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Anti-allodynic actions of intravenous opioids in the nerve injured rat: potential utility of heroin and dihydroetorphine against neuropathic pain

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Abstract

Neuropathic pain has been suggested to be resistant to treatment with opiates. Such perceived lack of opioid responsiveness may be due to the dose-range over which specific opioid compounds have been studied as well as the efficacy of these compounds. Dihydroetorphine is a novel opiate that demonstrates significantly greater analgesic potency compared to morphine, and which also demonstrates diminished capacity for producing physical dependence in laboratory animals. The present study compared the intravenous (i.v.) efficacy, potency and duration of action of dihydroetorphine, fentanyl, heroin and morphine in producing anti-allodynic actions in a rat model of neuropathic pain (ligation of the L5/L6 nerve roots). All compounds produced significant anti-allodynic activity with dihydroetorphine being the most potent (A_{50} of 0.2 μg kg^{-1}, i.v.). Morphine was approximately 7440 times less potent than dihydroetorphine while heroin and fentanyl were approximately 163.5 and 6.9 times less potent in producing anti-allodynic actions. Dihydroetorphine also showed a maximal effect at 0.6 μg kg^{-1} in all animals tested, while 100 μg kg^{-1} was required for heroin to produce a maximal effect. Fentanyl and morphine did not elicit a maximum anti-allodynic response (74 and 76%maximum possible effect (%MPE), respectively). As expected, fentanyl showed a relatively brief duration of action (approximately 20 min at the highest tested dose), while dihydroetorphine and morphine demonstrated anti-allodynic actions for up to 45 min. Heroin had the longest duration of action, producing significant anti-allodynic effects for up to 90 min. These data show that dihydroetorphine and heroin produce potent and long-lasting anti-allodynic actions in this model. Additionally, in contrast to morphine and fentanyl, both dihydroetorphine and heroin were able to achieve a maximal response. The remarkable potency, maximal efficacy and duration of action of these compounds, particularly dihydroetorphine, suggests that these compounds may warrant further examination as potential therapeutic treatments for neuropathic pain states.

Keywords: Neuropathic pain; Allodynia; Opioid; Efficacy

1. Introduction

Abnormal pain states which occur as a result of peripheral nerve damage due to either injury or disease are commonly referred to as neuropathic pains. These pain states are typified by an increased sensitivity to painful stimuli (hyperalgesia) and by the perception of normally innocuous stimuli as painful (allodynia). Opioid analgesics have been suggested to be somewhat limited in treating such pain (Arner and Meyerson, 1988), however some investigators have suggested that this may be due to administration of inadequate doses (Portenoy and Foley, 1986; Portenoy et al., 1990; Jadad et al., 1992). A number of animal models have been developed for studying the mechanisms of neuropathic pain and two such models using rats have received considerable attention. These models involve either loosely ligating the sciatic nerve (Bennett and Xie, 1988) or tightly ligating spinal nerves L5 and L6 prior to their joining with L4 to form the sciatic nerve (Kim and Chung, 1992). The latter model results in the development of allodynia to mechanical and thermal stimuli that are not aversive in normal animals with the sparing of motor function in the hindlimb. Opioid alkaloids, such as morphine, are somewhat effective when administered parenterally or supraspinally in this paradigm (Bian et al., 1995), but are essentially ineffective when administered spinally (Xu et al., 1993, Nichols et al., 1995,

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Yaksh et al., 1995). On the other hand, the opioid peptide [D-Ala^2, *N*-Me-Phe^4,Gly-ol^5]enkephalin (DAMGO), a high efficacy μ-opioid receptor agonist, produces significant anti-allodynic actions when administered spinally in this model (Nichols et al., 1995). This finding suggests that classical opioid alkaloids such as morphine may be of insufficient efficacy to possess substantial anti-allodynic properties following nerve injury when given by this route.

