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Experimental Studies of Potential Analgesics for the Treatment of Chemotherapy-Evoked Painful Peripheral Neuropathies

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ABSTRACT

Objective. We investigated potential analgesics for chemotherapy-evoked neuropathic pain using rats treated with paclitaxel.

Design. Drugs were tested in a repeated dosing paradigm (four daily injections). Topiramate was tested with a long-term treatment paradigm (12 days). A literature search was performed to summarize prior data.

Measures. Mechanical stimulation of the hind paw was used to assay antiallodynic and antihyperalgesic effects acutely and 24 hours after injection.

Results. Amitriptyline produced significant analgesia, but this was not apparent until after the second injection. Baclofen produced significant effects, but the response varied erratically. Mexiletine and NMED-126 (a mixed N- and T-type calcium channel blocker) produced consistent, significant analgesia when tested acutely, but the pain relief did not persist at 24 hours postinjection. Oxcarbazepine had no effect at any time. Tramadol produced consistent, near-complete analgesia when tested acutely, but the analgesia did not persist to 24 hours postinjection. Topiramate produced significant effects that were first evident after 6–8 days of dosing.

Conclusions. The present data and data from the literature review suggest that there are several potential treatments for chemotherapy-evoked neuropathic pain. Nonsteriodal anti-inflammatory drugs have little or no efficacy. Opioids have an effect, but probably only with high doses. At least some antidepressants are analgesic in these conditions. Some, but clearly not all, anticonvulsants and sodium channel blockers have efficacy. Tramadol is a particularly promising candidate. Topiramate, acetyl-L-carnitine, carbamazepine, and venlafaxine may have protective or restorative effects. Clinical trials of these candidates are needed to advance the treatment of chemotherapy-evoked pain.

Key Words. Allodynia; Amitriptyline; Baclofen; Calcium Channels; Chemotherapy; Hyperalgesia; Mexiletine; Oxcarbazepine; Neuropathic Pain; Paclitaxel; Topiramate; Tramadol

Introduction

Peripheral neuropathy is the dose-limiting side effect of chemotherapeutics in the taxane, vinca alkaloid, and platinum-complex classes. The neuropathy is sometimes accompanied by a chronic neuropathic pain syndrome. There are no epidemiological data concerning the percentage of patients who develop chemotherapy-evoked pain, but several reports indicate that it may affect 25–50% of patients, especially those whose cancers require high-dose therapy. Chemotherapy-evoked pain may resolve within weeks or months of drug termination, or it may last for years. Chemotherapy-evoked neuropathic pain is a leading cause of discontinuation of otherwise successful therapy, it restricts therapy to doses that are suboptimal for

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killing tumor cells, and it has a significant impact on the patients' quality of life (for reviews, see [1–3]).

Clinical experience suggests that some patients with chemotherapy-evoked pain obtain relief with tricyclic antidepressants (TCAs) and gabapentin [2,4–6]. However, to our knowledge there are only two preliminary reports of controlled clinical trials of analgesics specifically for the treatment of chemotherapy-evoked painful peripheral neuropathy [7,8].

Investigating potential analgesics for chemotherapy-evoked neuropathic pain is particularly difficult because cancer patients may have both inflammatory and neuropathic pain, and the latter may arise from multiple causes (chemotherapy, tumor effects, radiotherapy, surgical trauma, etc.). Animal models present a simpler situation. Animal models of posttraumatic painful peripheral neuropathy have an excellent record of predicting analgesic efficacy in patients with diabetic and postherpetic neuropathic pain [9], but it is unclear whether these data are relevant to the question of efficacy against chemotherapy-evoked neuropathic pain. For example, there is massive axonal degeneration in the models of posttraumatic painful peripheral neuropathy, while animals with paclitaxel-evoked neuropathic pain have no axonal degeneration at the level of the peripheral nerve (however, they do have a partial degeneration of the sensory axons' terminal arbors in the skin) [10,11]. Paclitaxel-treated rats have pronounced mechano-allodynia, cold-allodynia, and mechano-hyperalgesia, but little or no heat-hyperalgesia [12]; the nerve-trauma models produce the same symptoms, but also produce pronounced heat-hyperalgesia. Different mechanisms suggest the possibility of different pharmacological response profiles, and there is experimental evidence that this may indeed be true. For example, N-methyl-D-aspartate receptor blockers are effective in nerve-trauma models, but not effective for paclitaxel-evoked neuropathic pain [13].

Here we use a rat model of paclitaxel-evoked painful peripheral neuropathy [12] to investigate potential analgesics that might be of use clinically. Using animals with established paclitaxel-evoked mechano-allodynia and mechano-hyperalgesia, we examined the effects of amitriptyline, baclofen, mexiletine, oxcarbazepine, and tramadol. There is experimental and clinical evidence that ziconotide, an N-type calcium channel blocker, is effective for at least some kinds of neuropathic pain [14–16]. However, ziconotide is a polypeptide that must be administered intrathecally. Here we chose to examine NMED-126, a nonprotein orally available prototype of a new class of drugs that show state-dependent block of N-type calcium channels and additional block of T-type calcium channels [17]. State-dependent block may improve the side-effect profile of drugs acting on the N-type channel, and we have shown that ethosuximide, an antiepileptic drug that blocks T-type channels, produces excellent analgesia in paclitaxel-treated rats [13]. Repeated dosing is sometimes necessary to detect an analgesic effect [18–20]; thus, each of the drugs was tested after four consecutive daily injections.

