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ORIGINAL ARTICLE

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Cyclooxygenase inhibitors and thalidomide ameliorate vincristine-induced hyperalgesia in rats

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Abstract In this study ibuprofen (50.0 mg/kg, i.p.), rofecoxib (10.0 mg/kg, i.p.) and thalidomide (50.0 mg/kg, oral) were shown to prevent vincristine-induced mechanical hyperalgesia. Sprague-Dawley rats were injected every other day with vincristine (0.1 mg/kg) over 13 days. The animals were cotreated daily with vehicle (saline), ibuprofen, rofecoxib or thalidomide throughout the period of vincristine treatment. Mechanical withdrawal threshold to punctuate and radiant heat stimuli were determined prior to and then on alternate days throughout the treatment period. Vincristine vehicle-treated animals developed marked mechanical hyperalgesia from day 5 of chemotherapy and this lasted until the end of the experiment. Thermal thresholds were not altered by the administration of vincristine vehicle. Animals in the vincristine vehicle group neither gained nor lost weight during the treatment period. All three active drugs showed an antihyperalgesic effect on the responses to mechanical stimulation of the hind paw that was significant from day 5 for ibuprofen and thalidomide and from day 7 for rofecoxib. Thermal thresholds increased after the administration of both the NSAIDs and thalidomide. Rofecoxib was the only drug to show any beneficial effect in protecting the animals from failure to gain body weight.

Keywords Cyclooxygenase inhibitors · Thalidomide · Vincristine-induced hyperalgesia · Rats

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Introduction

Painful neuropathy is the most common dose-limiting effect of antineoplastic agents [26, 74]. Chemotherapy-induced peripheral pain is characterized by numbness, burning and tingling in a stocking-and-glove distribution [26] like that observed in diabetic and AIDS neuropathies [10, 15, 18, 22, 50, 61]. Patients can also complain of motor symptoms such as weakness and gait disturbances, and signs of motor dysfunction are also found in the physical examination [9, 12]. The incidence and severity of vincristine-induced neuropathy is such that nearly all patients experience discomfort by a third treatment cycle [12, 52, 56]. Vincristine-induced peripheral neuropathy is a dose-dependent side effect that is irreversible in most of the patients and it often affects survival, quality of life and the return to productivity in cancer patients [16, 17].

Rats also develop mechanical hyperalgesia following bolus intravenous [2], continuous intravenous [46] or bolus intraperitoneal administration of vincristine [75]. Although vincristine-induced neuropathy differs in regard to specific second messenger systems engaged in peripheral nerves compared to neuropathy produced by direct nerve damage [2], vincristine nevertheless induces abnormalities in primary afferent [71] and spinal processing of somatosensory information [75] similar to other models of experimental peripheral neuropathy [28, 32, 48]. This suggested the possibility that drugs effective for other neuropathic pain conditions may prove beneficial in this model.

Prostanoids, released both peripherally and centrally from arachidonic acid by the cyclooxygenase-1 and cyclooxygenase-2 enzymes (COX1 and COX2) in neuronal and non-neuronal cells, contribute to the generation of neuropathic pain produced by loose nerve ligation [37, 38] and contribute to inflammatory pain [40]. However, the optimal role of COX1 vs COX2 antagonists is unclear as non-selective inhibitors often have stronger analgesic properties than selective

antagonists [33, 38, 40, 69]. Meanwhile, tumor necrosis factor alpha (TNF-α) has emerged as another important mediator of pain following nerve injury [47, 63]. Mechanisms involved in the action of TNF-α in neuropathic pain may include alteration of nerve growth factor production by macrophages [35], increased synthesis of second messenger enzymes [1], activation of p38 MAPK [57], and direct stimulation of activity in nociceptors [65].

Thalidomide has shown great utility in the treatment of several inflammatory diseases including leprosy and rheumatoid arthritis [11], presumably due to inhibition of TNF synthesis and release [43, 55]. Clinical experience with thalidomide in the treatment of neuropathic pain is limited [53], but it has ameliorated the hyperalgesic response to mechanical and thermal stimuli in rats with chronic constriction sciatic nerve injury [23]. Thus, the goal of the present study was to evaluate the possible role of COX inhibitors and thalidomide in an animal model of vincristine-induced painful neuropathy. This model of painful neuropathy was used in the present study because in other models intravenous administration or higher dosages of vincristine have been demonstrated to cause a higher rate of mortality of the animals.

