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Novel depots of buprenorphine have a long-acting effect for the management of physical dependence to morphine

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Abstract

Buprenorphine is a promising new pharmacotherapy for the management of physical dependence to opioids. The aim of the study was to evaluate the duration of action of several novel depots of buprenorphine in the treatment of physical dependence to morphine in mice. Following intramuscular injection, the duration of action of several novel oil-based depots of buprenorphine base in morphine-dependent mice were evaluated. The traditional dosage form of buprenorphine hydrochloride in saline was used as control. We found that the depot of buprenorphine base in sesame oil produced a dose-related long-lasting effect. On an equimolar basis of 6 μmol kg^{-1}, its effect was 5.7-fold longer than that of buprenorphine hydrochloride in saline. When prepared in several other oleaginous vehicles (castor oil, cottonseed oil, peanut oil and soybean oil), buprenorphine base also produced a long-lasting effect, which was similar to buprenorphine base in sesame oil. In conclusion, buprenorphine base, when prepared in oleaginous vehicles and injected intramuscularly in mice, produced a long-lasting effect on physical dependence to morphine.

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Introduction

Buprenorphine, a semi-synthetic opioid derived from thebaine, is a promising new pharmacotherapy for the treatment of physical dependence to opioids, especially in the field of rapid detoxification (Brewer 1997; Kosten 2003; Tornay et al 2003). In receptor binding assays, buprenorphine has been characterized as an agonist–antagonist opioid with a partial agonist activity on the μ-receptors, an agonist activity on the κ_3-receptors and an antagonist activity on the κ_1-, κ_{2a}-, and κ_{2b}-receptors (Pick et al 1997; Davids & Gastpar 2004). Buprenorphine exhibits a unique profile that offers several advantages over other opioids for the management of physical dependence to opioids (Bickel & Amass 1995; Pick et al 1997; Barnett et al 2001). Firstly, its activity on the μ- and κ_3-receptors enables buprenorphine to attenuate the physical dependence of other opioids but with a lower abuse liability (Lewis 1985; Walsh et al 1995; Pick et al 1997). This activity also contributes to a superior safety profile of a ceiling effect on its side effects (e.g. respiratory depression) (Davids & Gastpar 2004; Law et al 2004). Also, buprenorphine has a very high lipid solubility, which is equivalent to that of fentanyl (Roy et al 1994). This characteristic allows the unimpeded transfer of buprenorphine through the blood–brain barrier (Roy et al 1994). Secondly, its antagonist activity on the κ_1-, κ_{2a}-, and κ_{2b}-receptors precludes dysphoric effects, which also results in a low abuse liability (Pick et al 1997; Barnett et al 2001; Davids & Gastpar 2004; Law et al 2004). Thirdly, its activity on opioid (μ- and κ-) receptors is quite different from the other opioids, such as morphine and methadone, leading to less cross-tolerance between buprenorphine and other opioids (Bulka et al 2004). Fourthly, buprenorphine has few drug interactions compared with methadone, an opioid commonly used in the treatment of opioid dependence. Both buprenorphine and its active metabolite, norbuprenorphine, are rapidly glucuronidated and inactivated (Davis 2005). It is for the above four reasons that buprenorphine is now considered the drug of choice for the treatment of physical dependence to opioids, especially in rapid detoxification.

Buprenorphine has been used in rapid detoxification for years (Brewer 1997; Kosten 2003; Assadi et al 2004). However, there is considerable variation in the proposed detoxification regimens (Nigam et al 1993; Janiri et al 1994; Assadi et al 2004). For example, dosage forms and routes of administration vary from tablets for sublingual uses to solution for intravenous and intramuscular uses (Janiri et al 1994; Umbricht et al 1999; Assadi et al 2004). The duration of treatment also differs, ranging from a few days to several weeks (Bickel et al 1988; Cheskin et al 1994; Assadi et al 2004). However, the typical detoxification regimen with buprenorphine is the use of sublingual tablets for a treatment duration of 4–8 days (Bickel & Amass 1995; Umbricht et al 1999). Though it is a commonly used method, the use of sublingual tablets for rapid detoxification has certain weaknesses. Firstly, patients need to visit the doctors' office continuously for a period of 4–8 days, which may attenuate the compliance of patients (Bickel & Amass 1995; Umbricht et al 1999). Secondly, an alternative option of high take-home doses may increase the risks of illicit diversion (Umbricht et al 1999; Sobel et al 2004). The use of a long-acting dosage form of buprenorphine as an intramuscular injection may be more practical.