Lastly, we have examined the effects of chronic dosing with topiramate. There is evidence showing that topiramate promotes neurite growth *in vitro*, accelerates regeneration after nerve crush [21], and delays the onset of the pain evoked in an animal model of posttraumatic painful peripheral neuropathy when given at the time of nerve injury and daily thereafter [22,23]. We examined the effects of topiramate given twice daily for 12 consecutive days.

We compare our results with a literature review of the experimental data on potential analgesics for the treatment of chemotherapy-evoked painful peripheral neuropathies.

Methods

These experiments conformed to the ethics guidelines of the International Association for the Study of Pain [24], the National Institutes of Health (USA), and the Canadian Institutes of Health Research. All experimental protocols were approved by the Facility Animal Care Committee of the Faculty of Medicine, McGill University in accordance with the regulations of the Canadian Council on Animal Care.

Animals

Adult male Sprague-Dawley rats (Harlan Inc.; Indianapolis, IN; Frederick, Maryland breeding colony; 300–350 g at the time of drug testing) were housed on sawdust bedding in plastic cages. Artificial lighting was provided on a fixed 12-hour light–dark cycle; food and water were available *ad libitum*.

Paclitaxel-Evoked Painful Peripheral Neuropathy

Paclitaxel (Taxol®, Bristol-Myers-Squibb, Canada, Montreal, Quebec; 6 mg/mL) was diluted with saline to a concentration of 2 mg/mL and injected

IP (2 mg/kg) on four alternate days (D0–D6). Post-paclitaxel tests with 4- and 15-g von Frey hairs were performed to confirm the presence of mechano-allodynia and mechano-hyperalgesia, respectively. Paclitaxel-evoked pain is first detectable on approximately D15 (i.e., about 1 week after the last dose of paclitaxel) and reaches peak severity on D20–D25 [12,13,25,26]. At the time of peak pain severity, animals were divided into groups with mechano-hypersensitivity of approximately equal severity and then randomly assigned to receive drug or vehicle. All subsequent tests were conducted by an observer blind as to group assignment.

Behavioral Testing

Animals were habituated to the behavioral testing environment, and baseline measurements of mechanical sensitivity were taken prior to paclitaxel administration. The animals were placed on an elevated wire mesh floor while confined beneath overturned mouse cages made of clear plastic. von Frey filaments with bending forces of 4 and 15 g were applied to the mid-plantar skin (avoiding the base of the tori) of each hind paw five times, with each application held for 5 seconds. Withdrawal responses to the von Frey filaments from both hind paws were counted and then expressed as an overall percentage response. Normal rats hardly ever withdraw from the 4-g stimulus; the increased level of responding seen after paclitaxel is thus indicative of mechano-allodynia. Normal animals withdraw from the 15-g stimulus 10–20% of the time, indicating that this is a barely painful stimulus. The increased level of responding seen after paclitaxel is thus indicative of mechano-hyperalgesia.

Drugs and Testing Protocol

In each case, the dose that was examined was equal to the largest dose that has been shown to be effective in at least one other neuropathic pain model. Doses and routes of administration are given below; all injection volumes were 1.0 mL/kg: Amitriptyline: 30 mg/kg, IP, N = 10/group [27–30]; Baclofen: 3 mg/kg, IP, N = 10/group [31, 32]; Mexiletine: 30 mg/kg, IP, N = 10/group [33–35]; Oxcarbazepine: 100 mg/kg, PO, N = 8/group [36,37]; Tramadol: 20 mg/kg, IP, N = 10/group [38,39]; and NMED-126: 30 mg/kg, PO, N = 10/group [17]. Topiramate was given twice daily at 20 mg/kg, PO per injection; N = 12/group [21,22]. Vehicle control injections were an equal volume of saline for all except NMED-126 (propylene glycol).

Amitriptyline, baclofen, mexiletine, NMED-126, oxcarbazepine, and tramadol were administered daily for four consecutive days. Animals were tested 0.5 or 1.0 hour postinjection (based on their apparent time of peak analgesic activity when tested in other animal models of neuropathic pain) and then 24 hours postinjection, just prior to the next day's injection. Thus, the first test after the first injection determined whether there was an acute analgesic response, and the 24-hour test determined whether there was a persistent (or delayed) analgesic response. Topiramate was given twice daily at 0900 hours and 1700 hours for 12 consecutive days. Behavioral effects were tested at 1200 hours on the 2nd, 4th, 6th, 8th, 10th, and 12th dosing days, and 2, 5, 8, and 12 days after the last dose.

Statistics

Effects on mechano-allodynia and mechano-hyperalgesia were assessed with repeated-measures ANOVA, followed by post hoc pair-wise comparisons with the control group with Bonferroni-corrected unpaired *t*-tests. Where significant differences were found between drug- and vehicle-treated groups, % antiallodynia (or percentage anti-hyperalgesia) scores were computed as follows: % antiallodynia/antihyperalgesia = [(vehicle group score) – (drug group score)] ÷ [(vehicle group score) – (naïve baseline score)] × 100.