A number of pharmacological factors influence the efficacy of drugs. The route of administration and bioavailability are relevant variables that contribute to the maximal effect that can be achieved with a given compound. Route of administration is known to affect the amount of drug that ultimately reaches the blood and hence, the brain. Clinically, opioids are often given i.v. or i.t. for severe pain (Foley, 1993). Since the normal synergistic interaction between brain and spinal opioid receptors appears to be significantly reduced following L5/L6 ligation (Bian et al., 1996), obtaining high levels in the brain is likely to be of paramount importance for the activity of opioid analgesics in this model. Morphine levels in brain rise rapidly following i.v. administration and this route has proven to be more efficient than parenteral routes in producing high morphine levels in brain (Way et al., 1960). Therefore, there may be some advantage to administering opioids intravenously for neuropathic pain.

Manipulations that render the morphine molecule more lipophilic also increase its bioavailability in the central nervous system (CNS). Of such morphine congeners, 3,6-diacetylmorphine, or heroin, is rapidly absorbed into the brain when given by a variety of routes and is rapidly converted to 6-acetylmorphine and morphine (Way et al., 1960). Higher levels of opioid can be obtained in the brain of rats upon administration of heroin compared to morphine, and at a faster rate (Way et al., 1965). Therefore, intravenous administration of heroin may result in a higher relative efficacy compared to parenteral administration of morphine and could prove to be more effective in chronic neuropathic pain models. The literature regarding the efficacy of heroin compared to morphine against various types of pain is equivocal. Generally, it has been found that heroin has no inherent advantage over morphine against postoperative pain other than an increase in potency (Sawynok, 1986). Although some studies have indicated that there may be fewer depressant effects produced by equianalgesic doses of heroin compared to morphine (Twycross, 1973), other studies have found the occurrence of adverse effects to be similar for these two compounds (Twycross, 1977; Kaiko et al., 1981). There are no reports that directly compare the efficacy and potency of heroin and morphine in neuropathic pain states either in animal models or in humans.

Fentanyl is an opioid commonly thought to have a higher relative efficacy at μ-opioid receptors than morphine (Adams et al., 1990). Fentanyl also has a faster onset of action than morphine due to its higher lipophilicity and the fact that a greater proportion of the administered dose reaches the brain compared to that of morphine (Mather, 1987). Therefore, comparison of intravenous fentanyl with morphine and heroin in the nerve-ligation model of neuropathic pain may determine if activity is limited to a greater extent by pharmacokinetic or pharmacodynamic variables, or a combination of both.

One other problem with opiates in patients with neuropathic pain is the possible development of physical dependence with chronic administration. All opiates that are full agonists will produce physical dependence with chronic administration. However dihydroetorphine, a compound that has been developed in China, has been purported to have a diminished degree of physical dependence in laboratory animals compared to morphine (Wang et al., 1995; Patrick et al., 1996; Aceto et al., 1996, 1997). Furthermore, dihydroetorphine displays significantly increased potency compared to morphine, with analgesic activity in a dose range of nanogram per kilogram (Huang and Qin, 1982). It is not known if dihydroetorphine has a higher intrinsic efficacy as well as potency compared to morphine, however. Therefore, this novel opiate may also possess pharmacological properties ideal for the treatment of neuropathic pain.

The present study utilized the L5/L6 ligation model of neuropathic pain of Kim and Chung (1992) to compare the potency, time course and relative anti-allodynic efficacy of i.v. morphine, heroin, fentanyl and dihydroetorphine. Comparison of opioid alkaloids with differing pharmacokinetic and pharmacodynamic properties may lead to identification of pharmacological features that will be advantageous for use in neuropathic pain states.

2. Methods

2.1. Animals

Male, Fischer 344 rats (200–300 g) were used for all experiments (Sasco, Lincoln, NB). Animals were housed individually in plexiglas cages with soft bedding material following implantation of intravenous catheters and nerve ligation as described below in a climate-controlled environment. Food and water were available ad libitum except during experimentation. Animals were kept on a 12 h light:dark cycle (dark 0500–1700) and all experimentation was performed during the dark phase of the cycle.