Methods

Sprague-Dawley male rats weighing between 180 and 220 g were used (Harlan, Houston, Tx.). The animals were housed individually and maintained on a 12/12 light/dark cycle, with lights on at 07:00 h. The ambient temperature in the animal facility was kept at 22°C. Food and water were given ad libitum. All experiments were conducted with the approval of the Institutional Animal Care and Use Committee at the MD Anderson Cancer Center and were in the complete compliance with the National Institutes of Health Guidelines for Use and Care of Laboratory Animals.

Drug administration protocols

A total of 34 rats were treated with intraperitoneal (i.p.) bolus injections of vincristine (0.1 mg/kg per day, diluted to 1 ml in saline) as in previous experiments [75]. Ibuprofen (Sigma) was administered at a dose of 50 mg/kg (i.p.) while rofecoxib (Merck) was administered at a dose of 10 mg/kg (i.p.) [8]. Both drugs were dissolved in saline. Thalidomide (Sigma) was administrated orally (50 mg/kg) using a metallic feeding needle. This dose of thalidomide has been demonstrated to be effective in another animal model of pain [6, 23]. From a stock solution of 10% DMSO, the thalidomide was diluted in saline to a final concentration of 2% DMSO before administration. Thalidomide and the NSAIDs were given daily 30 min prior to vincristine by a blinded investigator throughout the chemotherapy treatment period.

Behavioral analysis

Behavioral tests were conducted in a blinded fashion before and then on days 1, 3, 5, 7, 9, 11 and 13 of vincristine treatment. Responsiveness to mechanical and thermal stimulation was evaluated in both hind paws.

Mechanical stimulation

Rats were placed in a 10×10×20 cm Plexiglass chamber, which rested on a wire mesh. Following acclimation for 15–20 min, a series of von Frey monofilaments (range of bending forces 0.155, 0.6, 1.14, 2.82, 8.7, 14.6 g) were tested in ascending order. Each filament was applied five times to the mid-plantar side of each hind paw from beneath for about 1 s. Response threshold was defined as the lowest force that evoked a 50% or greater response frequency [75].

Thermal stimulation

Responsiveness to noxious heat was evaluated using a radiant heat source [25]. The rats were placed on a glass surface and loosely restrained using chambers as described above. Following acclimation, a radiant heat beam (diameter 5 mm^2) was directed onto the mid-plantar surface of the hind paw from beneath. The paw withdrawal latency was defined as the time from the beginning of the heat stimulus until the presence of a brisk lifting was present. Five withdrawal latencies were collected for each hind paw. An inter-stimulus interval of at least 1 min was used in order to avoid skin sensitization. A cutoff interval of 20 s was recorded for any trials where an earlier spontaneous withdrawal was not achieved to ensure protection of the skin from damage.

Data analysis

The 50% withdrawal threshold, thermal withdrawal latencies and percent of body weight changes are expressed as the means ± SE. To evaluate statistical significance, the effect of the drug over time was analyzed using ANOVA. The post hoc evaluation was performed using the Tukey test for mechanical, sustained paw elevation and thermal withdrawal latencies and the Mann-Whitney *U*-test for percent body weight change. A significant difference was considered for P values < 0.05.

Results

Group composition

Behavioral tests were conducted on 34 vincristine-treated rats. They were divided into four groups. Rats treated with vincristine-vehicle (saline, V.v.; $n = 14$), vincristine-ibuprofen 50 mg/kg (V.i.; $n = 8$),

vincristine-rofecoxib 10 mg/kg (V.r.; $n=6$) and vincristine-thalidomide 50 mg/kg (V.t.; $n=8$). No rats showed any sign of motor dysfunction, autotomy or guarding during the study.