Results

Amitriptyline

There was no indication of an antiallodynic or antihyperalgesic effect at 1.0 hour or 24 hours after the first injection of amitriptyline, and no effects were seen 1.0 hour after the second injection (Figure 1A). However, statistically significant reductions of 43–70% for both mechano-allodynia and mechano-hyperalgesia were noted 24 hours after the second injection. Similar reductions were seen at the 1.0- and 24-hour test points after the third and fourth injections. The effects seen after the third and fourth injections might have been due to acute analgesic effects or to a persistent (or permanent) analgesic response that was first noted at 24 hours after the second injection. To examine this question, we added an additional test 48 hours after the fourth injection. No analgesia was present at this time, suggesting that amitriptyline does not produce a permanent reversal of the pain syndrome.

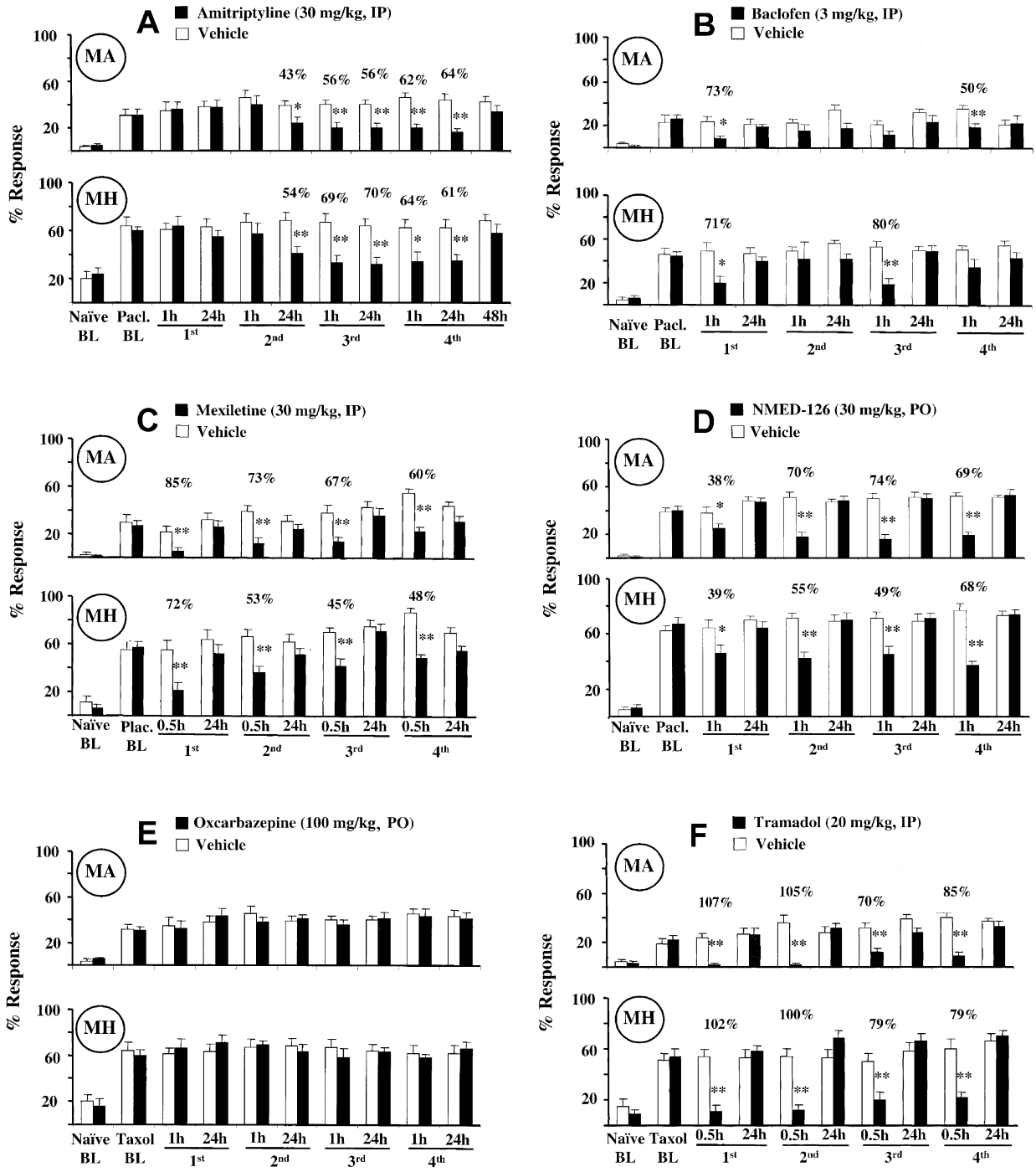

Figure 1 Effects of (A) amitriptyline, (B) baclofen, (C) mexiletine, (D) NMED-126, (E) oxcarbazepine, and (F) tramodol on paclitaxel-evoked mechano-allodynia (MA) and mechano-hyperalgesia (MH) 1 (or 0.5) and 24 hours after the 1st–4th daily injections. Percent maximum possible effect scores are noted for significant reductions. Naïve baseline (BL): response frequency prior to paclitaxel; paclitaxel baseline (Pacli. BL): elevated response frequency seen after paclitaxel treatment on the day prior to the first injection. $^{*}P < 0.05$; $^{**}P < 0.01$ relative to vehicle-injected group.