2.2. Surgical procedures

2.2.1. Implantation of jugular catheters

Animals were anesthetized with 50 mg kg^{-1} pentobarbital and 10 mg kg^{-1} atropine s.c. and chronic indwelling jugular catheters were implanted according to previously published methods (Martin et al., 1995, Weeks, 1962). Briefly, a catheter was inserted into the right exte-

rior facial vein and extended to just outside of the right auricle of the heart. The catheter continued subcutaneously from the neck to the back where it exited the animal between the scapulae. The exterior portion of the catheter was encased in a spring leash that was attached to a polyethylene plate encased in Teflon mesh and implanted subcutaneously. The catheter terminated at a fluid swivel. Following surgery animals were given 75,000 U of penicillin G procaine i.m. (Butler, Columbus, OH, USA) and all exterior wounds were dressed with antibiotic powder (Polysporin, Wellcome–Glaxo, Research Triangle Park, NC, USA). Catheter patency was maintained by hourly infusions of 0.2 ml of sterilized 0.9% (w/v) saline, pH 7.4 with 1.7 U/ml of heparin.

2.2.2. Ligation of L5 and L6 nerves

Following implantation of jugular catheters, the 5th and 6th lumbar nerves were ligated according to previously published methods (Kim and Chung, 1992). Prophylactic anesthesia was achieved by administering 10 mg kg^{-1} of methohexital (Brevital) i.v. as necessary through the jugular catheter. The 4th and 5th lumbar nerves were exteriorized following removal of the transverse process from the 5th lumbar vertebra using a small glass hook. The nerves were separated and L5 was ligated twice using 4.0 Vicryl silk suture with sufficient pressure to cause the nerve to bulge on each side of the ligature. The 6th lumbar nerve was exteriorized from underneath the iliac bone at the sciatic notch using a small glass hook and ligated similarly to the 5th lumbar nerve. All muscle layers and the skin were sutured using 4.0 chromic gut and exterior wounds were dressed with antibiotic powder (Polysporin, Wellcome–Glaxo).

2.3. Measurement of paw withdrawal threshold

Paw withdrawal threshold was determined according to previously published methods using von Frey filaments ranging in strength from 0.4 to 15.0 g (Nichols et al., 1995). At 5 to 7 days of recovery from surgery, the withdrawal threshold was determined and animals were considered to be allodynic if the withdrawal threshold was 4.0 g or less. Following the determination of the baseline withdrawal threshold (control), animals were administered drug in 0.2 ml of heparinized saline through the catheter, followed by a flush of 1.0 ml of heparinized saline. Withdrawal threshold was determined 1, 3, 5, 10, 20, 30, 45 or 60 min following drug administration. Withdrawal latencies were also determined 90 and 120 min after administration of 300 μg kg^{-1} of heroin due to the long duration of action of this dose.

2.4. Data analysis

Paw withdrawal threshold values were calculated prior to (Control Threshold) and following drug treatment (Threshold) using Dixon non-parametric statistics (Chaplan et al., 1994). For data analysis, these values were converted to percent maximum possible effect (%MPE), where:

$$\%\mathrm{MPE} = \frac{\mathrm{Threshold} - \mathrm{Control\,Threshold}}{15 - \mathrm{Control\,Threshold}} \times 100$$

The area under the curve (AUC) was calculated for each dose using the time course data and commercially available curve-fitting software (Prism2, Graph Pad, San Diego, CA, USA). Both %MPE and AUC were evaluated for dose-responsiveness using analysis of variance (ANOVA) and all doses were compared to saline or vehicle controls post hoc using the Bonferroni/Dunn method for multiple comparisons (Dunn, 1961) with commercially available software (SuperANOVA, Abacus Concepts, Berkeley, CA). The A_{50} values, standard error of the mean (S.E.M.) and 95% confidence intervals were calculated for each drug for the %MPE by fitting the data to a sigmoidal dose–response equation using commercially-available software (Prism2, Graph Pad).

