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# ABT-594 (a nicotinic acetylcholine agonist): anti-allodynia in a rat chemotherapy-induced pain model

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**Abstract**

ABT-594 ((*R*)-5-(2-azetidinylmethoxy)-2-chloropyridine) represents a novel class of broad-spectrum analgesics whose primary mechanism of action is activation of the neuronal nicotinic acetylcholine receptors. The present study characterized the effects of ABT-594 in a rat chemotherapy-induced neuropathic pain model, where it attenuated mechanical allodynia with an $ED_{50}$=40 nmol/kg (i.p.). This anti-allodynic effect was not blocked by systemic (i.p.) pretreatment with naloxone but was blocked completely with mecamylamine. Pretreatment with chlorisondamine (0.2–5 μmol/kg, i.p.) only partially blocked the effects of ABT-594 at the higher doses tested. In contrast, central (i.c.v.) pretreatment with chlorisondamine completely blocked ABT-594's anti-allodynic effect. Taken together, the data demonstrate that ABT-594 has a potent anti-allodynic effect in the rat vincristine model and that, in addition to its strong central site of action, ABT-594's effects are partially mediated by peripheral nicotinic acetylcholine receptors in this animal model of chemotherapy-induced neuropathic pain.


*Keywords:* Nicotinic acetylcholine receptor; Cancer pain; Neuropathic pain; Allodynia; Analgesia; Vincristine

## 1. Introduction

Improvements in the efficacy of cancer chemotherapeutics have resulted in a double-edged sword for cancer patients. As such formerly terminal illnesses have been attenuated to more chronic disease states, long-term pain has become an even more pressing issue for cancer survivors (Stute et al., 2003; Uhm and Yung, 1999). Despite the fact that approximately one-third to one-half of all patients receiving anticancer treatment suffer from pain, and greater than two-thirds in the more advanced disease states (Portenoy and Lesage, 1999), the World Health Organization's website for cancer pain relief currently lists only aspirin, paracetamol (acetaminophen) and opioids as recommended treatments (www.who.int/cancer/palliative/painladder/en/).

For the treatment of iatrogenic (i.e., chemotherapy-induced) neuropathic pain specifically, tricyclic antidepressants and anticonvulsants are suggested as the first line of defense (Uhm and Yung, 1999). Nevertheless, pain relief from tricyclic antidepressants is often insufficient in many patients, and these drugs have significant liabilities, including sedation and cardiovascular issues (Hempenstall and Rice, 2002; Uhm and Yung, 1999; Wolfe and Barohn, 2002). The anticonvulsant, gabapentin has been shown to be analgesic in a small, clinical trial of chemotherapy-induced neuropathic pain patients (Bosnjak et al., 2002). However, the drop out rate was high, in part due to the somnolence and dizziness often associated with gabapentin, and the mean pain attenuation was only approximately 50% in those patients remaining in the study. Opioids, in particular morphine, are often prescribed for cancer pain (Portenoy and Lesage, 1999), however, their adverse effects of respiratory depression, constipation, nausea and vomiting, combined with their potential for dependence and tolerance, make them less than ideal medications (Schug et al., 1992;

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Winkelmuller and Winkelmuller, 1996). Clearly the need exists for new pharmacotherapeutics for chemotherapy-induced neuropathic pain, either as stand-alone drugs or as supplements to already existing medications.