Baclofen

Inconsistent results were obtained with baclofen (Figure 1B). Significant reductions (71–73%) in mechano-allodynia and mechano-hyperalgesia were found 1.0 hour after the first injection, but no effects were found after the second injection. The third injection significantly reduced mech-

ano-hyperalgesia but had no effect on mechano-allodynia, while the fourth injection suppressed mechano-allodynia but had no effect on mechano-hyperalgesia. None of the significant effects persisted 24 hours postinjection.

Mexiletine

Significant reductions of 72–85% in mechano-allodynia and mechano-hyperalgesia were found 0.5 hours after the first injection, but the effects were no longer evident at 24 hours (Figure 1C). Significant reductions were found 0.5 hours after the second, third, and fourth injections; none of these effects persisted at 24 hours postinjection.

NMED-126

Significant reductions (38–39%) in mechano-allodynia and mechano-hyperalgesia were found 1.0 hour after the first injection, but the effects were no longer evident at 24 hours (Figure 1D). Significant and more pronounced (49–74%) reductions were found 1.0 hour after the second, third, and fourth injections; none of these effects persisted at 24 hours postinjection.

Oxcarbazepine

No effects on mechano-allodynia or mechano-hyperalgesia were found at any time after any of the injections (Figure 1E).

Tramadol

Mechano-allodynia and mechano-hyperalgesia were completely suppressed at 1.0 hour after the first injection of tramadol, but the effects did not persist to 24 hours postinjection (Figure 1F). Near-complete suppression of mechano-allodynia and mechano-hyperalgesia was also noted 1.0 hour after the second, third, and fourth injections, none of which persisted at 24 hours.

Topiramate

Dosing began on D14 (8 days after the last injection of paclitaxel) when mechano-allodynia and mechano-hyperalgesia were present. As expected, in the vehicle-treated animals significant mechano-allodynia and mechano-hyperalgesia continued to increase over the following 12 days (Figure 2). We did not detect any topiramate effect during the first 4 days of dosing, but significant antiallodynic effects were seen on the sixth day, and significant antiallodynic and antihyperalgesic effects (36–75%) were seen from the 8th to the 12th days (Figure 2). Pain suppression continued for at least the first 5 days after discontinuing topiramate, but mechano-allodynia and mechano-hyperalgesia returned by the eighth day after discontinuation.

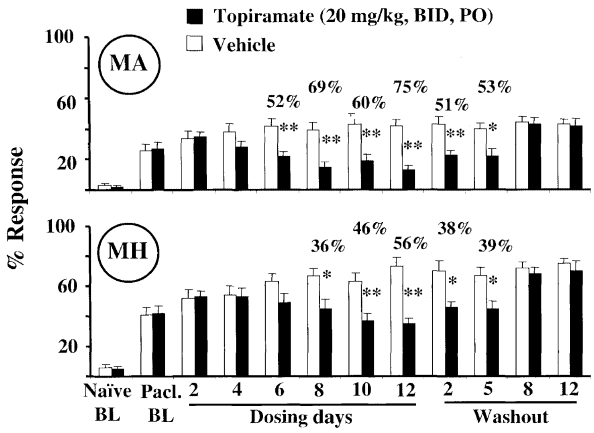

Figure 2 Effects of long-term treatment with topiramate (twice daily for 12 consecutive days) on paclitaxel-evoked mechano-allodynia (MA) and mechano-hyperalgesia (MH). When injections and behavioral tests were performed on the same day, the tests were conducted 3 hours after the first of that day's two injections. Percent maximum possible effect scores are noted for significant reductions. Naïve baseline (BL): response frequency prior to paclitaxel; paclitaxel baseline (Pacli. BL): elevated response frequency seen after paclitaxel treatment on the day prior to the first injection. Washout: Responses recorded after discontinuing topiramate injections. $^{*}P < 0.05$; $^{**}P < 0.01$ relative to vehicle-injected group.

Discussion

Our results add to a growing body of evidence from animal models on potential analgesic drugs for the treatment of chemotherapy-evoked neuropathic pain (Table 1).

Effects with Repeated Dosing

Potential analgesics are often tested for efficacy with a single administration, even in conditions of relatively long-standing pain. However, there is precedence for analgesic effects that are not detectable unless repeated doses are used [18–20]. Our results clearly demonstrate the advantages of a repeated dosing paradigm. For example, the effects of NMED-126 were modest after the first dose, but subsequent doses were highly effective (Figure 1D). It is particularly noteworthy that we would have missed amitriptyline's effect if we had examined the results of only a single administration. Unambiguous antiallodynia and antihyperalgesia were apparent only after 2–3 days of dosing (Figure 1A). Moreover, the first injection of

Table 1 Evidence from animal models for potential analgesics for chemotherapy-evoked painful peripheral neuropathy