2.5. Drugs and chemicals

Heroin hydrochloride, morphine sulfate, fentanyl hydrochloride and dihydroetorphine were obtained from the Drug Supply Program of the National Institute on Drug Abuse (Rockville, MD, USA). All drugs were dissolved in 0.9% (w/v) saline pH 7.4 except dihydroetorphine. Dihydroetorphine was dissolved in 10% (w/v) β-hydroxypropyl-cyclodextrin (Sigma, St. Louis, MO, USA) at 1 mg ml^{-1} and diluted to 1.5 μg ml^{-1} using 0.9% (w/v) saline pH 7.4. All subsequent dilution of dihydroetorphine were made with vehicle consisting of 0.015% (w/v) β-hydroxypropyl-cyclodextrin in 0.9% (w/v) saline pH 7.4. All drug doses are reported in terms of the free base.

3. Results

3.1. Potency and efficacy of intravenous opioids

All of the opiates used in the present study significantly elevated the paw withdrawal threshold in ligated animals, with the peak effect occurring at the earliest time point (1 min). Dihydroetorphine was the most potent compound tested with an A_{50} (S.E.M.) of 0.2 (0.031) μg kg^{-1} at 1 min following i.v. administration (Fig. 1; Table 1). Fentanyl likewise displayed potent anti-allodynic actions, however the maximum effect ($73.9 \pm 18.2\%$ MPE) was less than that of dihydroetorphine, which produced the maximal withdrawal threshold (15.0 g) in all animals tested at 1 min at a dose of 0.6 μg kg^{-1} (Figs. 1 and 2). The A_{50} of fentanyl at 1 min after infusion was 1.38 (0.31) μg kg^{-1}. Heroin was significantly more potent than morphine; the respective A_{50} values were 32.7 (3.3) and 1488

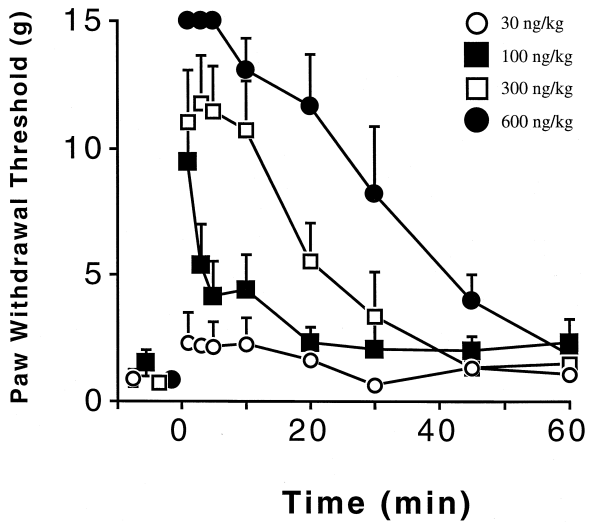

Fig. 1. Anti-allodynic effects of dihydroetorphine. Rats ($n = 8$) were administered dihydroetorphine i.v. and withdrawal thresholds were determined at the indicated times. Error bars denote S.E.M. Injection of vehicle (0.015% β-hydroxypropyl-cyclodextrin) had no significant effect at any of the time points. Control data are presented for each group at the lower left corner of the graph.

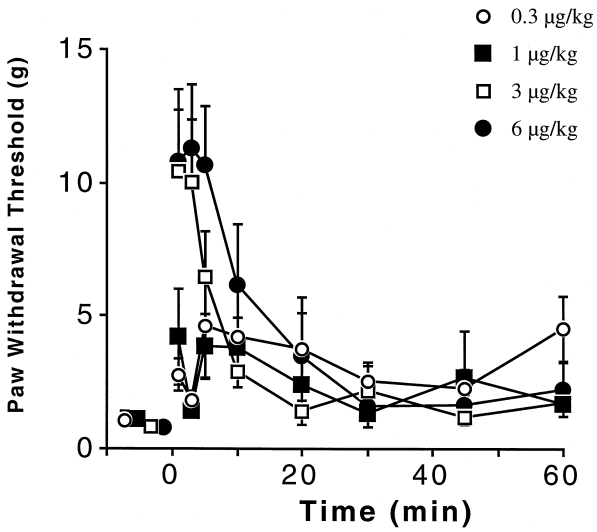

Fig. 2. Anti-allodynic effects of fentanyl. Rats ($n = 8$) were administered fentanyl i.v. and withdrawal thresholds were determined at the indicated times. Error bars denote S.E.M. Injection of vehicle (0.9% (w/v) saline pH 7.0) had no significant effect at any of the time points. Control data are presented for each group in the lower left corner of the graph.