Mechanical withdrawal data

Rats in the V.v. group showed statistically significant mechanical hyperalgesia beginning on day 5 of chemotherapy. The 50% withdrawal threshold at baseline was 5.08 ± 0.76 g and had dropped to 2.2 ± 0.55 g ($P < 0.05$) by day 5. On day 13 of the experiment, the 50% withdrawal threshold had further dropped to 1.16 ± 0.21 g ($P < 0.05$; Fig. 1). Mechanical hyperalgesia was significantly reduced in rats in the V.i. 50 group. On day 5 of the experiment, the 50% withdrawal threshold was 6.65 ± 2.14 g in the V.i. group ($P < 0.05$). The ibuprofen-treated rats maintained this antihyperalgesic effect until the end of the treatment period (day 13) at which time their 50% withdrawal threshold was 4.10 ± 1.5 g ($P < 0.01$; Fig. 1). Rofecoxib at a dose of 10 mg/kg also prevented vincristine-induced mechanical hyperalgesia. This effect was statistically significant on day 7 of the experiment (V.r. group 4.78 ± 1.24 g vs V.v. group 1.57 ± 0.23 g, $P < 0.01$), and again lasted until the end of the study (V.r. group 5.48 ± 2.11 g vs V.v. group 1.16 ± 0.21 g, $P < 0.01$). Thalidomide showed a significant antihyperalgesic effect beginning on day 7 (V.t. group 4.41 ± 1.27 vs V.v. group 1.57 ± 0.23 g, $P < 0.05$) and this also lasted until day 13 of the experiment (V.t. group 4.92 ± 1.54 g vs V.v. group 1.16 ± 0.21 g, $P < 0.05$; Fig. 1).

Thermal withdrawal data

V.v. animals did not show any change in responses to thermal stimuli over the course of chemotherapy in this study, which is in agreement with a previous study by our group (Fig. 2) [75]. V.i. animals showed a significant increase in thermal withdrawal threshold that became evident by day 3 of treatment ($P < 0.001$; Fig. 2) and this persisted to the end of the study. Rofecoxib and thalidomide had the same effect on the thermal thresholds with a significant increase for both these drugs evident by day 1 of combined therapy ($P < 0.01$) and again persisting to the end of the experiment (Fig. 2).

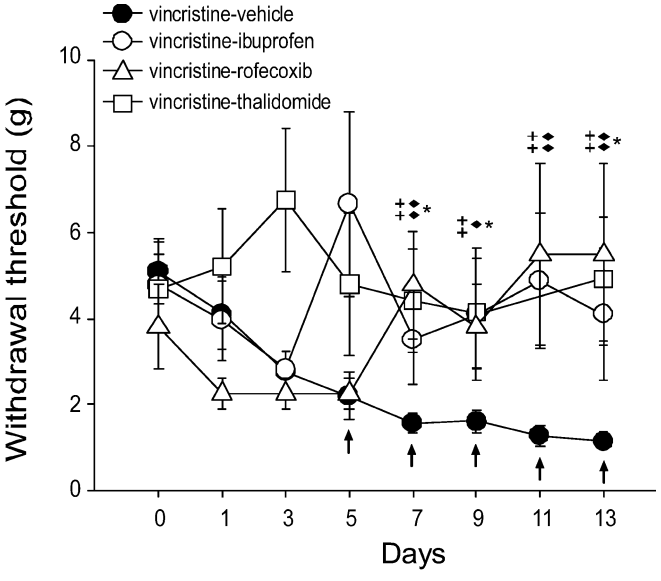

Fig. 1 The scatter-line graphs illustrate the 50% withdrawal threshold to mechanical stimulation of the hind paws with von Frey monofilaments across the treatment interval. The *filled circles* show the data for the animals treated with vincristine-vehicle (saline). A statistically significant decrease in 50% withdrawal threshold compared to the baseline level (day 0) was found beginning on day 5 in the vincristine-vehicle (V.v.) group ($^{\dagger}P < 0.05$ vs baseline, within-group comparison) and maintained throughout the treatment period. The vincristine-ibuprofen (V.i., *open circles*), vincristine-rofecoxib (V.r., *open triangles*) and vincristine-thalidomide (V.t., *open squares*) groups all showed 50% withdrawal thresholds that were significantly increased compared to that of the V.v. group beginning on day 7 of the treatment period and maintained for the remainder of the treatment period ($^{+}P < 0.05$, $^{++}P < 0.01$ for V.i. vs V.v.; $^{\blacklozenge}P < 0.05$, $^{\blacklozenge\blacklozenge}P < 0.01$ for V.r. vs V.v.; $^{*}P < 0.05$ for V.t. vs V.v.). There were no significant differences in 50% mechanical withdrawal thresholds among the V.i., V.r. or V.t. groups