Neuronal nicotinic acetylcholine receptor agonists are a group of compounds that have recently been determined to be analgesic across a broad-spectrum of preclinical pain models. In the early 1990s, epibatidine was isolated from the *Epipedobates tricolor* and was shown to be analgesic in the rodent tail-flick and hot plate assays of acute thermal pain (Qian et al., 1993; Spande et al., 1992). Several years later, it was determined that nicotinic acetylcholine receptor agonists with higher affinity for the α4β2 nicotinic acetylcholine receptor subunit (the predominant subtype in the central nervous system) relative to the α1β1δγ nicotinic acetylcholine receptor subunit (located at the neuromuscular junction) had analgesic efficacy with a larger therapeutic window from severe side effects than did epibatidine (Bannon et al., 1998b; Barlocco et al., 1998; Kesingland et al., 2000). However, not all groups are in agreement that the therapeutic window has been significantly improved (Boyce et al., 2000). α4β2-selective nicotinic acetylcholine receptor agonists have also been shown to be analgesic in at least three different preclinical models of neuropathic pain: spinal nerve ligation, partial sciatic nerve ligation and streptozotocin-induced diabetes (Bannon et al., 1998b,c; Kesingland et al., 2000). Utilizing systemic (i.p.) versus central (i.c.v.) dosing routes of administration with chlorisondamine (a nicotinic receptor antagonist that does not readily cross the blood–brain barrier), A-85380 (3-[2(s)-azetidinylmethoxy] pyridine; a α4β2 nicotinic acetylcholine receptor agonist) was determined to exert its anti-allodynic effects at both peripheral and central nervous system sites, respectively, in the rat spinal nerve ligation model (Rueter et al., 2003).

In the current study, the α4β2 nicotinic acetylcholine receptor agonist, ABT-594 ((*R*)-5-(2-azetidinylmethoxy)-2-chloropyridine) was tested in a rat model of chemotherapy-induced neuropathic pain to determine its anti-allodynic potential against this type of iatrogenic pain and to ascertain whether its site of action was in the peripheral and/or central nervous system.

## 2. Materials and methods

### 2.1. Animals, compounds, vehicles and dosing

Studies were carried out in accordance with the European Community guidelines for the use of experimental animals, and they were reviewed and approved by the Institutional Animal Care and Use Committee of Abbott Laboratories. Male Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA) of 250–350-g body weight were utilized for all studies. Mecamylamine hydrochloride and naloxone hydrochloride dihydrate were obtained from Sigma-Aldrich (St. Louis, MO), and chlorisondamine diiodide from Tocris Cookson Inc. (Ellisville, MO). ABT-594 *p*-toluenesulfonic acid salt was synthesized at Abbott Laboratories. All compound solutions were freshly made on the day of use and dissolved in 0.9% saline (%w/v). I.p. dosing volume was 1 ml/kg, while that for i.c.v. administration was 5 μl (infused via syringe pump over a period of 1 min). Except for the time course study (Fig. 1), pretreatment times were 15 min pre-testing for ABT-594. The antagonists were administered 15 min (5 μmol/kg mecamylamine and 25 μmol/kg naloxone, i.p.), 30 min (0.2–5 μmol/kg chlorisondamine, i.p.), or 24 h (16 nmol chlorisondamine, i.c.v.) prior to ABT-594 injection (Rueter et al., 2003).

### 2.2. Mini-osmotic pump implantation and intracerebroventricular (i.c.v.) cannulation

For experiments not involving i.c.v. administration, rats were anesthetized with halothane (5% to induce, 2–3% to maintain), and their right external jugular vein was catheterized (PE60 tubing) with a vincristine-filled mini-osmotic pump (0.5 μl/h, 14 days; Alzet Model 2002, Durect, Cupertino, CA) that had been primed overnight to deliver 30 $\mu g\ kg^{-1}\ day^{-1}$ vincristine sulfate (Sigma-Aldrich; St. Louis, MO) according to the procedure of Nozaki-Taguchi et al. (2001).

For experiments involving i.c.v. administration, simultaneous vincristine mini-osmotic pump implantation and i.c.v. cannulation were performed under sodium pentobarbital anesthesia (approximately 60 mg/kg Nembutal, i.p.) for the duration of both procedures. The rats were first implanted with the vincristine-primed mini-osmotic pumps according to the procedure above, and then i.c.v. cannulation was performed. For the i.c.v. surgery, a 22 gauge guide cannula (Plastics One, Roanoke, VA) was cut to a length of 5.0 mm below the pedestal, and this cannula was inserted into the

