

Study Of Analgesic Effect Of Venlafaxine Loaded Microneedle Patch In Neuropathic Pain In Rat

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Abstract

Neuropathic pain (NP) conditions develop due to disorders resulting from damage or disease of the central or peripheral nervous system or both. Venlafaxine is a serotonin and norepinephrine reuptake inhibitor prescribed for management peripheral diabetic neuropathy. In the present study, the effect of microneedle patch on hyperalgesia in rat was studied using thermal hyperalgesia, a mild thermal injury was induced to the plantar surface of the right hind paw of rat. The microneedle patches exhibited sharp needles, the patch was white, homogenous and opaque with surface pH of 5.58 and of 97.18%. The results obtained from the study reveal that microneedle patches could be easily prepared and exhibited a sustained effect in decreased hyperalgesia in thermally induced hyperalgesia in rats. The microneedle patches were able to significantly improve PWL for duration longer than the conventionally administered first line agent gabapentin.

Keywords: Microneedle, venlafaxine, neuropathic pain, anti-hyperalgesia, allodynia

INTRODUCTION

Neuropathic pain (NP) conditions develop due to disorders resulting from damage or disease of the central or peripheral nervous system or both^[1]. Due to different causative factors, NP conditions may be prevalent in general population. Though exact prevalence is difficult to estimate, previous studies have reported overall prevalence of NP in general population to be around 6-7%^[2]. NP conditions put significant economic burden on health care services and patients. Treatment of NP is a challenging task for a physician as not all of the treated patients get satisfactory treatment response. Sometimes it can cause extreme discomfort and adversely affecting quality of life of the patient^[3,4]. Two prominent symptoms of NP are allodynia i.e. even non noxious stimulus can elicit severe pain response and hyperalgesia i.e. increased pain response to noxious stimulus. Thermal hyperalgesia include cold hyperalgesia which is seen in 21% of patient suffering from postherpetic neuralgia whereas heat hyperalgesia is seen in 25% patient following nerve damage^[5]. Gabapentin (GBP), pregabalin and tricyclic antidepressants (TCA) are first line agents for various painful peripheral as well as central neuropathic conditions. Duloxetine and venlafaxine are other recommended first line drugs for peripheral diabetic neuropathy. Venlafaxine is a serotonin and norepinephrine reuptake inhibitor prescribed for management of depression and chronic pain^[6]. Transdermal delivery of venlafaxine has been found to improve its bioavailability in the treatment of diabetic neuropathy^[7]. The present investigation was conducted with an objective to study the effect to transdermal microneedle patch of venlafaxine on hyperalgesia caused in neuropathic pain and to compare the effect with gabapentin.

MATERIAL AND METHODS

Venlafaxine was purchased from Yarrow Pharmaceuticals, Mumbai. Gabapentin capsules were purchased from local pharmacy store (Gabapin-100, Intas pharma).

Preparation and evaluation of venlafaxine loaded microneedle patch

PVA (5.0 %w/v) was dissolved in distilled water by heating on magnetic stirrer at 80°C for 20 min. Chitosan was dissolved in 2 mL of 2%v/v acetic acid. The chitosan solution was added to the PVA solution. The required quantity of venlafaxine (20 mg) was dispersed in 1 mL distilled water and added to the polymer solution. The prepared polymer gel solution containing venlafaxine was transferred into micro-molds and immediately centrifuged at 1500 rpm for 10 minutes for even and uniform distribution and to remove the air spaces. After completion of the process the micro centrifuge tube was removed from the centrifuge and dried for 2 days and then kept in freezer for 30 minutes at 4 °C for easy separation of microneedle patch from the micro molds. The fabricated patches were peeled off from the molds using forcep, stored in butter paper in desiccators.

Anti-nociceptive evaluation

Animal

Male Wistar rats (200-250g), were housed in clean environment with a 12 hour light /dark cycle. Food and water were provided ad libitum. The experimental procedures were approved by Institutional Animal Ethical Committee.

Experimental Protocol

Rats were randomly assigned to three groups (6 rats in each group): a placebo group (IP normal saline, IP NS), a standard group (hyperalgesia + oral gabapentin 10 mg/Kg) and a microneedle patch group (hyperalgesia + microneedle venlafaxine 10 mg/Kg).