To develop a long-acting dosage form of buprenorphine for intramuscular injection, several depots of buprenorphine base in oleaginous vehicles were designed and developed. The aim of the study was to evaluate whether these depots had a long-acting effect for the treatment of physical dependence to opioids. In the study, physical dependence was induced by long-term administration of morphine in mice and was precipitated by administration of an opioid antagonist, naloxone.

Materials and Methods

Animals

Adult male NRL mice (National Laboratory Animal Center, Taiwan), 25–30 g, were used. They were housed in groups of six for at least 1 week in a climate-controlled room maintained at 21°C and approximately 50% relative humidity. Lighting was on a 12-h light–dark cycle, with food and water freely available, except during the time of testing. All tests were performed in accordance with the recommendations and policies of the International Association for the Study of Pain and the protocol was approved by the Animal Investigation Committee of Chi-Mei Medical Center.

Preparation of medications

Buprenorphine hydrochloride was purchased from Macfarlan Smith (Edinburgh, UK), and buprenorphine base was obtained using a method of precipitation (Roy et al 1994). Morphine sulfate was purchased from the National Bureau of Controlled Drugs, Taiwan, whereas naloxone hydrochloride dihydrate was purchased from Sigma-Aldrich (St Louis, MO, USA). Morphine sulfate and naloxone hydrochloride dihydrate were prepared in 0.9% saline. Buprenorphine hydrochloride was prepared in either 0.9% saline or injectable sesame oil (Sigma, MO, USA), whereas buprenorphine base was prepared in injectable vegetable oils (sesame oil, castor oil (Riedel-de Haën, Seelze, Germany), cottonseed oil (Sigma), peanut oil (Sigma) or soybean oil (Sigma)). Morphine and naloxone were injected subcutaneously, whereas buprenorphine (hydrochloride or base) of different preparations was injected intramuscularly. The site for subcutaneous injection was 2 cm below the neck at the midline of the back, whereas the site for intramuscular injection was the biceps femoris and semitendinosus of the right hind leg of mice. The volume of injection was $3\,mL\,kg^{-1}$ for all the medications at both injection sites.

Study protocol

Five studies were performed. In study 1, an animal model of physical dependence to morphine was set up. In study 2, a dose–response study of the traditional dosage form of buprenorphine hydrochloride in saline for the treatment of morphine dependence was performed. In study 3, the effects of three different dosage forms of buprenorphine on morphine dependence were evaluated. In study 4, a dose–response study of a novel dosage form of buprenorphine in sesame oil for the treatment of morphine dependence was performed. In study 5, the effects of five different oil-based dosage forms of buprenorphine on morphine dependence were evaluated.

Dosing regimen in study 1

In study 1, an animal model of physical dependence to morphine was induced in mice by thrice daily subcutaneous injections (at 0800, 1400, and 2000 h) of morphine for 7 days according to an escalating dosing schedule of 20 and $40\,mg\,kg^{-1}$ on days 1 and 2, and $80\,mg\,kg^{-1}$ on days 3–7, respectively. The severity of morphine dependence was assessed by measuring the withdrawal jumping after a combination of a single subcutaneous morphine $40\,mg\,kg^{-1}$ followed 3 h later with a single subcutaneous injection of naloxone $50\,mg\,kg^{-1}$ (at 1100, 1400 or 1700 h) (Kest et al 2001, 2002). This morphine–naloxone injection has been widely used as a standard regimen to precipitate the dependence to morphine, and the jumping response has been the most reliable withdrawal sign in mice (Kest et al 2001, 2002).

Immediately after naloxone injection, mice were placed into individual Plexiglas observation cages (30 cm high × 11 cm long × 11 cm wide). The jumping response was recorded, which was defined as the simultaneous removal of all four paws from the horizontal surface over the next 30 min (Kest et al 2001, 2002). All mice received only one injection of naloxone during the whole testing period. The number of mice at each time point of naloxone injection was six.

Dosing regimen in studies 2–5

In study 2, the physical dependence was induced by daily subcutaneous injection of morphine according to the dosing schedule demonstrated in study 1. On the morning (0800 h) of day 4, mice further received either 0.06, 0.6 or $6\,\mu mol\,kg^{-1}$ of buprenorphine hydrochloride intramuscular injection in the left hind leg ($3\,mL\,kg^{-1}$). Following the administration of buprenorphine hydrochloride, the withdrawal jumping was measured by giving the morphine–naloxone injection, which was demonstrated in study 1. A control group with no injection of buprenorphine

hydrochloride was used. All mice received only one injection of naloxone during the whole testing period. The number of mice at each time point of naloxone injection was six.

