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Recovery Sleep Does Not Mitigate the Effects of Prior Sleep Loss on Paclitaxel-Induced Mechanical Hypersensitivity in Sprague-Dawley Rats

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Abstract

Society has a rapidly growing accumulative sleep debt due to employment obligations and lifestyle choices that limit sleep opportunities. The degree to which poor sleep may set the stage for adverse symptom outcomes among more than 1.7 million persons who will be diagnosed with cancer is not entirely understood. Paclitaxel (PAC), a commonly used chemotherapy agent, is associated with painful, debilitating peripheral neuropathy of the hands and feet, which may persist long after adjuvant therapy is completed. The aims of this preclinical study were to determine the accumulative and sustained effects of sleep restriction on PAC-induced mechanical sensitivity in animals and whether there are male–female differences in mechanical sensitivity in PAC-injected animals. Sixty-two adult Sprague-Dawley rats ($n = 31$ females) were assigned to three cycles of intraperitoneal injections of PAC (1 mg/kg) versus vehicle (VEH; 1 ml/kg) every other day at light onset for 7 days, followed by seven drug-free days and to sleep restriction versus unperturbed sleep. Sleep restriction involved gentle handling to maintain wakefulness during the first 6 hr of lights on immediately following an injection; otherwise, sleep was unperturbed. Mechanical sensitivity was assessed via von Frey filaments, using the up–down method. Mechanical sensitivity data were Log_{10} transformed to meet the assumption of normality for repeated measures analysis of variance. Chronic sleep restriction of the PAC-injected animals resulted in significantly increased mechanical sensitivity that progressively worsened despite sleep recovery opportunities. If these relationships hold in humans, targeted sleep interventions employed during a PAC protocol may improve pain outcomes.

Keywords

paclitaxel; mechanical sensitivity; rats; chronic sleep loss; pain

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An estimated 1.7 million people from the United States will be diagnosed with cancer this year (American Cancer Society, 2013). Many will undergo adjuvant therapy and experience a variety of unintended treatment-induced effects, for example, pain. Paclitaxel (PAC), a commonly used chemotherapy agent for solid tumor cancers, is associated with a length-dependent, axonal neuropathy that predominantly affects sensory nerves (Cavaletti & Marmiroli, 2004). Chemotherapy-induced peripheral neuropathy (CIPN) occurs in a stocking and glove distribution, primarily affecting the hands and feet. CIPN affects the person's ability to button clothing, engage in cooking and gardening, and ambulate (Bakitas, 2007). Dougherty, Cata, Cordella, Burton, and Weng (2004) asked persons undergoing PAC therapy to indicate areas of neuropathic pain by shading in their affected areas on a human figure. Research participants shaded in hands, fingertips, feet, and toes. CIPN incidence may be upward of 80–90% among those undergoing a PAC protocol (Bristol-Meyers Squibb Company, 2007). The risk for CIPN occurrence and for greater severity is associated with the intensity of the protocol, either high dose or fewer recovery days between doses, and/or with the accumulative effect of repetitive cycles (Argyriou, Koltzenburg, Polychronopoulos, Papapetropoulos, & Kalofonos, 2008). Regardless of its etiology, CIPN can be painful and debilitating, resulting in quality-of-life decrements (Bakitas, 2007; Bezjak et al., 2004), dose reductions for some, and treatment cessation for others (Mielke et al., 2003).

A number of preclinical studies have determined the effects of PAC on mechanical sensitivity. Researchers studying rat models using PAC doses ranging from 0.1 mg/kg to 32 mg/kg (accumulative dose ranging from 2 to 135 mg/kg) have reported significant mechanical hypersensitivity in 14–100% of the animals (Authier, Gillet, Fialip, Eschalier, & Coudore, 2000; Cavaletti et al., 1997; Cavaletti, Tredici, Braga, & Tazzari, 1995; Flatters & Bennett, 2004, 2006; Polomano, Mannes, Clark, & Bennett, 2001). In rodent models, mechanical hypersensitivity may emerge as soon as 1 hr after administration of a single dose of PAC (1 mg/kg) and resolve after 24 hr (Dina, Chen, Reichling, & Levine, 2001). Researchers conducting experiments using repeated PAC dosing paradigms have reported varied mechanical hypersensitivity prevalence over time, with peak prevalence occurring anywhere from Day 9 to Day 30 after the first dose (Dina et al., 2001; Flatters & Bennett, 2004, 2006; Polomano et al., 2001) and near complete mechanical hypersensitivity resolution by Day 155 (Flatters & Bennett, 2004, 2006).