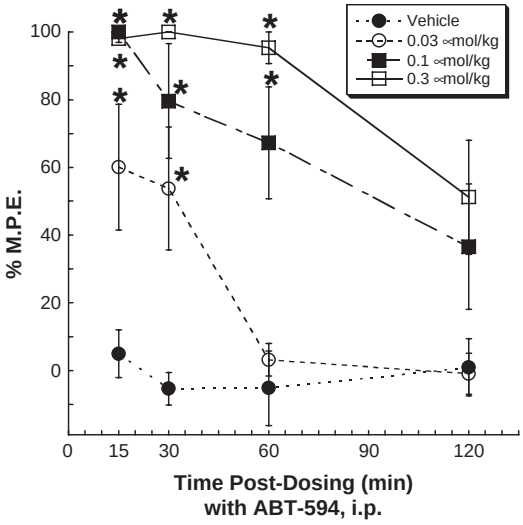


Fig. 1. Time- and dose-response anti-allodynic effects of ABT-594, i.p. Mean±S.E.M.; $n$=6. *$P$<0.05 versus time-matched vehicle control.

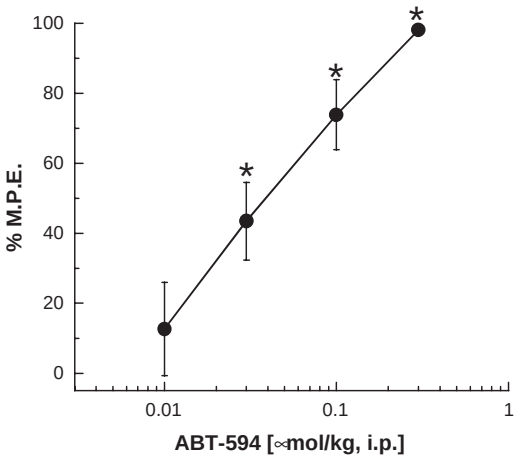


Fig. 2. Dose-response anti-allodynic effect of ABT-594 (15 min pretreatment, i.p.). Mean±S.E.M.; $n$=6–12. *$P$<0.05 versus vehicle control.

brain using the stereotaxic coordinates of 1.0 mm posterior, 1.6 mm lateral and 4.5 mm ventral from bregma. Three skull screws were attached for stability, and the implant was covered with cranioplastic acrylic. Once the acrylic had dried, a stainless steel stylet was inserted into the guide cannula and kept in place until the time of i.c.v. dosing, at which time it was replaced with a 28 gauge internal cannula that extended approximately 1.0 mm beyond the length of the guide cannula.

### 2.3. Mechanical allodynia testing

Mechanical allodynia thresholds were assessed by placing the animals onto an elevated aluminum screen with a 1.27×1.27 $cm^2$ grid to provide access to the ventral side of the hind paws. An inverted, clear plastic cage (29×18×12 $cm^3$, l×w×h) was placed over each rat, and the animals were allowed to acclimate to the test environment for 20 min prior to baseline testing. Paw withdrawal thresholds were determined in both hind paws of each animal using calibrated von Frey monofilaments (Stoelting, Wood Dale, IL) according to an up–down procedure (Chaplan et al., 1994), and the results were reported as the mean value of these two readings. For each compound tested, a percent maximal protective effect (%M.P.E.) was calculated according to the formula: ([post-drug threshold−baseline threshold]/[maximum threshold−baseline threshold])×100%, where the maximum threshold was equal to 15 g.

Compounds were tested in rats 1–3 weeks post-implantation of the vincristine-primed, mini-osmotic pumps: a time period in which mechanical allodynia is most severe and relatively stable (Lynch et al., 2004). Only rats with baseline paw withdrawal thresholds ≤6 g force were utilized. For each experiment, each rat was treated with only one dosing condition ($n$=5–18 rats/group), and a minimum of 4 days was allowed as a washout period between subsequent experiments with a different compound.

### 2.4. $ED_{50}$ determinations and statistical analysis

$ED_{50}$ values were estimated using linear regression via Prism software (v 3.02; GraphPad Software, San Diego, CA). Data were analyzed by the Wilcoxon's signed rank test for paired comparisons, and by the Friedman test (followed by Dunn's multiple comparisons test) for repeated measures (GraphPad).