In studies 3, 4 and 5, the dosing regimens for the induction of physical dependence and withdrawal jumping were the same as those described in study 2. On the morning (0800 h) of day 4, mice received one of the dosage forms of buprenorphine for intramuscular injection. In study 3, mice received either buprenorphine hydrochloride in saline or in sesame oil, or buprenorphine base in sesame oil 6 μmol kg^{-1}. In study 4, mice received buprenorphine base in sesame oil at 0.6, 6 or 60 μmol kg^{-1}. In study 5, mice received one of the five formulations of buprenorphine 6 μmol kg^{-1} in oils: sesame oil, castor oil, cottonseed oil, peanut oil or soybean oil. A control group with no injection of buprenorphine was used in each study. All mice received only one injection of naloxone during the whole testing period. The number of mice at each time point of naloxone injection was six. The solubility profiles of buprenorphine in different dosage forms were also determined.

Data analysis

Values are expressed as mean ± s.e.m. In study 1, a one-way analysis of variance with one-way repeated measure followed by the Dunnett test was used to evaluate the differences between days at each specific time point of testing (i.e. 1100, 1400 or 1700 h). In studies 2–5, a two-way analysis of variance with one-way repeated measure followed by the Dunnett test was used to evaluate the differences between the medication groups and the control group at each time point of testing. Also, the Bonferroni test was used as post-hoc analysis to evaluate the differences between medication groups. For all testing, the Bonferroni correction was used when appropriate. $P < 0.05$ was considered significant.

Results

In study 1, an animal model of physical dependence to morphine in mice was induced by daily subcutaneous injection of morphine. The severity of physical dependence to morphine, which was precipitated by the administration of naloxone, was evaluated by the number of jumps (Figure 1). Following escalating doses of morphine administration, the severity of physical dependence increased daily and reached a plateau between days 4 and 7 (Figure 1). The number of jumps on days 4–7 were not different between each other at each specific time point of testing (i.e. 1100, 1400, or 1700 h). In study 2, the severity of physical dependence to morphine was attenuated by intramuscular injection of buprenorphine hydrochloride in saline, a traditional dosage form. Buprenorphine hydrochloride 0.06, 0.6 and 6 μmol kg^{-1} produced a duration of action of 3, 9 and 9 h, respectively (Table 1, Figure 2). The effects of buprenorphine hydrochloride 0.6 and 6 μmol kg^{-1} on morphine dependence were not significantly different. In study 3, the severity of physical dependence to morphine was also attenuated by different preparations of buprenorphine. On an equimolar basis of 6 μmol kg^{-1}, buprenorphine hydrochloride in saline and sesame oil, and buprenorphine base in