(33) μg kg^{-1} at 1 min following administration (Figs. 3 and 4). The maximum effect that could be achieved with morphine (76 ± 12.1% MPE) was less than that of dihydroetorphine and heroin and comparable to that achieved with fentanyl. Since the maximum effect of fentanyl and morphine were less than those achieved with dihydroetorphine and heroin, the A_{50}s are not the predicted doses of these compounds that produce 50% MPE, but rather the doses that produce half of the maximum effect of each compound. The predicted doses of fentanyl and morphine that produce 50% MPE are 1.83 μg kg^{-1} and 1827 μg kg^{-1}, respectively. Therefore, the respective potency ratios of dihydoretorphine, fentanyl and heroin to morphine for producing 50% MPE 1 min after i.v. administration are 9135, 998 and 56.

Administration of 6 μg kg^{-1} of fentanyl or 3 mg kg^{-1} of morphine i.v. resulted in a sedated state characterized by the animal lying prostrate on the floor of the enclosure and was accompanied by shallow, intermittent breathing. This condition lasted for 3–5 min following fentanyl administration and for up to 30 min following injection of morphine in all animals. Application of the von Frey filaments resulted in slow withdrawal of the paw from the stimulus, compared to abrupt withdrawal and/or flinching of the paw with lower doses of fentanyl and morphine and with all doses of dihydroetorphine and heroin. Due to these side effects and the difference in response to the von Frey filament stimulus, higher doses of fentanyl and morphine were not tested.

Table 1
Comparison of potency 1 min after i.v. infusion

	A_{50} (μg/kg)	95% C.L.	Potency ratio
Dihydroetorphine	0.20	0.07–0.35	7440
Fentanyl	1.38	0.88–5.00	1078
Heroin	32.7	20.1–44.8	46
Morphine	1488	303–2500	1

A_{50} values and 95% confidence limits (95% C.L.) were determined by fitting the dose–effect data at 1 min after infusion to a sigmoidal dose–effect equation as described in Section 2.

3.2. Time-course of anti-allodynic effects of dihydroetorphine and other opioids

Of all the compounds tested, heroin displayed the longest duration of action and fentanyl the shortest. The

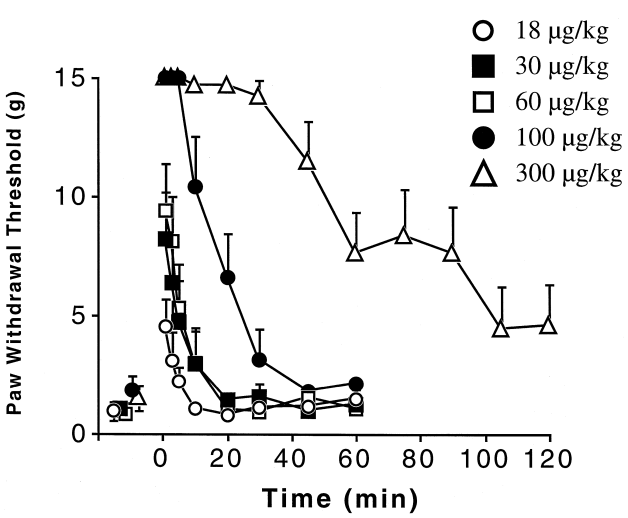

Fig. 3. Anti-allodynic effects of heroin. Rats ($n = 8$) were administered heroin i.v. and withdrawal thresholds were determined at the indicated times. Error bars denote S.E.M. Control data are presented in the lower left corner of the graph.