These studies used either all male (Authier et al., 2000; Dina et al., 2001; Flatters & Bennett, 2004, 2006; Polomano et al., 2001) or all female rats (Cavaletti et al., 1995, 1997; Cliffer et al., 1998) and used the outbred rat strains Sprague-Dawley (Authier et al., 2000; Cliffer et al., 1998; Dina et al., 2001; Flatters & Bennett, 2004, 2006; Polomano et al., 2001) or Wistar (Cavaletti et al., 1995, 1997). Researchers in a comparative study of 10 inbred mouse strains for PAC-induced mechanical hypersensitivity (4 mg/kg accumulative dose) reported that male mice demonstrate greater mechanical sensitivity than female mice (S. B. Smith, Crager, & Mogil, 2004). By contrast, using male and female Sprague-Dawley rats, Hwang, Kim, Kim, Kwon, and Kim (2012) injected four every other day 2 mg/kg doses of PAC for a total of 8 mg/kg and reported no sex differences in mechanical hypersensitivity. Because the PAC protocols varied between studies with respect to their schedule/timing and accumulative dose, it is difficult to make meaningful comparisons across studies, and little is

thus known regarding possible sex differences in PAC-induced mechanical hypersensitivity. Mogil (2012) reports that the relationship between sex and pain is complex; not all rodent models of pain show sex differences. Nevertheless, it is important to determine whether there are sex differences in CIPN.

Poor sleep is a common occurrence throughout the cancer and treatment trajectories (Palesh et al., 2010; Savard, Ivers, Villa, Caplette-Gingras, & Morin, 2011; Savard & Morin, 2001; Savard, Villa, Ivers, Simard, & Morin, 2009), and co-occurring pain and poor sleep during cancer treatment are associated with increased numbers of other symptoms, as well as an increased risk for mortality (Kozachik & Bandeen-Roche, 2008). There is abundant evidence from clinical and rodent model literature that testifies to the adverse effects of poor sleep quality or sleep loss on enhancing/amplifying pain sensitivity (Kundermann, Hemmeter-Spernal, Huber, Krieg, & Lautenbacher, 2008; Lautenbacher, Kundermann, & Krieg, 2006; Lentz, Landis, Rothermel, & Shaver, 1999; May et al., 2005; Nascimento, Andersen, Hipólido, Nobrega, & Tufik, 2007; Onen, Alloui, Jourdan, Eschalier, & Dubray, 2001; Roehrs, Hyde, Blaisdell, Greenwald, & Roth, 2006; Roehrs & Roth, 2005; B. H. Smith, Macfarlane, & Torrance, 2007). Recent evidence suggests that sleep disruption may increase risks for pain through alterations in neuromodulatory pain systems (M. T. Smith, Edwards, McCann, & Haythornthwaite, 2007).

The 2006 Institute of Medicine report *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem* brought to the forefront the growing problem of inadequate sleep: More than 70 million Americans are burdened with insomnia. In addition, countless thousands have persistent shortened sleep hours or poor sleep quality due to lifestyle choices, such as sustained engagement in social media, shift work, or familial obligations that reduce sleep opportunities. Given the ever-increasing prevalence of societal sleep disturbance/sleep loss, one may reasonably speculate that a large proportion of persons diagnosed with cancer will enter the cancer experience with preexisting poor sleep. Determining the consequences of inadequate sleep on chemotherapy-induced pain is warranted. The effects of restricted sleep opportunities on PAC-induced neuropathic pain have not yet been reported. In the present study, we explored the accumulative and sustained effects of a sleep restriction protocol on PAC-induced mechanical sensitivity in the Sprague-Dawley rat.