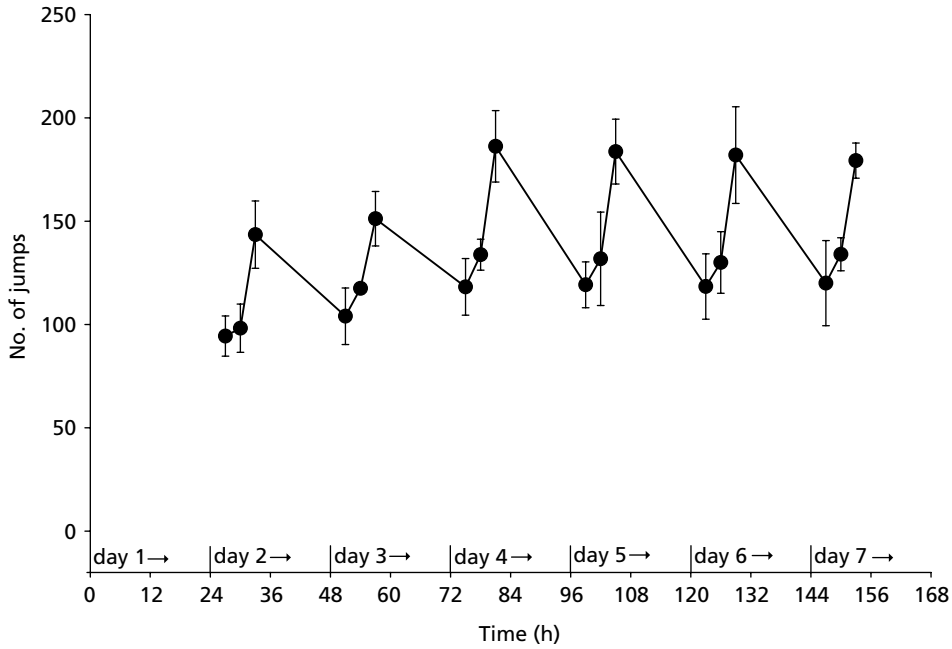

Figure 1 The induction of physical dependence to morphine in mice. Physical dependence was induced by escalating daily doses of subcutaneous morphine and precipitated by a single dose of subcutaneous naloxone as withdrawal jumping. Six mice were used at each time-point of testing and all mice received only one injection of naloxone. Values are expressed as mean ± s.e.m. The number of jumps between days 4 and 7 were not different at each specific time point of testing (i.e. 1100, 1400 or 1700 h).

Table 1 The solubility profiles and duration of action of buprenorphine in different dosage forms

Medication	Solubility (dosage form)	Duration of action
Buprenorphine hydrochloride in saline	17 mg mL^{-1} (solution)	
0.06 μmol kg^{-1}		3 h
0.6 μmol kg^{-1}		9 h
6 μmol kg^{-1}		9 h
Buprenorphine hydrochloride in sesame oil	0.13 mg mL^{-1} (suspension)	
6 μmol kg^{-1}		27 h
Buprenorphine base in sesame oil	10.8 mg mL^{-1} (solution)	
0.6 μmol kg^{-1}		9 h
6 μmol kg^{-1}		51 h
60 μmol kg^{-1}		75 h
Buprenorphine base in castor oil	8.2 mg mL^{-1} (solution)	
6 μmol kg^{-1}		51 h
Buprenorphine base in cottonseed oil	9.6 mg mL^{-1} (solution)	
6 μmol kg^{-1}		51 h
Buprenorphine base in peanut oil	9.4 mg mL^{-1} (solution)	
6 μmol kg^{-1}		51 h
Buprenorphine base in soybean oil	6.9 mg mL^{-1} (solution)	
6 μmol kg^{-1}		51 h

The attenuating effects of intramuscular buprenorphine in different dosage forms on morphine dependence in mice were evaluated. The solubility of each dosage form was determined at an ambient temperature of 21°C. The duration of action of each dosage form was obtained from Figures 2–5.

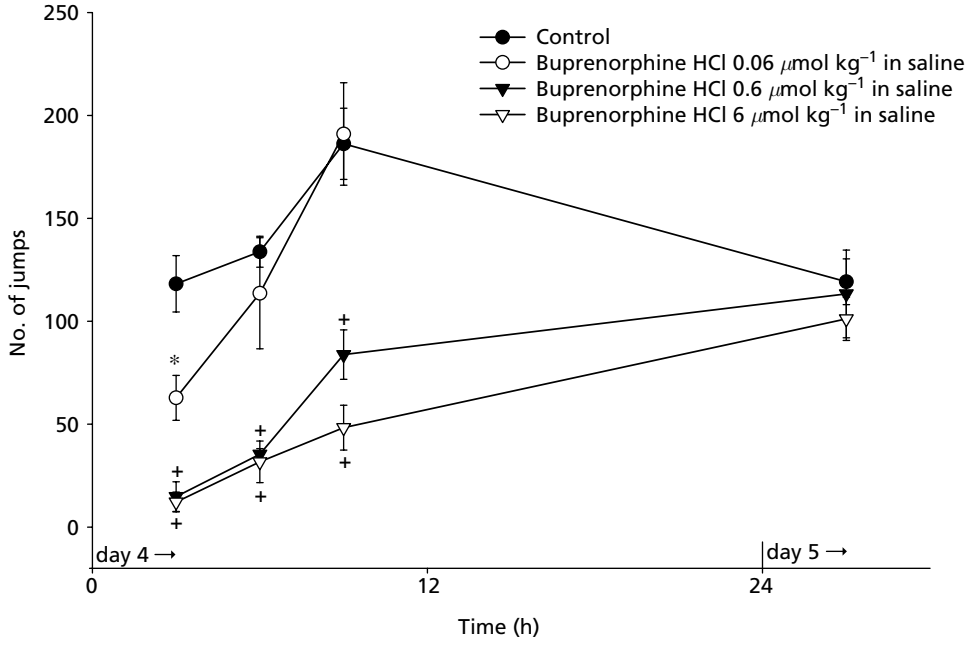

Figure 2 Dose–response study of buprenorphine hydrochloride in saline for the treatment of morphine dependence in mice. Buprenorphine hydrochloride was given intramuscularly on day 4 following the induction of morphine dependence. Six mice were used at each time-point of testing and all mice received only one injection of naloxone. Values are expressed as mean ± s.e.m. $^{*}P < 0.05$, $^{+}P < 0.01$ vs control.