Drug	Chemotherapy Model	Symptoms	Effect	Dose & Route	Reference
Antidepressants					
Amitriptyline	Paclitaxel	MA, MH	+ (repeated dosing)	30 mg/kg, IP	*Loc cit.*
Desipramine	Vincristine	MA	No effect (single dose)	10–100 μmol/kg, IP (2.7–27 mg/kg)	[43]
Venlafaxine	Vincristine	MA	+	10 & 40 mg/kg, SC	[45]
Tramadol	Paclitaxel	MA, MH	+	20 mg/kg, IP	*Loc cit.*
Antiepileptics					
Carbamazepine	Vincristine	MA	+	3000 μmol/kg, PO (709 mg/kg)	[43]
Ethosuximide	Paclitaxel	MA, MH, CA	+	100 & 450 mg/kg, IP	[13]
	Vincristine	MA, MH	+	300 mg/kg, IP	[13]
Gabapentin	Paclitaxel	MA, MH	+	100 mg/kg, IP	[20]
	Vincristine	MA, MH	+	100 mg/kg, IP	[20]
	Paclitaxel	MA	+	250–500 μmol/kg, PO (43–86 mg/kg)	[43]
	Paclitaxel (mouse)	MA, HH	+	30 mg/kg, IP	[63]
Lamotrigine	Vincristine	MA	+	150 μmol/kg, PO (38 mg/kg)	[43]
Oxcarbazepine	Paclitaxel	MA, MH	No effect	100 mg/kg, PO	*Loc cit.*
Pregabalin	Vincristine	MA	+	80 mg/kg, IP	[34]
Topiramate	Paclitaxel	MA, MH	+ (neuroprotective?)	20 mg/kg, PO, bid × 12	*Loc cit.*
Sodium channel blockers					
Lidocaine	Vincristine	MA	+	45 mg/kg, IP	[34]
Mexiletine	Paclitaxel	MA, MH	+	30 mg/kg, IP	*Loc cit.*
	Vincristine	MA	+	30 mg/kg, IP	[34]
Tetrodotoxin	Vincristine	MA	No effect	8 μg/kg, IP	[34]
NSAIDs					
Acetaminophen	Vincristine	MA	+ (high dose)	600–1200 μmol/kg, PO (91–182 mg/kg)	[43]
Aspirin	Vincristine	MA	No effect	30–300 μmol/kg, PO (5.4–54 mg/kg)	[43]
Celecoxib	Vincristine	MA	No effect	25–250 μmol/kg, IP (10–100 mg/kg)	[43]
Ibuprofen	Vincristine	MA	No effect	100–1000 μmol/kg, PO (20–200 mg/kg)	[43]
Ibuprofen	Vincristine	MA, HH	+ (prophylactic paradigm)	50 mg/kg, IP, daily × 13	[73]
Rofecoxib	Vincristine	MA, HH	+ (prophylactic paradigm)	10 mg/kg, IP, daily × 13	[73]
Glutamate receptor blockers					
Dextromethorphan	Vincristine	MA	+	80–300 μmol/kg, PO (22–81 mg/kg)	[43]
MK-801	Paclitaxel	MA, MH	No effect	0.2 mg/kg, IP	[13]
MPEP	Vincristine	MA	+	30 mg/kg, IP	[76]
Opioids					
Morphine	Paclitaxel	MA, MH	+/– (high dose)	8 mg/kg, IP	[13]
	Vincristine	MA	+/– (high dose)	0.8–3.0 μmol/kg, IP (0.2–0.9 mg/kg)	[43]
	Vincristine	MA	+/– (high dose)	5 mg/kg, IP	[34]
Miscellaneous					
ABT-594	Vincristine	MA	+	0.03–0.3 μmol/kg, IP (6–60 μg/kg)	[77]
Acetyl-L-carnitine	Paclitaxel	MA, MH	+ (treatment paradigm)	100 mg/kg, PO	[25]
	Paclitaxel	MA, MH	+ (prophylactic paradigm)	50 & 100 mg/kg, PO daily × 21	[25]
	Paclitaxel	MH	+ (treatment & prophylactic paradigms)	100 mg/kg, SC daily	[75]

Table 1 Continued

Drug	Chemotherapy Model	Symptoms	Effect	Dose & Route	Reference
	Vincristine	MH	+ (treatment & prophylactic paradigms)	100 mg/kg, SC daily	[75]
	Cisplatin	MH	+ (treatment & prophylactic paradigms)	100 mg/kg, SC daily	[75]
	Oxaliplatin	MH	+ (treatment & prophylactic paradigms)	100 mg/kg, SC daily	[74]
Baclofen	Paclitaxel	MA, MH	+/– (inconsistant effect)	3 mg/kg, IP	*Loc cit.*
Clonidine	Vincristine	MA	+	0.4–1.5 μmol/kg, IP (84–345 μg/kg)	[43]
NMED-126	Paclitaxel	MA, MH	+	30 mg/kg, PO	*Loc cit.*
Thalidomide	Vincristine	MA, HH	+ (prophylactic paradigm)	50 mg/kg, PO, daily × 13	[73]

Loc cit.: data from current report. MK-801: an N-methyl-D-aspartate receptor blocker. MPEP: a metabotropic glutamate receptor type-5 blocker. NMED-126: a mixed N- and T-type calcium channel blocker. ABT-594: an epibatidine derivative and α4β2 nicotinic acetylcholine receptor blocker. Treatment paradigm: drug given to animals with established chemotherapy-evoked pain. Prophylactic paradigm: drug given during period of chemotherapy administration. All studies used rat models except where noted.
CA = cold-allodynia; HH = heat-hyperalgesia; MA = mechano-allodynia; MH = mechano-hyperalgesia; NSAID = nonsteriodal anti-inflammatory drug.

baclofen appeared to indicate excellent analgesic potential, but subsequent doses revealed an inconsistent pattern of responding (Figure 1B).