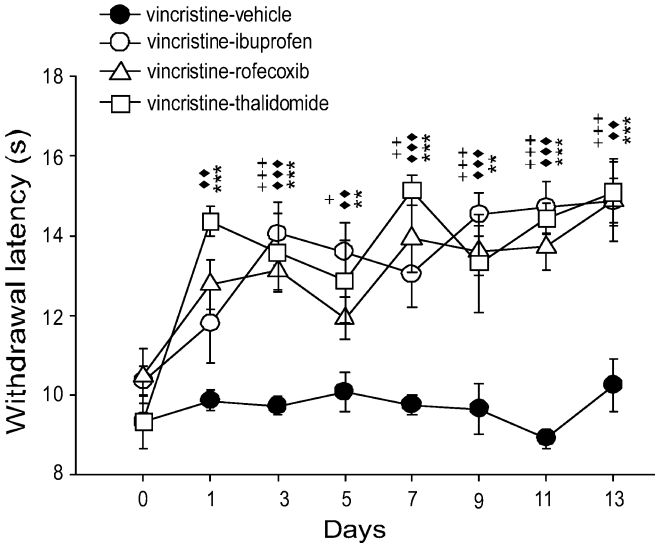

Fig. 2 The scatter-line graphs illustrate the mean latency to withdrawal from radiant heat of the hind paws in rats treated with vincristine-vehicle (V.v., *filled circles*), vincristine-ibuprofen (V.i., *open circles*), vincristine-rofecoxib (V.r., *open triangles*) and vincristine-thalidomide (V.t., *open squares*). The V.v. rats did not show any significant change in paw withdrawal latency to radiant heat across the treatment period. In contrast, all of the remaining groups showed a significant increase in withdrawal latency beginning on day 1 for the V.r. and V.t. groups and on day 3 for the V.i. group compared to the V.v. group. Withdrawal latency remained significantly increased compared to the V.v. group for the remainder of the treatment period ($^{+}P < 0.05$, $^{++}P < 0.01$, $^{+++}P < 0.001$ for V.i. vs V.v.; $^{\blacklozenge\blacklozenge}P < 0.01$, $^{\blacklozenge\blacklozenge\blacklozenge}P < 0.001$ for V.r. vs V.v.; $^{**}P < 0.01$, $^{***}P < 0.001$ for V.t. vs V.v.). There were no significant differences in paw withdrawal latencies among the V.i., V.r. or V.t. groups

Comparison between the V.i., V.r. and the V.t. groups did not demonstrate significant differences in thermal withdrawal latencies among these groups at any time point.

Body weight changes

Similar to previous observations by Weng et al. [75], V.v. treated rats failed to gain weight for the first week of chemotherapy and showed only a marginally significant increase in body weight over the duration of the treatment period (Fig. 3). On days 11 and 13 of the study the V.v. animals showed an increase in body weight of $2.09 \pm 2.77\%$ and $2.19 \pm 1.90\%$, respectively, compared to baseline ($P < 0.05$). Ibuprofen did not have any beneficial effect on body weight. V.r. rats showed improved maintenance of body weight gain as a statistically significant increase in weight gain was sustained from day 7 ($5.75 \pm 1.71\%$, $P < 0.001$) to the end of the experiment (Fig. 3). Finally, thalidomide did not have any beneficial effect on maintenance of body weight; in fact, the animals in the V.t. group were the only rats that failed to show any significant weight gain over the treatment period. Statistical comparisons between the different treatment groups showed that the V.r. rats markedly recovered weight from day 9 compared to V.v. animals