sesame oil, produced a duration of action of 9, 27 and 51 h, respectively (Table 1, Figure 3). Among the dosage forms, buprenorphine base in sesame oil produced the longest duration of action. In study 4, buprenorphine base prepared in sesame oil also produced a dose-related effect on attenuating the severity of morphine dependence (Table 1, Figure 4). The duration of action of buprenorphine base in sesame oil 0.6, 6 and 60 μmol kg^{-1} was 9, 51 and 75 h, respectively (Table 1, Figure 4). A higher dose had a longer duration of action. In study 5, the effects of buprenorphine base in five oleaginous vehicles on attenuating morphine dependence were evaluated. On an equimolar basis, buprenorphine base when prepared in sesame oil, castor oil, cottonseed oil, peanut oil or soybean oil

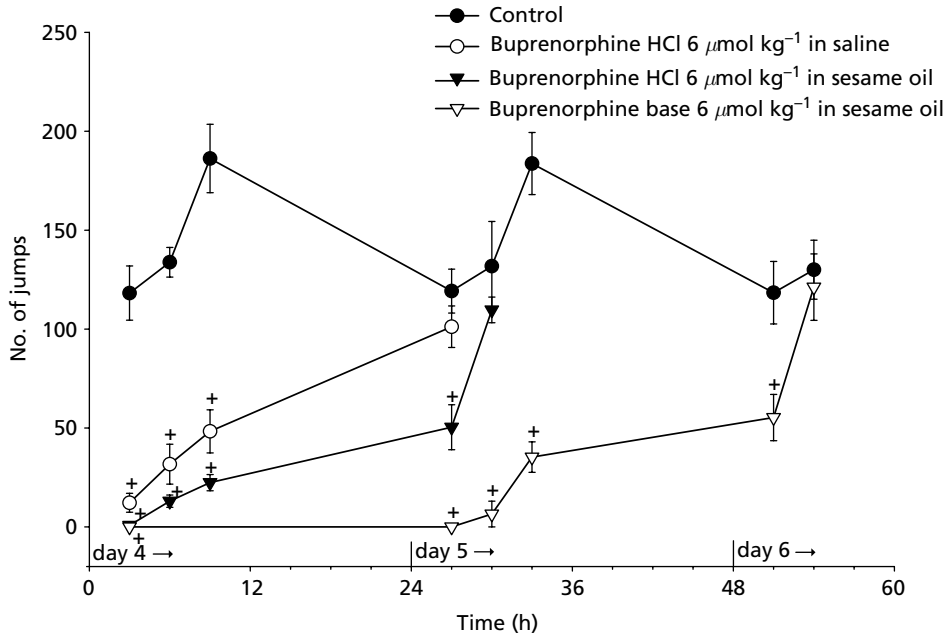

Figure 3 The effect of three different dosage forms of buprenorphine on morphine dependence in mice. Six mice were used at each time point of testing and all mice received only one injection of naloxone. Values are expressed as mean ± s.e.m. $^{+}P < 0.01$ vs control.