A delay in the onset of analgesia has been noted by others with different drugs and different neuropathic pain models. The analgesic effects of TCAs (amitriptyline, desipramine, and clomipramine) and baclofen following repeated dosing were superior to the efficacy of a single dose in a model of painful peripheral neuropathy due to nerve trauma [27,32]. There is conflicting evidence as to whether TCAs are effective in animal models of posttraumatic and diabetic painful peripheral neuropathies [30,31,40,41]. All of these studies examined the effects of a single dose; perhaps more consistent results would be obtained if repeated doses were used. We have seen a clear delay in the onset of analgesia using gabapentin in both paclitaxel- and vincristine-treated rats [20]. Patel et al. [42] noted a pronounced delay for gabapentin in a model of posttraumatic painful peripheral neuropathy, and Hao et al. [19] noted a pronounced delay for gabapentin in rats with neuropathic pain due to spinal cord injury. Similarly, the analgesic effects of topiramate in chronic constriction injury (CCI) rats are unambiguous only after repeated dosing [18].

Analgesic effects with a delayed onset may be of importance when animal models are used to screen large numbers of novel compounds. Preclinical screening is expensive, and having to examine each test compound with a repeated dosing paradigm may be impractical. But failure to do so may miss drugs with promising activity.

Amitriptyline and Other Antidepressants

We found that amitriptyline produced partial, but statistically significant, antiallodynic and antihyperalgesic effects, although these were apparent only after repeated dosing. Clinical practice suggests that TCAs relieve chemotherapy-evoked neuropathic pain [2,4], and our animal data support this conclusion. Lynch et al. [43] saw no antiallodynic effects with a single injection of desipramine in rats with vincristine-evoked neuropathic pain. TCA analgesia may be specific to only some kinds of neuropathic pain symptoms [44]. For example, in rats with streptozocin-evoked painful diabetic peripheral neuropathy [28], amitriptyline reduced static mechano-allodynia (produced by von Frey hair stimulation), but had no effect on dynamic mechano-allodynia (produced by stroking the skin with a cotton swab).

Venlafaxine is not a tricyclic molecule but, like the TCAs, it is believed to act via inhibition of the reuptake of serotonin and norepinephrine. In animals with vincristine-evoked neuropathic pain, Marchand et al. [45] observed decreased mechano-allodynia with a single dose of venlafaxine. There is a case report of a patient with paclitaxel-evoked neuropathy who experienced marked improvement in sensory symptoms with venlafaxine [46]. Oxaliplatin infusion commonly evokes an acute onset syndrome of pain and paraesthesiae that relents in several hours; a chronic neuropathic pain syndrome is seen more rarely. Pre-administration of venlafaxine, but not carbamazepine, prevents the acute syndrome [47,48], and a pre-

liminary study suggests that venlafaxine may also be effective in the treatment of the chronic syndrome [49].

The ability of TCAs to relieve neuropathic pain is generally believed to be due to their blockade of serotonin and norepinephrine reuptake, with the latter of perhaps greater importance. This mechanism of action may account for the analgesic effect shown here. However, it is now clear that amitriptyline and other TCAs (but not all) also produce a significant block of voltage-gated sodium channels, and that this mechanism may contribute to their effects against neuropathic pain (reviewed in [50]). As discussed below, sodium channel blockers do have analgesic efficacy against paclitaxel-evoked neuropathic pain; thus this mechanism may also be relevant to the amitriptyline effect shown here. In addition, there are data suggesting that the effects of some TCAs against neuropathic pain may involve a peripheral site of action via adenosine receptors [51].

Baclofen and GABAergic Drugs

We found that baclofen, a gamma amino butyric acid type-B (GABA-B) receptor agonist, had significant antiallodynic and antihyperalgesic effects (Figure 1B). However, the day-to-day variability of baclofen's effect was greater than what we saw with any of the other drugs. We found no evidence of increased efficacy with repeated dosing, in contrast to what Idanpaan-Heikkila and Guilbaud [32] reported in rats with neuropathic pain due to an injured trigeminal nerve. The dose that we tested (3 mg/kg, IP) is approximately the highest that can be used without producing potentially confounding motor impairment.

Pain transmission in the spinal cord dorsal horn is modulated by local-circuit inhibitory interneurons that use GABA as their neurotransmitter. Two types of GABA receptors are present. GABA-A receptors have a binding site for benzodiazepine anxiolytics; these drugs have no known effect on neuropathic pain. Baclofen is an agonist at the GABA-B receptor, and several reports suggest that it has analgesic activity in the normal animal and augmented analgesic activity following traumatic nerve injury [30–32,42,52]. Baclofen may also produce an analgesic effect via GABA receptors in the brain [53].

Mexiletine and Other Sodium Channel Blockers

We found that mexiletine produced partial, but statistically significant, decreases in mechano-allodynia and mechano-hyperalgesia (Figure 1C). Systemic administration of mexiletine and lidocaine, but not tetrodotoxin, has been shown to relieve mechano-allodynia in rats with vincristine-evoked neuropathic pain [34].