## 3. Results

Previous studies have shown that rats continuously infused with low concentrations of vincristine, i.v., develop persistent mechanical allodynia as compared to vehicle-infused rats (Lynch et al., 2004; Nozaki-Taguchi et al., 2001). In the current study, vincristine-infused rats that were determined as having mechanical allodynia were dosed with 0.03, 0.1 and 0.3 μmol/kg ABT-594 (i.p.), and the time course of anti-allodynic effects was followed (Fig. 1). Significant anti-allodynia was found at 15, 30 and 60 min post-dosing, and a trend toward attenuation was still present at 2 h for the two highest doses ($P$=0.08). Because anti-allodynia was maximal at 15 min pretreatment, this time point was utilized for all subsequent studies. When the dose range of 0.01–0.3 μmol/kg of ABT-594 was tested, an $ED_{50}$ value of 40 nmol/kg was determined, with the reduction of mechanical allodynia nearly 100% at 0.3 μmol/kg (Fig. 2).

Mechanistic studies were then performed using 0.3 μmol/kg ABT-594 to determine its pharmacological mechanism and sites of action in this model. Fifteen minute pretreatment (i.e., 15 min prior to ABT-594 injection) with a high dose of the opioid receptor antagonist naloxone (25 μmol/kg, or 10 mg/kg, i.p.) had no effect on reducing

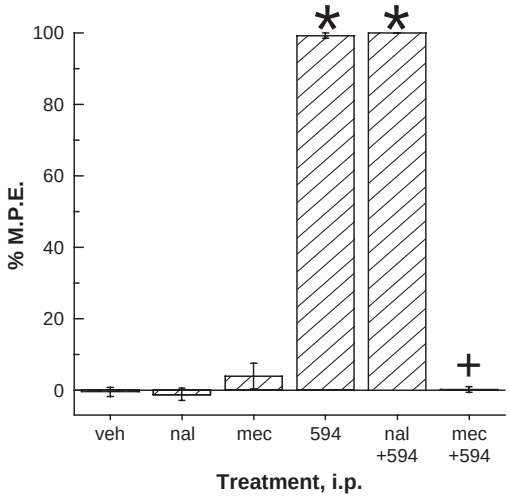


Fig. 3. The anti-allodynic effect of ABT-594 (0.3 μmol/kg, i.p.; 15 min pretesting) is blocked by pretreatment with mecamylamine (5 μmol/kg, i.p.; 15 min pre-ABT-594), but not naloxone (25 μmol/kg, i.p.; 15 min pre-ABT-594). Mean±S.E.M.; $n$=6–18. *$P$<0.05 versus vehicle control. +$P$<0.05 versus ABT-594.

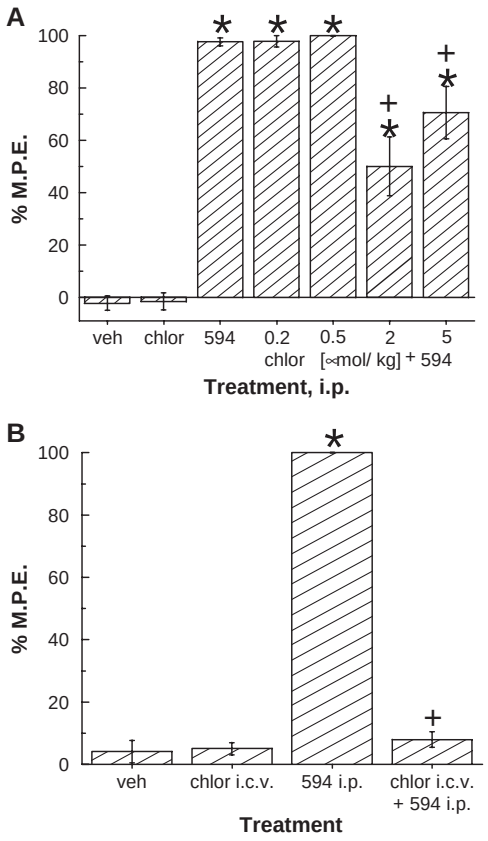


Fig. 4. The anti-allodynic effect of ABT-594 (0.3 μmol/kg, i.p.; 15 min pre-testing) is (A) only partially blocked by pretreatment with higher doses of chlorisondamine (i.p.; 30 min pre-ABT-594), but (B) completely blocked by pretreatment with chlorisondamine, i.c.v. (16 nmol; 24 h pre-ABT-594). Mean±S.E.M.; $n$=5–11. *$p$<0.05 versus vehicle control. +$P$<0.05 versus ABT-594.