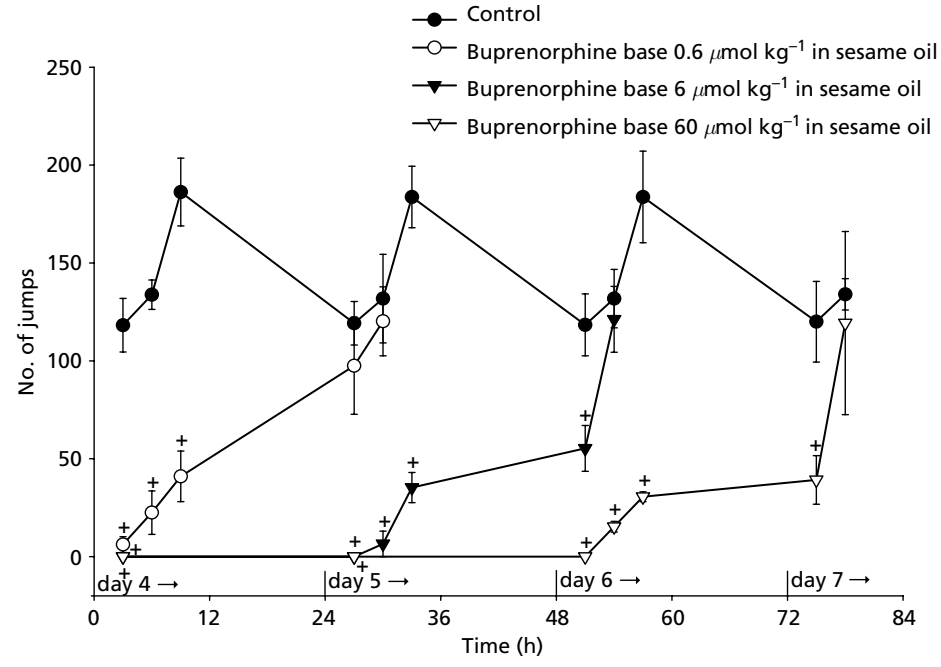

Figure 4 Dose–response study of buprenorphine base in sesame oil for the treatment of morphine dependence in mice. Six mice were used at each time point of testing and all mice received only one injection of naloxone. Values are expressed as mean ± s.e.m. $^{+}P < 0.01$ vs control.

produced similar potencies on attenuating morphine dependence, with a duration of action of 51 h (Table 1, Figure 5). The differences between groups were not significant. The solubility profiles of buprenorphine in different dosage forms are shown in Table 1.

Discussion

We found that intramuscular injection of a novel dosage form of buprenorphine base in sesame oil produced a dose-related long-lasting effect. On an equimolar basis of 6 μmol kg^{-1}, this

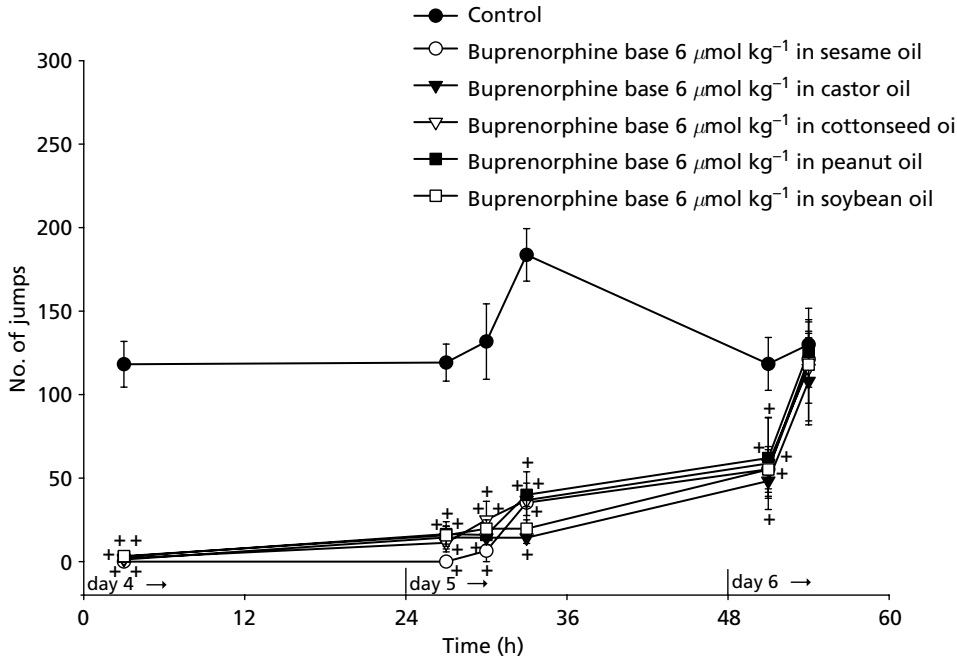

Figure 5 The effect of five different oil-based dosage forms of buprenorphine on morphine dependence in mice. Six mice were used at each time point of testing and all mice received only one injection of naloxone. Values are expressed as mean ± s.e.m. $^{+}P < 0.01$ vs control.

effect was 5.7-fold longer than that of the traditional dosage form of buprenorphine hydrochloride in saline (Table 1). Buprenorphine base when prepared in several other oleaginous vehicles, such as castor oil, cottonseed oil, peanut oil and soybean oil, also produced long-lasting effects, which were similar to that of buprenorphine base in sesame oil.