The efficacy of sodium channel blockers to inhibit neuropathic pain in animal models of post-traumatic peripheral neuropathy is generally thought to be at least partly due to their effect on ectopic spontaneous discharge in injured nociceptors [54]. The ectopic spontaneous discharge seen after nerve injury is generated from the proximal end of the severed axon and also from the dorsal root ganglion cell bodies of neurons with axonal damage; the ectopic discharge from both of these locations is blocked by low levels of lidocaine [54]. We have demonstrated abnormal spontaneous discharge in Aδ- and C-fibers in rats with paclitaxel- and vincristine-evoked neuropathic pain [55], and we have shown that these rats have a partial degeneration of their intraepidermal sensory terminal arbors [11]. It is thus possible that the analgesic effect seen here was due to suppression of spontaneous discharge in nociceptors with degenerating terminal arbors. There is also evidence for a site of action for sodium channel blockers in the spinal cord dorsal horn [56].

Traumatic nerve injury evokes dramatic changes in the expression of the various types of voltage-gated sodium channels in primary afferent neurons (reviewed in [50]), but it is not known whether this happens in the chemotherapy models. Joshi et al. [57] have shown that blocking voltage-gated sodium channels of the $Na_v1.8$ subtype with the antisense method reduces mechano-allodynia in CCI rats, but has no effect on the mechano-allodynia of vincristine-treated rats.

NMED-126 and Other Calcium Channel Blockers

We found modest (38–39%), but statistically significant, suppression of mechano-allodynia and mechano-hyperalgesia after the first injection of NMED-126 (Figure 1D). The three subsequent injections yielded distinctly larger analgesic responses (49–74%).

NMED-126 is known to block N-type voltage-gated calcium channels, and recent data suggest that it also has clinically significant actions at T-type channels [17]. Actions at both N- and T-type channels may contribute to the effect shown here. The N-type blocker, ziconotide, is effective when given intrathecally in animal models of posttraumatic painful peripheral neuropathy [14,15]. It is also effective in patients with cancer pain [58], although it is unclear whether the patients in this

study had pain due to chemotherapy. We have previously shown that ethosuximide, a first-generation antiepileptic drug with significant activity at T-type channels, blocks mechano-allodynia, mechano-hyperalgesia, and cold-allodynia in the paclitaxel and vincristine models [13]. There is additional evidence that T-type channel blockers may be useful analgesics for neuropathic pain (e.g., [59,60]).

Gabapentin and pregabalin may work via binding to calcium channels that contain the alpha-2-delta type-1 subunit (for reviews, see [61,62]). Gabapentin is analgesic in paclitaxel-treated and vincristine-treated rats [20,43] and paclitaxel-treated mice [63]. Encouraging results have been obtained in open-label trials of gabapentin as an opioid adjunct in cancer patients with neuropathic pain, but it is unclear whether the responders in these studies had pain due to chemotherapy [5,6]. A preliminary report of a double-blind, randomized, placebo-controlled trial of gabapentin in cancer patients with chemotherapy-evoked pain found no evidence for an analgesic effect [7].

Oxcarbazepine, Carbamazepine, and Other Antiepileptics

We saw no sign of activity with oxcarbazepine at 100 mg/kg, PO (Figure 1E). This is a surprising result in that oxcarbazepine's mechanism of action is believed to be largely due to block of voltage-gated sodium channels [64], and we and others have found that sodium channel blockers are effective against chemotherapy-evoked pain (see above). Oxcarbazepine's parent compound, carbamazepine, relieves mechano-allodynia in vincristine-treated rats [43]. Inconsistent results with oxcarbazepine have been found in animal models of posttraumatic painful peripheral neuropathy in the rat: Jang et al. [37] found an analgesic effect, while Fox et al. [36] did not (however, they did find efficacy for both oxcarbazepine and carbamazepine when guinea pigs were used). Oxcarbazepine suppresses mechano-allodynia and heat-hyperalgesia in diabetic rats [65]. Lamotrigine, another anticonvulsant whose mechanism of action is believed to be at least partly via block of sodium channels, blocks mechano-allodynia in vincristine-treated rats [43]. However, a preliminary analysis of a controlled trial in patients with chemotherapy-evoked neuropathic pain suggests that lamotrigine is without clinical benefit [8]. There is evidence [66] that prophylactic treatment with carbamazepine prevents oxaliplatin-evoked peripheral neuropathy (and thus would presumably block the development of neuropathic pain as well). The mechanism of action for such an effect is unknown.

Tramadol

We found near-total suppression of mechano-allodynia and mechano-hyperalgesia with tramadol (Figure 1F). Tramadol is believed to have two clinically significant mechanisms of action: a TCA-like blockade of serotonin and norepinephrine reuptake, and an agonist effect at mu-opioid receptors. There is evidence for an additional mechanism via nitric oxide that is specific for neuropathic pain [67,68]. It is unclear whether tramadol's opioid effect contributes to the effect reported here. We have found that paclitaxel-evoked pain is only partly blocked by high doses of morphine [13] and the same has been found for vincristine-evoked pain [34,43]. The analgesic response to tramadol is enhanced on the side ipsilateral to a traumatic nerve injury, and the enhanced effect is only partially reversed by naloxone [38]. It is possible that tramadol's mechanisms of action are synergistic, particularly in the case of its analgesic effect against neuropathic pain.