300 μg kg^{-1} dose of heroin produced 100% MPE for 30 min in seven of the eight animals tested and displayed significant anti-allodynic actions for up to 90 min in six animals (Fig. 3). The 100 μg kg^{-1} dose produced significant anti-allodynic effects for up to 30 min and the lower doses of heroin were effective for up to 15 min after i.v. administration. In contrast, the effects of fentanyl lasted only 20 min at even the highest dose tested and did not produce 100% MPE in any of the animals (Fig. 2). The effects of dihydroetorphine and morphine were intermediate to those of heroin and fentanyl with respect to time. The 0.6 μg kg^{-1} dose of dihydroetorphine produced 100% MPE in all animals for up to 5 min and significant anti-allodynic actions for up to 45 min, with the other doses producing anti-allodynic actions for 30 min after administration (Fig. 1). Morphine did not produce 100% MPE in any of the animals tested but did have significant anti-allodynic actions for up to 45 min following administration of 3 mg kg^{-1} (Fig. 4). Therefore differences exist with these compounds in degree of potency, maximum effect and duration of action.

3.3. Integrated effects of dihydroetorphine and other opioids with respect to time of action

Integration of the anti-allodynic effects of each dose over time provides for a direct comparison of these compounds that considers both potency, maximum effect and duration of action (Fig. 5). Heroin was the most effective of all compounds in producing significant anti-allodynic actions for a prolonged period of time, and this is evident by a greater maximum in the dose–effect curve for the area under the curve (AUC) (Fig. 5). Dihydroetorphine and morphine produced similar maximum AUC values that were significantly less than that of heroin and the maximum AUC produced by fentanyl was substantially less than all other compounds tested. Using the data presented in Fig. 5, the potency ratios for the A_{50} values of dihydroetorphine, fentanyl and heroin to morphine are 6234, 512 and 14, respectively, using AUC measures. Since the maximum AUC values have a greater discrepancy than the maximum %MPE, the potency ratios are better calculated by computing the theoretical dose that yields a given AUC for each compound. The potency ratios for dihydroetorphine and heroin to morphine for producing an AUC value of 2000% MPE · min are 7714 and 21.5, respectively. Since the maximum AUC produced by fentanyl was so much lower compared to the other compounds, a potency ratio with morphine could not be calculated for producing an AUC value of 2000% MPE · min.

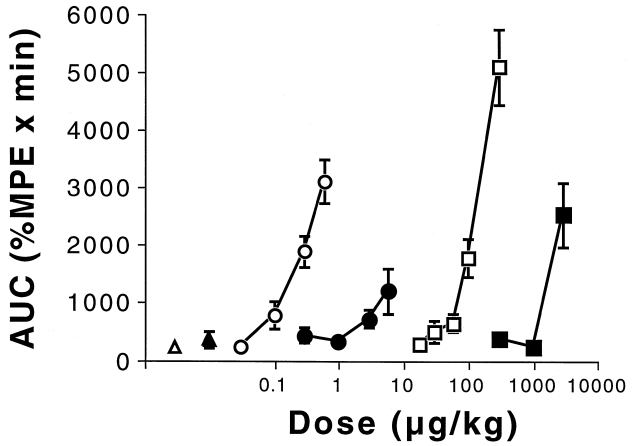

Fig. 5. Integrated anti-allodynic effects of opioids over time. Area under the curve was calculated from the time-course for 0.9% saline (△), 0.015% β-hydroxypropyl-cyclodextrin (▲), and each dose of dihydroetorphine (○), fentanyl (●), heroin (□) and morphine (■). Error bars denote S.E.M.

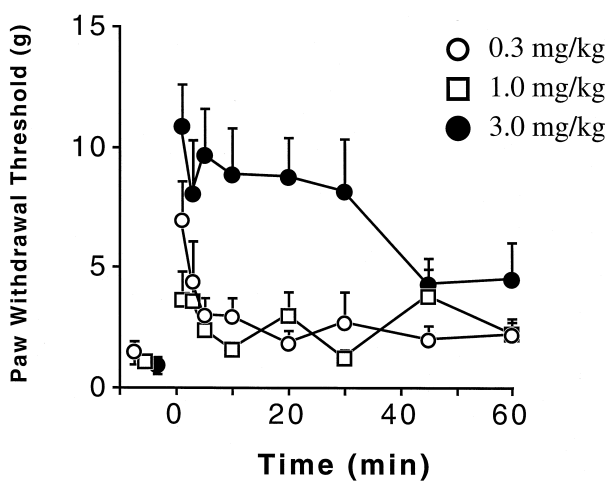

Fig. 4. Anti-allodynic effects of morphine. Rats ($n = 8$) were administered morphine i.v. and withdrawal thresholds were determined at the indicated times. Error bars denote S.E.M. Control data are presented in the lower left corner of the graft.