Materials and Methods

Study Design

For this longitudinal study, we employed a $2 \times 2 \times 2$ factorial design, with sleep (restricted vs. undisturbed), drug (PAC 1 mg/kg vs. 0.9% saline VEH 1 ml/kg), and sex as main effects to determine (1) the accumulative and sustained effects of sleep restriction on PAC-induced mechanical sensitivity and (2) whether there are male–female differences in mechanical sensitivity among PAC-injected rats. Briefly, rats were habituated to a testing room for 15, 30, and 30 min over consecutive days and then underwent habituation for 30 min followed by baseline von Frey testing for up to 3 days. Rats with bilateral 50% paw withdrawal threshold (PWT) ≥ 10 g on the last day of preprotocol testing were entered into the study. On protocol Days 1, 3, 5 and 7, animals were given intraperitoneal (i.p.) injections of either

PAC (1 mg/kg) or 0.9% saline (VEH, 1 ml/kg) just prior to lights on. Rats assigned to restricted sleep were kept awake via gentle handling for the first 6 hr of lights on that immediately followed an injection. On protocol Days 8–14, the 7-day period between drug injection series, with the exception of von Frey testing, all rats had undisturbed sleep opportunities. This 14-day cycle was repeated twice, for a total of three cycles, to model a clinical protocol of adjuvant chemotherapy that a human might undergo, with repeated active drug and rest phases, as shown in Figure 1. The study described herein is part of a larger study.

Procedures

Animals—The 62 Sprague-Dawley rats ($n = 31$ females) used for this study were bred in house to eliminate the impact of institutionalized rearing, shipping, and acclimatization into a new environment. Breeders were purchased from Harlan Sprague-Dawley (Indianapolis, IN) and acclimatized for a minimum of 21 days before breeding. Pups were weaned at 21 days of age and housed with same-sex littermates. Rats were entered into the study at 14–16 weeks of age, at which time they were individually housed in standard plastic cages with bedding. Standard rat chow and water were available ad libitum. Rats were maintained on a 12:12-hr light:dark cycle (lights on at 0800 hr) in an environmental temperature of 23°C ($\pm 2^\circ$).

Animal welfare—This study was approved by the Johns Hopkins University Animal Care and Use Committee. The care and use of the study animals conformed to the National Institutes of Health rules *Guide for the Care and Use of Laboratory Animals* (National Academy of Sciences).

Animal health assessment during the PAC protocol—Rats were weighed 3 times per week throughout the protocol and visualized daily for signs of anorexia, apathy/lack of movement, alopecia, piloerection, porphyrin staining, and dehydration.

Mechanical sensitivity testing—Assessment of mechanical sensitivity of both hind paws was performed during the latter 6 hr of the light phase using eight von Frey filaments with logarithmically incremental bending forces, ranging from 0.45 to 16.69 g, via the up–down method (Dixon, 1980). Specifically, the von Frey filament was applied with bending force for 5–7 s to the hind paw plantar surface between the footpads, beginning with the fourth strongest filament. If a brisk paw withdrawal was elicited, the next weaker von Frey filament was applied. In the absence of such a response, the next stronger von Frey filament was applied. This procedure yielded a range of four to nine applications per paw and resulted in the fewest perturbations of the paw versus other testing methods. Given that others have reported changes in response to von Frey testing when animals were distracted by grooming (Callahan, Gil, Levesque, & Mogil, 2008), we waited for animals to cease grooming before we presented the von Frey filament. The 50% PWT was calculated according to the methods of Dixon (1980); von Frey filaments were calibrated between each assay.

Sleep restriction—Rats assigned to sleep restriction were gently handled to maintain wakefulness during the first 6 hr of the light phase that immediately followed each injection. This restricted the rats' sleep opportunities to the latter 6 hr of the light phase and the entire dark phase. While rats are known to have periods of sleep throughout the 24-hr day (Opp, 1998), as nocturnal mammals, they sleep more during the light phase than during the dark phase. Researchers have reported that Sprague-Dawley rats spend more than half of the 12-hr light phase sleeping, versus sleeping about one third of the 12-hr dark phase (Darsaud et al., 2004; Opp, 1998). Rats were not disturbed at other times, except for mechanical sensitivity testing and injections. Gently handling the rats provided tactile stimulation by, and engagement with, the investigators that maintained the rats' wakefulness and provided a chronic partial sleep loss that was designed to model the human experience of insomnia (Edinger & Means, 2005).

