 2.2 mM lidocaine.[5] The clinical applicability of perineural tramadol at such high concentrations seems to be limited due to possible systemic side effects. Tramadol alone, administered by epidural route, has a longer analgesic effect compared to bupivacaine.[20] It quickens sensory and motor block appearence when added to lidocaine for IVRA.[19]

Tramadol added to mepivacaine during axillary block prolonged both sensory and motor block durations.[10,11,13] Our study indicates that a concentration of at least 1.5% is required for producing a sensory block and the generated block lasts approximately 50 minutes. Taken together with our results, this suggests that the analgesic effect produced by tramadol when used as an adjuvant, may be due to a different mechanism of action rather than a local anesthetic-like effect. The prolonged analgesic effect observed in Kapral et al.'s[10] study may be due to potentialization of those agents or due to modulation of the analgesic effect by tramadol through different receptors. Kaabachi et al.[13] found that 100 and 200 mg of tramadol added to lidocaine 1.5% with epinephrine 1/200,000 revealed significant dose related prolongation of motor and sensory blocks in axillary nerve. However, the onset of the block was delayed with 200 mg of tramadol. Robaux et al.[11] also found similar effectiveness on block duration with 200 mg tramadol added to 1.5% mepivacaine, however they did not observe any difference in the onset of the block. In contrast to these, another study showed no improvement in the duration of block when 100 mg tramadol was added to 300 mg ropivacaine.[12] We believe that the use of ropivacaine, which has a longer duration of local anesthetic action than lidocaine, might have masked the effectiveness of the lower dose of tramadol.

Tramadol is classified as an atypical opioid. The reason for such a classification is the different mechanism of action compared to other opioids since it exerts analgesic effects through both opioid and nonopioid mechanisms.[1] The first of these mechanisms is through opioid receptors while the second is through monoaminergic pathways.[21-23] Tramadol binds to opioid receptors less than morphine and its affinity to μ-receptors is higher than for other receptors.[21] Tramadol inhibits re-uptake of norepinephrine and serotonin that play a role in pain modulation and increases their concentrations in the central nervous system, thus producing analgesia by presynaptic stimulation in the central neuronal synapses.[22-27] It has therefore been postulated that the analgesic effect of tramadol may be antagonized by both opioid and alpha-2 adrenoreceptor antagonists.[28] However, Collart et al.[29] reported that they were unable to antagonize the antinociceptive and analgesic effects of oral tramadol by naloxone. They suggested that both opioid and nonopioid mechanisms may be in effect. Tsai et al.[7] also pointed out that inability of naloxone to reverse the block created by tramadol in the rat sciatic nerve is an evidence to alternative route of effects, probably direct and indirect local anesthetic mechanisms. It was shown that tramadol itself has a blocking effect on frog sciatic nerve while this effect can not be reversed by naloxane or ([D-Ala2, N-MePhe4, Gly-ol]-enkephalin) (DAMGO) which argues against an action via μ-opioid receptors, noradrenaline and 5-hydroxytryptamine.[6] Dalkilic et al.[9] showed that tramadol reduces the axonal excitability by acting dose dependently on channel activity rather than the passive conduction parameters of neural tisssue and fast conduction fibers were found to be more sus-

ceptible to tramadol. Similar to lidocaine, tramadol showed a more prominent action in a hydrophilic manner on potassium channels as compared to sodium channels.[8] The results of the previous studies which have been conducted in animals,are in favor of a local anesthetic-like effectiveness of tramadol rather than an action via the opioid receptors.

In conclusion, we found that tramadol injected perineurally to the sural nerve creates a short-term block in sensory nerve conduction in a dose-dependent manner. However, higher doses will be required to provide a clinically useful block and we believe that such high doses may limit clinical applicability due to systemic side effects.