Topiramate

There are reasons to believe that topiramate might be useful for the treatment of neuropathic pain via two different mechanisms—a direct analgesic effect and an indirect analgesic effect via an action that prevents or promotes recovery from injury to sensory axons. For example, Shadiack et al. [18] have shown that a single injection of topiramate to an animal with established posttraumatic painful peripheral neuropathy (CCI) has a modest analgesic effect, and excellent analgesia is seen after 2 or 3 days of repeated dosing [18]. These effects are not likely to be due to a neuroprotective mechanism, because 2 days is far too short a time for significant regeneration after trauma to the sciatic nerve at mid-thigh level. When administered prophylactically (i.e., at the time of nerve trauma and daily thereafter), topiramate delays the onset of pain and reduces its severity [22,23,69]. These effects may be due to a neuroprotective mechanism, or to the delayed onset of a direct analgesic action.

We gave topiramate for 12 consecutive days to animals with established paclitaxel-evoked pain. We did not see an acute analgesic effect (Figure 2). Antiallodynic efficacy did not appear until the sixth day of dosing, and antihyperalgesic efficacy did not appear until the eighth day. With

the paclitaxel model used here, there is no axonal degeneration at the level of the peripheral nerve, but there is degeneration of the sensory axon's intraepidermal terminal arbor [10,11]. The degeneration does not appear to progress to the level of the nerve fascicles that lie just below the epidermis (unpublished observations), and this means that the degeneration extends for a distance of only about 0.1 mm. This is in marked contrast to the nerve-trauma models, where the degeneration of peripheral nerve axons extends for tens of millimeters. It is thus possible that the 6–8 days of delay in the appearance of analgesia in our experiment represents a neuroprotective action that allows recovery from paclitaxel-evoked degeneration of the sensory terminal arbors. The delayed return of pain after discontinuing topiramate may be due to the withdrawal of a neuroprotective effect, or to a pharmacodynamic mechanism. There is evidence that topiramate speeds recovery after nerve trauma and promotes the growth of axons [21]. Moreover, topiramate improves impaired mitochondrial function [70], and it has been hypothesized that the fundamental pathological mechanism in paclitaxel-evoked peripheral neuropathy is a toxic effect on axonal mitochondria [10].

Clinical trials suggest that topiramate may be analgesic for some neuropathic pain syndromes [71], but controlled trials conducted in patients with painful diabetic neuropathy have failed to show efficacy [72]. It may be that topiramate's analgesic effect will be prominent only in those conditions where its protective and restorative actions can come into play, and thus little effect would be expected in diabetic patients whose pain is associated with advanced nerve damage. There is preliminary clinical evidence suggesting that topiramate may be effective in the treatment of oxaliplatin-evoked pain [49].

Conclusions

Table 1 summarizes our findings and the results of the 12 other animal studies that have been published on potential analgesics for the treatment of chemotherapy-evoked painful peripheral neuropathy. Most of the work has been conducted with models of paclitaxel- and vincristine-evoked pain, while oxaliplatin and cisplatin have received little study. The clinical symptoms of chemotherapy-evoked pain have not been studied in great detail, but they appear to be similar in patients receiving taxane, vinca alkaloid, and platinum-complex agents. However, the cause(s) of the pain produced by these agents is unknown, and it is premature to assume that they will all respond to the same analgesics.

Treatment with nonsteriodal anti-inflammatory drugs (except for high doses of acetaminophen) does not have efficacy. However, there is evidence that prophylactic dosing (i.e., coadministration with the chemotherapeutic) with the anti-inflammatory agents, ibuprofen and rofecoxib, or thalidomide (an inhibitor of tumor necrosis factor-alpha release), prevents the development of vincristine-evoked mechano-allodynia [73]. The mechanism for such a protective effect is not known. High doses of morphine produce only partial relief when given to established chemotherapy-evoked pain. There is clear evidence that TCAs might be of clinical benefit. Tramadol appears to be a particularly promising choice, although it is unclear whether its opioid actions contribute to its efficacy. Some, but clearly not all, antiepileptics may have clinical benefit. Ethosuximide and gabapentin are promising examples [13,20]. At least some sodium channel blockers also seem to have activity (e.g., mexiletine), although the usual narrow therapeutic window of these compounds would be expected clinically. Topiramate, acetyl-L-carnitine, venlafaxine, carbamazepine, and anti-inflammatory agents have potential as drugs that might both treat and prevent chemotherapy-evoked pain [25,46,47,66, 73–75]. Several classes of drugs that are under development may be useful in the treatment of chemotherapy-evoked pain. For example, drugs that act on both N- and T-type calcium channels (e.g., NMED-126) appear to be promising candidates for future development.

In the absence of controlled clinical trials, physicians have little to guide them in their attempts to relieve chemotherapy-evoked pain. Accumulating evidence from animal studies indicates that these are potentially treatable conditions, and that it might even be possible to prevent them. One can hope that the laboratory results described here will soon be evaluated in the clinic.

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