PAC preparation and administration—PAC (Henry Schein, Indianapolis, IN) comes in a multiuse vial 6 mg/ml, and it was diluted to a final concentration of 1 mg/ml in bacteriostatic 0.9% saline just prior to injection. In order to model a clinical protocol of adjuvant chemotherapy that a patient might undergo, we employed an every other day dosing of PAC 1 mg/kg for four doses, added a 7-day recovery period that began the day after the fourth dose of PAC, and repeated this 14-day cycle twice, for a total of three cycles (see Figure 1). Animals received an accumulative PAC dose of 12 mg/kg, which is equivalent to a clinically relevant dose for humans (Scripture, Figg, & Sparreboom, 2005).

Data Transformation and Statistical Analyses

To meet the assumption of normality of our dependent variable (50% PWT), we Log_{10} transformed the 50% PWT values (Mills et al., 2012). We used IBM SPSS Statistics 20 to analyze the data. We ran repeated measures analysis of variance (RMA-NOVA) with Fisher's least significant difference (LSD) test to determine differences in group means over a period of time that allowed us to determine the accumulative effects of sleep loss and drug by accumulative dose: 4 mg/kg, 8 mg/kg, and 12 mg/kg. To determine whether recovery sleep periods were sufficient to attenuate the effects of sleep loss on 50% PWT during the active drug phase, we ran RMANOVA with LSD after the two, 7-day intercycles (7 days after accumulative doses of 4 mg/kg and 8 mg/kg) and 7 days after receipt of an accumulative dose of 12 mg/kg. Model building included main effects and construction of two-way and three-way interaction terms. Mauchly's test was conducted to confirm the assumption of sphericity. A p value of .05 was used to determine statistical significance.

Results

We found neither main nor interaction effects of sex on PAC-induced mechanical sensitivity, thus, we pooled the data for analyses.

Immediate, Accumulative Effects of Sleep Restriction and PAC on Mechanical Sensitivity

The accumulative effects of restricted sleep resulted in significantly reduced 50% PWT among PAC- and VEH-injected rats, $F(1, 60) = 11.27$, $p = .001$, and the accumulative effects of PAC resulted in significantly reduced 50% PWT, $F(1, 60) = 11.05$, $p = .002$. We ran

independent *t*-tests with Bonferroni correction to determine whether there were significant differences in 50% PWT between the PAC-injected rats that were sleep restricted (PAC-SR) versus PAC-injected rats with undisturbed sleep (PAC-SL). PAC-SR rats exhibited 50% PWTs that were significantly lower than those of PAC-SL rats after accumulative PAC doses of 4 mg/kg (mean difference = -0.28 , 95% confidence interval [CI] [-0.33 , -0.23], $p = .000$), 8 mg/kg (mean difference = -0.29 , 95% CI [-0.34 , -0.13], $p = .000$), and 12 mg/kg (mean difference = -0.22 , 95% CI [-0.27 , -0.17], $p = .000$; see Figure 2). Sleep restriction of control rats (VEH-injected) reduced the 50% PWT to the same extent as that observed in PAC-SL rats.

Sustained Effects of Sleep Restriction and PAC on Mechanical Sensitivity

As described earlier, the drug protocol included 7-day, intercycle, recovery periods in which rats were not injected with PAC or VEH and, other than von Frey hair (VFH) testing, had undisturbed sleep opportunities. Our model for the sustained effects of restricted sleep on PAC-induced mechanical sensitivity showed significant drug effects, $F(1, 60) = 18.17$, $p = .000$, and drug by sleep effects, $F(1, 58) = 10.73$, $p = .002$. PAC-SR rats exhibited a significantly reduced 50% PWT that demonstrated a downward trajectory over time (see Figure 3). During each of the three 7-day drug-free and sleep recovery periods, VEH-SR rats exhibited recovery of 50% PWTs to baseline.