4. Discussion

The present data suggest that heroin and dihydroetorphine could be more useful agents for the treatment of neuropathic pain than fentanyl or morphine, at least by the intravenous route of administration. This is due to the fact that the maximum %MPE is greater with these compounds than morphine or fentanyl at doses that do not cause significant sedation and ataxia. Furthermore, the duration of action of heroin is greater than any of the other compounds. The reported diminished physical dependence liability of dihydroetorphine compared to other opioids may render this compound a useful agent for further investigation against chronic pain states (Wang et al., 1995; Aceto et al., 1996; Patrick et al., 1996). Fentanyl, although quite potent, would seem to be of little benefit when given intravenously due to its lower efficacy and short duration of action.

Morphine given intravenously produced significant anti-allodynic actions, and the efficacy of morphine i.v. in the present study is similar to that reported for parenteral or intracerebroventricular administration (Bian et al., 1995). The potency of morphine i.v. was not dramatically enhanced as well when the present data are compared to studies using parenteral administration (Bian et al., 1995). Therefore, the i.v. route appears to offer no advantage over other routes of administration for morphine in this model. Fentanyl, although substantially more potent than morphine i.v., displayed similar efficacy, and the relatively short duration of action compared to the other compounds tested would seem to suggest that this compound would be of little benefit when given intravenously. These data suggest that morphine and fentanyl have significant pharmacokinetic limitations in the present model. One problem with evaluating the anti-allodynic actions of morphine and fentanyl was the occurrence of sedation, ataxia and respiratory depression at the highest doses examined. The responses recorded at these doses of morphine and fentanyl were also notably dissimilar from the abrupt withdrawal or flinching of the paw upon application of the von Frey filaments. It is possible that increasing the doses of these compounds further would result in a maximum score, however as these responses were not observed following any dose of dihydroetorphine or heroin, morphine and fentanyl would still seem to be less desirable agents due to the occurrence of these side effects at doses that produce less than maximum anti-allodynic effects.

The enhanced efficacy of heroin compared to morphine was a surprising aspect of this study. The clinical utility of heroin compared to morphine has been debated for some time. Some investigators have suggested that heroin might be more beneficial than morphine due to the production of less sedation and nausea and results in a patient that is more alert (Twycross, 1973). However, studies specifically designed to compare heroin and morphine have found little differences in the occurrence of side effects produced by these compounds when potency differences are taken into account (Twycross, 1977). Others have found heroin to have no greater benefit than morphine against cancer pain with the exception of possessing slightly higher potency (Kaiko et al., 1981). The problems in comparing many of the clinical studies of heroin and morphine are the use of other medications in addition to the opiates and the definition of terms relating to side effects (Sawynok, 1986). When potency differences are taken into account, there appears to be little advantage to using heroin compared to morphine for cancer and postoperative pain (Sawynok, 1986). However, the mechanisms of pain related to peripheral nerve injury probably differ from those related to postoperative or cancer-related pain, and these findings may not necessarily be extended to heroin use for neuropathic pain states.

The pharmacokinetic differences between heroin and morphine have been documented for some time, and are assumed to be largely responsible for the potency differences between these compounds (Way et al., 1960, 1965). Following intravenous injection of heroin in patients with chronic pain, blood levels of heroin rise and decrease rapidly followed by slower and more sustained levels of 6-acetylmorphine and morphine (Inturrisi et al., 1984). Since 6-acetylmorphine, but not heroin, has been shown to bind to opiate receptors in vitro (Inturrisi et al., 1983), the differences between parenteral heroin and morphine have been attributed to this metabolite of heroin (Inturrisi et al., 1984). The pharmacological properties of 6-acetylmorphine that are distinct from those of morphine could contribute to its higher efficacy in the present model. Most notably, heroin produces analgesic actions through δ-opioid receptors to a greater extent than does morphine in some strains of mice (Rady et al., 1994). Therefore, it is possible that heroin produces its anti-allodynic effects through activation of both μ- and δ-opioid receptors while morphine acts primarily at the μ-opioid receptor subtype. Given that δ-opioid receptor agonists potentiate the analgesic effects of μ-opioids (Heyman et al., 1989; Jiang et al., 1990; Porreca et al., 1992), such interactions could explain the increased effectiveness of heroin compared to morphine. Further studies examining the effects of selective μ- and δ-opioid antagonists will be useful for determining the anti-allodynic mechanism(s) of heroin compared to morphine in this model and determining if the differences in the efficacy of these compounds are pharmacodynamic, pharmacokinetic or both.