ABT-594-mediated anti-allodynia (Fig. 3). In contrast, the non-selective nicotinic acetylcholine receptor antagonist, mecamylamine (15 min pretreatment with 5 μmol/kg, i.p.) completely abolished the anti-allodynic effect of ABT-594 (Fig. 3). Chlorisondamine (30 min pretreatment with 0.2–5 μmol/kg, i.p.), a non-selective nicotinic acetylcholine receptor antagonist that does not readily cross the blood–brain barrier (Clarke et al., 1994), only partially attenuated the anti-allodynic effect of ABT-594 at high doses (Fig. 4A). In contrast, when chlorisondamine was administered centrally (24 h pretreatment with 16 nmol, i.c.v.), a complete blockade of ABT-594 occurred (Fig. 4B).

## 4. Discussion

Neuronal nicotinic acetylcholine receptor agonists represent one of the few novel approaches to pain management since the discovery of Tramadol (Ultram®). In preclinical models, α4β2 nicotinic acetylcholine receptor agonists (such as ABT-594) have been shown to be broad-spectrum analgesics, with effects in the formalin test of persistent chemical pain, complete Freund adjuvant model of mechanical hyperalgesia, and hot box, hot plate and tail-flick models of acute thermal pain (Bannon et al., 1998a; Bardin et al., 2003; Curzon et al., 1998; Decker et al., 1988; Kesingland et al., 2000). In animal models of neuropathic pain, ABT-594 has been shown to reduce mechanical hyperalgesia in diabetic rats at a dose of 300 nmol/kg, and mechanical allodynia in spinal nerve ligation rats at 100 nmol/kg ($ED_{50}$ value of approximately 150 nmol/kg), i.p. (Bannon et al., 1998b,c). In the rat partial sciatic nerve ligation model of neuropathic pain, a calculated $ED_{50}$ value of 27 μg/kg (i.e., approximately 70 nmol/kg), s.c., was determined for the reversal of mechanical hyperalgesia (Kesingland et al., 2000). In the current, chemotherapy-induced neuropathic pain rat model, the $ED_{50}$ value for ABT-594 was calculated to be 40 nmol/kg, i.p., for mechanical allodynia. In contrast, the first identifiable side effects of ABT-594 have been reported to be reduced activity and/or ptosis at approximately 0.02 mg/kg (approximately 50 nmol/kg), s.c. (Boyce et al., 2000). Preconvulsive activity was reported at doses approximately 10-fold higher (Boyce et al., 2000).

The anti-allodynic effect of ABT-594 in the rat chemotherapy-induced neuropathic pain model was found to be completely blocked by i.c.v. administration of chlorisondamine (a quaternary compound that does not readily cross the blood–brain barrier), but only partially blocked by i.p. administration of chlorisondamine, suggesting that modulation of descending inhibition plays a crucial role in the ability of nicotinic acetylcholine receptor agonists to attenuate mechanical allodynia during vincristine-induced peripheral neuropathy. Higher doses of systemically administered chlorisondamine were not tested as 10 mg/kg (approximately 16 μmol/kg) has previously been demonstrated to result in complete central nicotinic blockade, albeit by 24 h post-dosing, the earliest time point tested (Clarke et al., 1994).

In contrast to the effects of chlorisondamine in the current study in vincristine-infused rats, in the rat spinal nerve ligation model of neuropathic pain, both central (16 nmol, i.c.v.) and systemic (0.4 μmol/kg, i.p.) administration of chlorisondamine have been reported to completely block a comparable degree of anti-allodynia (similarly assessed utilizing von Frey monofilaments) produced by another nicotinic acetylcholine receptor agonist, A-85380 (Rueter et al., 2003). The peripheral nervous system site of action of A-85380 in the latter model has recently been traced to level of the dorsal root ganglion, where direct infusion at the level of L5 resulted in attenuation of mechanical allodynia in spinal nerve ligation rats (Rueter et al., 2003). A similar dose of systemically administered chlorisondamine (0.5 μmol/kg, i.p.) did not attenuate the anti-allodynic effects of A-85380 in the rat vincristine model (unpublished observations).