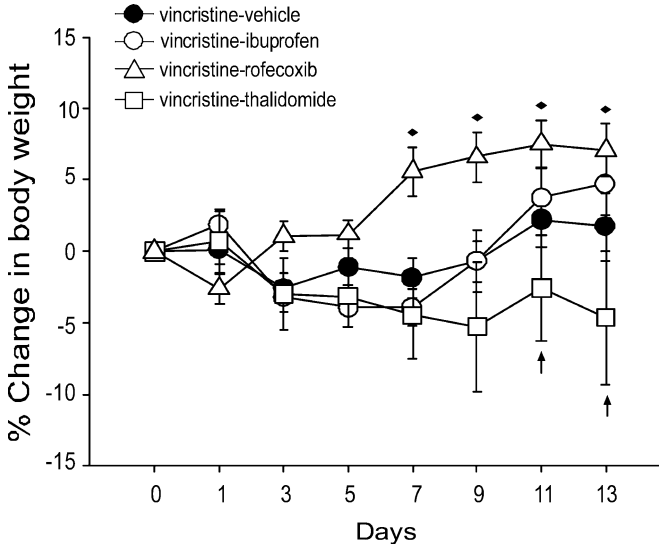

Fig. 3 The scatter-line graphs show the mean percent change in body weight for the vincristine-vehicle (V.v., *filled circles*) vincristine-ibuprofen (V.i., *open circles*), vincristine-rofecoxib (V.r., *open triangles*) and vincristine-thalidomide (V.t., *open squares*) treated animals. Rats in the vincristine-vehicle (V.v.) group neither a significant gain or loss in weight over the first week of treatment but then began to significantly gain weight over the second week (day 11 of treatment, $^{\dagger}P < 0.05$ vs baseline, within-group comparison) and maintained this trend for the remainder of the treatment period. The V.i. and V.t. groups showed changes in body weight that were not significantly different from the changes in the V.v. group. Finally, the V.r. group showed the most increase in body weight during the treatment period with this difference becoming significantly different from the V.v. group by day 7 and remaining so for the duration of the treatment period ($^{\blacklozenge}P < 0.05$)

($7.51 \pm 1.6\%$ vs $-1.84 \pm 1.39\%$, $P < 0.05$) and the recovery lasted until day 13 ($7.06 \pm 1.84\%$ vs $1.74 \pm 2.35\%$, $P < 0.05$; Fig. 3). There were n statistically significant differences in weight gain between the V.t. and V.i. rats compared to the V.v. rats at any point of the experiment.

Discussion

The data shown here demonstrate that ibuprofen, rofecoxib and thalidomide each ameliorate the development of vincristine-induced mechanical hyperalgesia. The exact mechanism by which vincristine induces sensory dysfunction is not well understood. The potential for vincristine to interact with neuronal microtubules, presumably altering axonal trafficking of enzymes, neuropeptides and trophic factors so resulting in primary afferent dysfunction has been suggested as one obvious possible mechanism [24, 59, 71]. Indeed changes in primary afferent fiber morphology and physiology including disorientation of microtubules in a small percentage of C fibers, increased incidence of periaxonal swelling, slowing of conduction velocity in subsets of A and C fibers and an increased responsiveness of a subgroup of C fibers to mechanical and heat stimulation have all been shown in rats with vincristine-induced hyperalgesia [70, 71]. Nevertheless, there is no direct evidence to support the mechanisms outlined above. On the other hand, the data shown here suggest that in addition to possible effects on microtubules, the induction of prostaglandins and other proinflammatory mediators such as cytokines by chemotherapy drugs might not only participate in but also in fact drive the genesis and maintenance of chemotherapy-induced neuropathic pain. It is well known that ibuprofen blocks both constitutively expressed COX-1 and inducible COX-2 enzyme activities [41], whereas rofecoxib specifically blocks activity of COX-2 [14]. Thalidomide is a potent inhibitor of TNF-α synthesis [43] and release [55] and inhibits the intracellular signaling of both TNF-α and IL-1β through nuclear factor kappa B (NF-κB) [29, 36].