Rat Health During the PAC Protocol

Rats tolerated the PAC injections without exhibiting any obvious adverse health effects. None of the PAC-injected rats exhibited loss of appetite (i.e., rat chow was consumed), piloerection, porphyrin staining, or alopecia, and weight loss was negligible. After the first cycle of injections, rats lost 1% of body weight, irrespective of drug assignment. The addition of restricted sleep did not enhance weight reduction. From the second cycle through the end of the protocol, rats steadily gained weight and there were no significant differences in weight gain by drug or sleep assignment. Rats continued to groom and were social and explorative/inquisitive with handling.

Resilience Against PAC-Induced Mechanical Sensitivity

Not all PAC-injected rats developed mechanical sensitivity. Indeed, 4 of the 21 (18%, $n = 2$ female) PAC-SL rats exhibited 50% PWT throughout the protocol that remained at baseline level; all of the PAC-SR rats developed mechanical hypersensitivity.

Discussion

This rodent study is the first to our knowledge that employed chronic sleep restriction in conjunction with a PAC protocol to model the human condition of sleep-onset insomnia and adjuvant chemotherapy in order to determine the effects of chronic partial sleep loss on chemotherapy-induced mechanical sensitivity. Although others have reported the adverse effects of sleep loss on sensitivity to noxious stimuli (Onen et al., 2001; Roehrs et al., 2006; M.T. Smith et al., 2007), this study is the first to show that partial sleep loss in control conditions induces mechanical hypersensitivity that is comparable to that caused by PAC. Our findings are important additions to the body of knowledge concerning the impact of

sleep loss on symptoms (mechanical hypersensitivity) associated with PAC chemotherapy. Our results suggest that (1) there may be an accumulative effect of sleep loss on PAC-induced mechanical hypersensitivity, (2) recovery sleep opportunities may not be sufficient to overcome the adverse effects of sleep loss on PAC-induced mechanical hypersensitivity, and (3) undisturbed sleep opportunities throughout the PAC protocol may provide a buffer against the progression of mechanical hypersensitivity apparent during accumulative dosing.

We did not, in this study, conduct morphological examination nor did we determine potential mechanisms by which interactions between sleep loss and PAC manifest as increased and sustained mechanical hypersensitivity. One plausible mechanism by which restricted sleep induces mechanical hypersensitivity may be sleep loss-induced reductions in growth hormone (GH) secretion. GH is an important anabolic hormone that is critical for growth and maintaining health of tissues and internal organs. Bertani and colleagues (2010) mapped out the GH secretory pattern in Sprague-Dawley rats, showing GH increases during the last 2 hr of the dark period and peaks about 2 hr after lights on. This light-phase GH secretory pattern follows the pattern of percentage of time that Sprague-Dawley rats spend in slow wave sleep (SWS; Opp, 1998). Humans exhibit similar GH peaks, such that they are closely aligned with SWS (Van Cauter, Plat, & Copinschi, 1998). In this study, we deprived rats of sleep during the first 6 hr of the light period, after which rats underwent testing for mechanical sensitivity. Given that the lights-on phase of the photoperiod is when GH levels rise, peak, and are sustained, the design of our protocol may have prevented the rise and more sustained high levels of GH. Whether our significant reduction in 50% PWT in the PAC-SR rats, compared to the PAC-SL rats, was due to the sleep loss, per se, or due to a cascade of events that our sleep restriction protocol initiated, our data demonstrate that the chronic partial sleep loss paradigm exerted detrimental effects on 50% PWT among PAC- and VEH-injected rats. However, those detrimental effects on 50% PWT were sustained only among the PAC-injected rats. Recovery sleep was sufficient for VEH-SR rats to fully recover to baseline 50% PWT, whereas the adverse effects of sleep loss on 50% PWT among PAC-injected rats were enduring, despite the 7-day recovery sleep periods.

During the 42-day protocol, the control rats demonstrated minor reductions in 50% PWT. All rats were habituated to the testing room and underwent baseline VFH testing over a number of days. Other researchers who have employed repeated VFH testing during the light phase of the photoperiod have shown similar levels of increased mechanical sensitivity in Sprague-Dawley rats assigned to sham condition (Loram et al., 2012).