Physical dependence to opioids (e.g. morphine) can be inferred from multiple behavioral and physiological signs following precipitation of withdrawal with an opioid antagonist (e.g. naloxone) (El-Kadi & Sharif 1994; Kest et al 2001, 2002). Among such signs, jumping is widely considered the most reliable index of withdrawal intensity in rodents and is the most commonly used (Kest et al 2001, 2002). Also, the jumping frequency in response to opioid withdrawal in mice correlates well with the severity of physical dependence to opioids in man (El-Kadi & Sharif 1994; Kest et al 2001, 2002). In this study, therefore, withdrawal jumping was used for evaluating the severity of morphine dependence.

Using an animal model of withdrawal jumping in mice, the severity of physical dependence to morphine was determined. We found that the traditional dosage form of buprenorphine hydrochloride in saline significantly attenuated the severity of morphine dependence but with a relatively short duration of action, whereas the novel dosage forms of buprenorphine base in oleaginous vehicles produced a long-lasting effect (Table 1).

In a previous study, the partition coefficient of buprenorphine base in an octanol–water preparation was found to be 1217 (Roy et al 1994). This datum showed that buprenorphine base has a high lipophilicity and should be thermodynamically stable in oleaginous vehicle, which produces a slow releasing profile of buprenorphine from the vehicle (Roy et al 1994).

Pharmaceutically, the duration of action of a drug may be controlled by a change in dosage form – the chemical form of the drug (base or salt), the physical state of the preparation (suspension or solution) and the vehicle used (oleaginous or aqueous solution). Drugs in base form are more oil-soluble whereas drugs in salt form are more water-soluble, and drugs in oleaginous solution have a longer duration of action than those in aqueous solution (Liu et al 2004; Allen et al 2005a). To obtain a longer duration of action, buprenorphine base was prepared in oleaginous vehicles, such as sesame oil, castor oil, etc., as solutions. We further found that these dosage forms had a long-lasting effect.

Although buprenorphine hydrochloride when prepared in sesame oil had a duration longer than that of the traditional dosage form, its duration of action was shorter than that of buprenorphine base in sesame oil (Table 1, Figure 3). This phenomenon may be explained, at least in part, by the following reason. Due to a limitation of solubility of buprenorphine hydrochloride in sesame oil, the dosage form of buprenorphine hydrochloride in sesame oil was an oleaginous suspension at the given dose of 6 μmol kg^{-1} (Table 1). Because a drug must be in solution to be absorbed and released into the systemic circulation, a drug in suspension form may retard these processes (Liu et al 2004; Allen et al 2005a). This may be the reason why buprenorphine hydrochloride in sesame oil has a longer duration than that of the traditional dosage form. Moreover, since the salt form of buprenorphine (buprenorphine hydrochloride) may partition more easily into the aqueous tissue fluid than the buprenorphine base, as a result, a shorter duration of action for buprenorphine hydrochloride in sesame oil was observed and the duration of action for buprenorphine base in sesame oil was significantly longer (Liu et al 2004; Allen et al 2005a).

In our study, we also found that buprenorphine base when prepared in oleaginous vehicles (i.e. sesame oil, castor oil, cottonseed oil, peanut oil and soybean oil) had similar long duration of action (Table 1, Figure 5). The similarity in the duration of action between these dosage forms may be explained, at least in part, by their similarity in solubility (Table 1). The differences among the solubility profiles of buprenorphine base in these oils were minor when compared with the solubility of buprenorphine hydrochloride in sesame oil (Table 1).

The safety of intramuscular injections of injectable vegetable oils, such as sesame oil, castor oil, cottonseed oil, peanut oil and soybean oil, is well documented (Liu et al 2004; Allen et al 2005a, b). Several clinically long-acting drugs are formulated in these oleaginous vehicles and injected intramuscularly (e.g., dimercaprol, progesterone, testosterone, etc.) (Liu et al 2004; Allen et al 2005a, b). In our study, we followed these methods.