Evaluation of microneedle patch in neuropathic pain

In the present study, to induce clear thermal hyperalgesia, a mild thermal injury was induced to the plantar surface of the right hind paw of rat. The rat was first anaesthetized in an induction box with halothane (2%). Any spontaneous movements or movements in response to toe pinch were carefully observed. After absence of any such movements, plantar surface of the right hind paw of the rat was kept for duration of 45 seconds on the surface of eddy's hot plate analgesiometer. The temperature of the hot plate analgesiometer was maintained between 51.5° to 53.5°C. During this procedure, mild pressure was applied on the hind paw in order to ensure uniform exposure of the plantar surface of the paw. After the removal of paw from the surface, a significant thermal hyperalgesia was observed by 30 min and this was sustained for approximately 3hrs. This procedure did not produce blistering of paw during the subsequent 24-h interval. To measure the thermal escape latency, the rat was placed on hot-plate surface, which was maintained between 51.5° to 53.5°C. The rats were again placed on the hot plate analgesiometer and the time until the brisk hind paw withdrawal response was recorded by a stop watch. In order to prevent any injury to animal, a cut off time of 20 seconds was used. Micro-needle patch was applied 30 min after the thermal injury and experiments to test efficacy of drugs were started after 30 min of drug administration^[8]. Animals were divided into 3 groups, each of 6 animals. Control group received saline (0.9%). The paw withdrawal latency (PWL) were measured at 30, 60, 90, 120 and 150 min after the drug administration.

Statistical Analysis

Statistical analysis was done by using graphpad prism version 5.01. Data were expressed as mean ± S.E.M. differences between vehicle, control and treatment groups were tested using one-way ANOVA followed by multiple comparisons by the post hoc Dunnett's test (for comparison with control group. A p values less than 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

The current study was undertaken to demonstrate AHA activity of venlafaxine microneedle patches in rat model of thermal hyperalgesia and to compare with AHA activity of the microneedle patch with gabapentin, which is currently available first line agent for various neuropathic pain conditions.

The microneedle patches exhibited sharp needles, the patch was white, homogenous and opaque with surface pH of 5.58. The drug content in the microneedle patches was found to be 97.18%.

Using thermal hyperalgesia model in rats, PWLs were measured as an indicator of Anti-hyperalgesic activity. As per results presented in Table 1, the microneedle patch of venlafaxine produced AHA effect (increased PWL) when compared to control at all the time points. Also it was observed that at 120 min, the effect of the standard drug gabapentin started to decrease (as indicated by a decrease in PWL compared to 90 min) but the microneedle patch was able to maintain the increase in PWL at the same time and even after 150 min of administration.

Table 1. Effect of drug treatment on PWL in rat

Drug	Time post drug administration				
	30 min	60 min	90 min	120 min	150 min
Control	7.82 ± 0.407	7.84 ± 0.222	7.91 ± 0.247	7.97 ± 0.179	7.87 ± 0.170
Gabapentin	10.58 ± 0.463	11.30 ± 0.282	14.028 ± 0.453	13.78 ± 0.273	13.37 ± 0.415
Venlafaxine microneedle	9.21 ± 0.285	10.18 ± 0.273	11.02 ± 0.228	11.42 ± 0.236	11.74 ± 0.219

GBP exerts its action by binding to $\alpha 2\delta$ subunit of calcium channels and decreasing the release of several neurotransmitters such as glutamate, norepinephrine and Substance P suppressing the hyper-excitability of peripheral neurons causing pain relief^[9,10]. GBP exert AHA action probably by acting in brain stem

thereby causing descending inhibition and anti-allodynic action probably by altering microglial functions [11].

Present study showed that efficacy of venlafaxine microneedle patch in reducing hyperalgesia is lower than GBP but since the microneedle patches are expected to be sustained release formulations, the effect was found to be continued even when the effect of gabapentin started to diminish.

CONCLUSION

The present investigation was undertaken with an objective to study the effect of venlafaxine microneedle patch an alternate delivery system for Venlafaxine, to obtain sustained action in neuropathic pain condition in rat. The results obtained from the study reveal that microneedle patches could be easily prepared and exhibited a sustained effect in decreased hyperalgesia in thermally induced hyperalgesia in rats. The microneedle patches were able to significantly improve PWL for duration longer than the conventionally administered first line agent gabapentin.

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