Dihydroetorphine is a potent analgesic that has been used in China for some time. This compound is approximately 1000 to 1500 times more potent than morphine in the mouse tail-flick (Huang and Qin, 1982) or tail-pinch (Tokuyama et al., 1994) assays. There is some discrepancy in the literature regarding the selectivity of this compound, however. Some investigators report potency ratios of several hundred between the K_i values for inhibition of μ- vs. δ-opioid receptor binding in mouse brain membranes (Wang et al., 1995). Others have found little evidence of selectivity for μ-, δ- or κ-opioid receptors with dihydroetorphine in receptor binding studies (Katsumata et al., 1995). In whole animal studies, the selective μ-opioid receptor antagonist β-funaltrexamine is more effective than δ- or κ-opioid receptor antagonists at inhibiting the analgesic effects of dihydroetorphine (Wang et al., 1995). Most of the excitement surrounding the clinical potential of dihydroetorphine is in regard to its limited ability to produce physical dependence in laboratory animals (Tokuyama et al., 1994; Wang et al., 1995; Patrick et al., 1996; Aceto et al., 1996, 1997). Chronic infusion of 10 to 40 $\mu g\ kg^{-1}\ day^{-1}$ of dihydroetorphine produces less physical dependence than morphine as evidenced by a reduced withdrawal syndrome upon cessation of drug treatment (Patrick et al., 1996). Infusions of 0.6 $\mu g\ kg^{-1}$ of dihydroetorphine were found to be maximally effective in the present model of allodynia and produced significant

effects for 30–40 min. Therefore, chronic treatment at this dosage would likely result in milder physical dependence compared to chronic morphine treatment. Possible administration of opioids with reduced physical dependence is of great potential interest in chronic pain conditions. Given the increased efficacy of dihydroetorphine compared to morphine or fentanyl against neuropathic pain in the rat, this compound may prove more useful against these pain syndromes clinically than currently available medications.

Abuse liability is also a major concern with opioid analgesics. Our earlier studies have found that dihydroetorphine substitutes for heroin in a rat self-administration paradigm (Martin et al., 1997). Dihydroetorphine is approximately 3000 times more potent than morphine in maintaining self-administration in rats, indicating a significant abuse potential. Dihydroetorphine is approximately 7000–9000 times more potent than morphine in producing anti-allodynic actions in the present study, however indicating a lower relative abuse potential compared to anti-allodynic efficacy and potency. The potency ratio for heroin compared to morphine in maintaining self-administration is approximately 5 compared to a potency ratio of 50 for producing anti-allodynic effects in the present study. It is worth noting that the doses of dihydroetorphine and heroin used for the present study maintain robust self-administration in rats (Martin et al., 1997). Therefore, although dihydroetorphine may have diminished potential for producing physical dependence, it possesses significant abuse liability at doses that possess significant anti-allodynic actions.

Dihydroetorphine and heroin i.v. are therefore more efficacious than morphine or fentanyl against allodynia produced by peripheral nerve injury in rats. The mechanisms by which these compounds produce enhanced anti-allodynic effects compared to morphine or fentanyl warrant further investigation. In addition, it would be helpful to determine if differences exist in the efficacy of dihydroetorphine and heroin compared to morphine or fentanyl against other manifestations of peripheral nerve injury, such as hyperalgesia. Hopefully, such studies will provide information for the development of agents that are useful in the treatment of neuropathic pain in humans.

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