The apparent difference found, in the peripheral nervous system site of action of nicotinic acetylcholine receptor agonists between the vincristine and spinal nerve ligation

models, does not appear to be due to a difference in the relative binding affinities of the nicotinic acetylcholine receptor agonists tested because the $K_i$ values for ABT-594 and A-85380 are equal ($K_i$=0.4–0.5 nM for α4β2; inhibition of [$^3$H](−)-cystine binding in rat brain) (Donnelly-Roberts et al., 1998; Sullivan et al., 1996). Thus, while A-853830 and ABT-594 have equal rat $K_i$ values and produced comparable degrees of attenuation of mechanical allodynia in the rat spinal nerve ligation and vincristine studies, respectively, an intraperitoneal doses of 0.4 μmol/kg chlorisondamine completely blocked the effect of the agonist in the former study, but doses of chlorisondamine up to approximately 10-fold higher could only partially block the effect of the agonist in the latter assay.

The mechanism behind the stronger peripheral site of action of nicotinic acetylcholine receptor agonists in spinal nerve ligation rats compared to in vincristine-infused rats was not determined in the current study. However, the following hypothesis is presented. It has been demonstrated that nicotinic acetylcholine receptors are expressed within the dorsal root ganglion, where functional, multiple nicotinic acetylcholine receptor subtypes have been reported (Boyd et al., 1991; Genzen et al., 2001). However, the prevalence of α4β2-like responses (i.e., those of the nicotinic acetylcholine receptor subtype where ABT-594 is a potent agonist) is normally very low: it has been found in only 2% (6/266) of dorsal root ganglion neurons in naïve rats (Genzen et al., 2001). We speculate that, after nerve damage and for reasons unknown, an up-regulation of nicotinic acetylcholine receptors (in particular, those with the α4β2 subunit) may be occurring in the dorsal root ganglions of spinal nerve ligation rats, but not (or to a lesser extent) in vincristine-infused rats. Indeed, within the spinal cord itself, differential expression of nicotinic subunits has been found between neuropathic pain models in that α4 and β2 were unchanged after spinal nerve ligation, but β2 was up-regulated (α4 was not examined) after sciatic nerve transection (Vincler and Eisenach, 2004; Yang et al., 2004). In the dorsal root ganglions of spinal nerve ligation and vincristine-infused rats, differential up-regulation has already been demonstrated with calcium channel α2δ-1 subunit protein levels, which were increased in spinal nerve ligation, but not vincristine-infused rats (Luo et al., 2002). This group also reported the interesting positive correlation that gabapentin (i.p.) was anti-allodynic in the spinal nerve ligation, but not vincristine-infused rats (Luo et al., 2002). Future research may examine changes in dorsal root ganglion nicotinic acetylcholine receptor α4β2 subunit expression and functionality across various preclinical neuropathic pain models, including the rat chemotherapy-induced model utilized in the current study, and their relationship to the peripheral effects of nicotinic acetylcholine receptor agonists.

In summary, the α4β2 nicotinic acetylcholine receptor agonist, ABT-594 was found to attenuate mechanical allodynia in a continuous infusion, rat vincristine model of chemotherapy-induced neuropathic pain, with an $ED_{50}$ value (40 nmol/kg, i.p.) that was slightly less than doses previously reported to produce any side effects (Boyce et al., 2000). The anti-allodynic effect of ABT-594 was not opioid-related, and its nicotinic acetylcholine receptor-related mechanism of action was determined to be mainly at the level of the central nervous system, but with a smaller, peripherally related component. The latter finding was in contrast to the robust central and peripheral effects of nicotinic acetylcholine receptor agonists that have previously been reported in the rat spinal nerve ligation model, thus suggesting differences between these two neuropathic pain models, at least in terms of the peripheral sites of action of nicotinic acetylcholine receptor agonists during attenuation of mechanical allodynia.

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