Although at first counterintuitive, the induction of proinflammatory mediators by chemotherapy drugs is a well-established fact. In vitro studies have demonstrated that microtubule-disrupting agents such as vincristine and Taxol induce the synthesis of prostaglandins, including PGE-2, in human mammary epithelial cells and in human and murine macrophages by increasing the transcription of COX-2 mRNA [42, 66, 67]. Vincristine and Taxol also increase IL-1β mRNA expression in human peripheral blood mononuclear cells [19, 60, 62] which would be expected to result in increased local and circulating levels of additional proinflammatory cytokines. Indeed, increased release of tumor necrosis factor alpha (TNF-α) is also induced by chemotherapy drugs from human monocytes [51]. Increased proinflammatory cytokines would then induce increased expression of

COX-2 mRNA in the central nervous system [54] and facilitate the release of algesic agents, such as substance P from primary afferent neurons [44]. Consistent with the data shown here, COX inhibitors block increased prostaglandin synthesis by Taxol [42].

Prostanoids and cytokines have well-established roles in many models of neuropathic and inflammatory pain and hyperalgesia. Hyperalgesia is observed in the sickness behavior induced by lipopolysaccharide that can be blocked by antagonists to interleukin-1 [72, 73, 76]. In models of both neuropathic and inflammatory pain, increased numbers of activated astrocytes, a potential source of the cytokines TNF, IL-1β, IL-15 and IL-6, are observed in the spinal cord segments to which the affected afferent nerves project [4, 21]. Neuropathic pain can be induced by surrounding a peripheral nerve with a chromic gut suture [7] or producing structural damage to peripheral axons [30, 58] that leads to an inflammatory reaction at the site of injury, or by simply surrounding peripheral nerves with an immune stimulant such as zymosan [5, 6, 13]. Inflammatory cells including COX-1 and COX-2 enzyme-expressing macrophages, neutrophils, and $CD4^+$ and $CD8^+$ T cells infiltrate the site [38], levels of cytokines increase (IL-1, and particularly TNF), and endoneural swelling and neuropathic pain ensues [5, 6]. Mechanisms by which cytokines might produce pain include directly producing discharges of nociceptive nerve fibers [34, 64], altering the trafficking of growth factors along nerve fibers resulting in phenotypic changes in sensory endings [45], inducing an alteration of glial cell-mediated support of neural activities such as synaptic glutamate reuptake [27] or inducing the degeneration of neurons and the retraction of cell processes [3]. The inflammatory cascade leading to nerve constriction pain can be blocked by compounds effective against chemotherapy-induced pain including the COX-2 antagonist ketorolac [37] and thalidomide [23], while inflammatory neuritis is blocked by either thalidomide or the immunosuppressant cyclosporin A [5, 6]. The reduction in constriction neuropathy-induced pain by thalidomide is paralleled by reductions in endoneural levels of TNF-α [23]. Similarly, the effects of COX antagonists in reducing neuropathic pain could be related to their actions in reducing cytokine release [31] as well as their effects in reducing prostanoids.

Cytokine induction by chemotherapy drugs would also provide a mechanistic explanation for both the weight loss observed in the vincristine-vehicle animals and the effects of the nonsteroidal antiinflammatory drugs in preventing this occurrence. Anorexia and weight loss are among the behavioral manifestations of IL-1β, TNF-α and IL-6 when administered into the CNS [20]. IL-1β-mediated anorexia depends on the activation of NF-κB, followed by induction of activity of the COX-1 and COX-2 enzymes as well as activity in inducible nitric oxide synthase [49]. IL-1β hypophagia in mice is mediated by COX-1 activity in an early phase followed by COX-2 in a more prolonged phase [68]. Although thalidomide has shown some utility in the treatment of cancer-related cachexia [39], the failure of thalidomide in generating any beneficial effect on body weight may suggest little role for TNF-α in this aspect of vincristine's effects.

The data presented in this study provide encouragement for future clinical and animal research in order to validate the findings and determine the utility of NSAIDs and thalidomide in the prevention of chemotherapy-induced neuropathy.

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