References

1. Shipton EA. Tramadol--present and future. Anaesth Intensive Care 2000;28(4):363-74.
2. Siddik-Sayyid S, Aouad-Maroun M, Sleiman D, Sfeir M, Baraka A. Epidural tramadol for postoperative pain after Cesarean section. Can J Anaesth 1999;46(8):731-5.
3. Scott LJ, Perry CM. Tramadol: a review of its use in perioperative pain. Drugs 2000;60(1):139-76.
4. Pang WW, Mok MS, Chang DP, Huang MH. Local anesthetic effect of tramadol, metoclopramide, and lidocaine following intradermal injection. Reg Anesth Pain Med 1998;23(6):580-3.
5. Mert T, Gunes Y, Guven M, Gunay I, Ozcengiz D. Comparison of nerve conduction blocks by an opioid and a local anesthetic. Eur J Pharmacol 2002;439(1-3):77-81.
6. Katsuki R, Fujita T, Koga A, Liu T, Nakatsuka T, Nakashima M, et al. Tramadol, but not its major metabolite (mono-O-demethyl tramadol) depresses compound action potentials in frog sciatic nerves. Br J Pharmacol 2006;149(3):319-27.
7. Tsai YC, Chang PJ, Jou IM. Direct tramadol application on sciatic nerve inhibits spinal somatosensory evoked potentials in rats. Anesth Analg 2001;92(6):1547-51.
8. Güven M, Mert T, Günay I. Effects of tramadol on nerve action potentials in rat: comparisons with benzocaine and lidocaine. Int J Neurosci 2005;115(3):339-49.
9. Dalkilic N, Tuncer S, Bariskaner H, Kiziltan E. Effect of tramadol on the rat sciatic nerve conduction: a numerical analysis and conduction velocity distribution study. Yakugaku Zasshi 2009;129(4):485-93.
10. Kapral S, Gollmann G, Waltl B, Likar R, Sladen RN, Weinstabl C, et al. Tramadol added to mepivacaine prolongs the duration of an axillary brachial plexus blockade. Anesth Analg 1999;88(4):853-6.
11. Robaux S, Blunt C, Viel E, Cuvillon P, Nouguier P, Dautel G, et al. Tramadol added to 1.5% mepivacaine for axillary brachial plexus block improves postoperative analgesia dose-dependently. Anesth Analg 2004;98(4):1172-7.
12. Kesimci E, Izdes S, Gozdemir M, Kanbak O. Tramadol does not prolong the effect of ropivacaine 7.5 mg/ml for axillary brachial plexus block. Acta Anaesthesiol Scand 2007;51(6):736-41.
13. Kaabachi O, Ouezini R, Koubaa W, Ghrab B, Zargouni A, Ben Abdelaziz A. Tramadol as an adjuvant to lidocaine for axillary brachial plexus block. Anesth Analg 2009;108(1):367-70.
14. Oztürk E, Zinnuroğlu M, Sezer OA, Gökyar I, Beyazova M, Kaya K. Effects of perineural tramadol on sensory and motor conduction of ulnar nerve. J Opioid Manag 2008;4(6):345-9.
15. Kaya K, Babacan A, Beyazova M, Bölükbasi N, Akçabay M, Karadenizli Y. Effects of perineural opioids on nerve conduction of N. suralis in man. Acta Neurol Scand 1992;85(5):337-9.
16. Beyazova M, Babacan A, Bilir E, Akçabay M, Kaya K, Baysal AI. Perineural pethidine: effects of different doses on nerve conduction. Eur J Anaesthesiol 1993;10(5):353-6.
17. Oh SJ. Clinical electromyography. Nerve Conduction Studies. Baltimore: Williams and Wilkins; 1993. p. 250.
18. Stein C, Pflüger M, Yassouridis A, Hoelzl J, Lehrberger K, Welte C, et al. No tolerance to peripheral morphine analgesia in presence of opioid expression in inflamed synovia. J Clin Invest 1996;98(3):793-9.
19. Acalovschi I, Cristea T, Margarit S, Gavrus R. Tramadol added to lidocaine for intravenous regional anesthesia. Anesth Analg 2001;92(1):209-14.
20. Delilkan AE, Vijayan R. Epidural tramadol for postoperative pain relief. Anaesthesia 1993;48(4):328-31.
21. Hennies HH, Friderichs E, Schneider J. Receptor binding, analgesic and antitussive potency of tramadol and other selected opioids. Arzneimittelforschung 1988;38(7):877-80.
22. Kayser V, Besson JM, Guilbaud G. Evidence for a noradrenergic component in the antinociceptive effect of the analgesic agent tramadol in an animal model of clinical pain, the arthritic rat. Eur J Pharmacol 1992;224(1):83-8.
23. Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. J Pharmacol Exp Ther 1992;260(1):275-85.
24. Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL, et al. Complementary and synergistic antinociceptive interaction between the enantiomers of tramadol. J Pharmacol Exp Ther 1993;267(1):331-40.
25. Raffa RB. A novel approach to the pharmacology of analgesics. Am J Med 1996;101(1A):40S-46S.
26. Raffa RB, Friderichs E. The basic science aspect of tramadol hydrochloride. Pain Reviews 1996;4:249-271.
27. Schug SA, Dickenson AH, Strauburger W, et al. Current concepts on the mechanism of action of tramadol. In: Abstract Booklet on Symposium "Current concepts on the mechanism of action of tramadol". 9th World Congress on Pain. Austria Center Vienna, 25 August 1999.
28. Bamigbade TA, Langford RM. Tramadol hydrochloride: an overview of current use. Hosp Med 1998;59(5):373-6.
29. Collart L, Luthy C, Dayer P. Partial inhibition of tramadol antinociceptive effect by naloxane in man. Br J Clin Pharmacol 1993;35:73 P.