Of the 21 rats in the PAC-SL group, 4 (18%; $n = 2$ female) did not exhibit 50% PWT less than their baseline 50% PWT at any point during the protocol. Clinically, not all patients who undergo PAC therapy experience neuropathy. A review of prior work has shown that the incidence of Grade 2/4 neuropathy in patients undergoing PAC is 27% (Carlson & Ocean, 2011). Authier, Gillet, Fialip, Eschalier, and Coudore (2000) employed a high-dose PAC protocol in male Sprague-Dawley rats that resulted in mechanical sensitivity in only 14% of the rats ($n = 2$). Another important consideration is our per-injection dosing strategy. We used 1 mg/kg per dose rather than the 2 mg/kg per dose that some have used because we hypothesized that sleep restriction would exacerbate PAC-induced mechanical hypersensitivity. As such, we selected the PAC dose that would not induce a maximum

response in and of itself, so that the combined impact of sleep loss and PAC could be revealed. Indeed, all of the PAC-SR rats exhibited a mean 50% PWT <3 g at the testing sessions that immediately followed each cycle of PAC (after accumulative doses of 4 mg/kg, 8 mg/kg, and 12 mg/kg), whereas the PAC-SL opportunities exhibited mean 50% PWT in the 5–6 g range at the same time points. The Bennett lab operationalizes mechanoallodynia as a positive response to the 4-g VFH filament and mechanohyperalgesia as a positive response to the 15-g VFH filament (Flatters & Bennett, 2004, 2006; Siau, Xiao, & Bennett, 2006). Our findings suggest that sleep loss during PAC therapy may serve as a priming factor to facilitate emergence of mechanoallodynia.

Clinically, cancer patients report sleep disturbance throughout treatment (Kozachik & Bandeen-Roche, 2008; Palesh et al., 2010; Savard et al., 2011; Savard & Morin, 2001; Sharma et al., 2012), often with co-occurring pain complaints (Coleman et al., 2011; Kozachik & Bandeen-Roche, 2008; Sharma et al., 2012; Stepanski et al., 2009). While investigators have reported a bidirectional association between pain and poor sleep (Lautenbacher et al., 2006; Onen et al., 2001; Roehrs & Roth, 2005; Roehrs et al., 2006), the extent to which poor sleep during adjuvant therapy for cancer contributes to the overall symptom experience is not entirely clear. Persons with cancer undergoing adjuvant therapy who complain of pain, insomnia, or both report higher numbers of other symptoms than those who do not complain of pain or poor sleep (Kozachik & Bandeen-Roche, 2008). Nurses in the oncology setting are perfectly positioned to assess for sleep disturbances relative to chemotherapy receipt and educate the patient and family on a variety of sleep hygiene interventions to facilitate sleep.

Although complaints of poor sleep during adjuvant PAC therapy are neither dose limiting nor dose delaying, the results of our study suggest that sleep loss may contribute to and exacerbate PAC-induced neuropathic pain. Neuropathy and neuropathic pain are dose-limiting side effects of not only PAC but also a number of other chemotherapeutic agents, such as epothilones, vinca alkaloids, and platinum-containing compounds (Argyriou, Marmiroli, Cavaletti, & Kalofonos, 2011; Cavaletti & Marmiroli, 2004). Our findings suggest that insomnia may be a potential therapeutic target for symptom (pain) management during adjuvant therapy, particularly for patients undergoing PAC therapy. Future intervention studies designed to target co-occurring pain and sleep disturbance are warranted.

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Figure 2.

Immediate, accumulative effects of sleep restriction concurrent with paclitaxel versus unperturbed sleep on Log_{10} (50% paw withdrawal threshold) of rats. Error bars represent $\pm$ SEM. Paclitaxel/restricted Sleep: $n = 15$; paclitaxel/sleep: $n = 21$; vehicle/restricted sleep: $n = 7$; vehicle/sleep: $n = 19$.

Note. BL = baseline; SEM = standard error of the mean.

Figure 3.

Sustained effects of sleep restriction versus unperturbed sleep on Log₁₀ (50% paw withdrawal threshold) of rats. Error bars represent ±SEM. Paclitaxel/restricted sleep: $n = 15$; paclitaxel/sleep: $n = 21$; vehicle/restricted sleep: $n = 7$; vehicle/sleep: $n = 19$.

Note. SEM = standard error of the mean.