Using a poly (lactic/glycolic) acid-based polymeric microcapsule sustained-release technology, a depot formulation of microencapsulated buprenorphine base suspended in water-soluble medium was developed and studied in two previous reports (Sigmon et al 2004; Sobel et al 2004). Following subcutaneous injection in opioid-dependent subjects, a single dose of this formulation provided a more effective relief from opioid withdrawal than did placebo, as demonstrated by significantly fewer buprenorphine participants requiring supplemental medication for withdrawal suppression during an observatory interval of 4–6 weeks (Sigmon et al 2004; Sobel et al 2004). There were two major differences between the previous studies and our report. Firstly, two different dosage forms were formulated. In previous studies, a microencapsulated buprenorphine base in water-soluble vehicle was formulated (Sigmon et al 2004; Sobel et al 2004), whereas in our study, buprenorphine base in oleaginous vehicle was formulated. Secondly, two different sites of injection (subcutaneous and intramuscular) were used (Sigmon et al 2004; Sobel et al 2004). These two major differences could significantly influence the duration of the drug's effect. The depot of buprenorphine with a duration of action of 4–6 weeks is more suitable for maintenance therapy, whereas those with a duration of action of days are suitable for rapid detoxification in opioid-dependent patients.

For rapid detoxification, injecting a long-acting drug as an intramuscular injection may be more practical. An intramuscular injection of buprenorphine base in oleaginous vehicle for rapid detoxification may have the potential advantages of enhancing the compliance of patients via reducing the frequency of dosing, reducing the risk of illicit diversion of buprenorphine via eliminating the need for take-home medication and reducing the overall health-care costs. Intramuscular injection of the depots of buprenorphine base in oleaginous vehicles may be an alternative method to sublingual buprenorphine for rapid detoxification in patients with opioid dependence.

Conclusions

Buprenorphine base when prepared in oleaginous vehicles produced a long-acting effect for the treatment of physical dependence to morphine in mice. Intramuscular injection of the depots of buprenorphine base in oleaginous vehicles may be an alternative method to sublingual buprenorphine for rapid detoxification in patients with opioid dependence.

References

Allen, L. V., Popovich, N. G., Ansel, H. C. (2005a) Drug dosage form and drug delivery system design: biopharmaceutic and pharmacokinetics considerations. In: *Ansel's pharmaceutical dosage forms and drug delivery systems*. 8th edn, Lippincott Williams & Wilkins, Philadelphia, pp 142–185

Allen, L. V., Popovich, N. G., Ansel, H. C. (2005b) Sterile dosage forms and delivery systems: Parenterals. In: *Ansel's pharmaceutical dosage forms and drug delivery systems*. 8th edn, Lippincott Williams & Wilkins, Philadelphia, pp 443–505

Assadi, S. M., Hafezi, M., Mokri, A., Razzaghi, E. M., Ghaeli, P. (2004) Opioid detoxification using high doses of buprenorphine in 24 hours: a randomized, double blind, controlled clinical trial. *J. Subst. Abuse Treat*. **27**: 75–82

Barnett, P. G., Rodgers, J. H., Bloch, D. A. (2001) A meta-analysis comparing buprenorphine to methadone for treatment of opiate dependence. *Addiction* **96**: 683–690

Bickel, W. K., Amass, L. (1995) Buprenorphine treatment of opioid dependence: a review. *Exp. Clin. Psychopharmacol*. **3**: 477–489

Bickel, W. K., Stitzer, M. L., Bigelow, G. E., Liebson, I.A., Jasinski, D. R., Johnson, R. E. (1988) A clinical trial of buprenorphine: comparison with methadone in the detoxification of heroin addicts. *Clin. Pharmacol. Ther*. **43**: 72–78

Brewer, C. (1997) Ultra-rapid, antagonist-precipitated opiate detoxification under general anesthesia or sedation. *Addict. Biol*. **2**: 291–302

Bulka, A., Kouya, P. F., Bottiger, Y., Svensson, J. O., Xu, X. J., Wiesenfeld-Hallin, Z. (2004) Comparison of the antinociceptive effect of morphine, methadone, buprenorphine and codeine in two substrains of Sprague-Dawley rats. *Eur. J. Pharmacol*. **492**: 27–34

Cheskin, L. J., Fudala, P. J., Johnson, R. E. (1994) A controlled comparison of buprenorphine and clonidine for acute detoxification from opioids. *Drug Alcohol Depend*. **36**: 115–121

Davids, E., Gastpar, M. (2004) Buprenorphine in the treatment of opioid dependence. *Eur. Neuropsychopharmacol*. **14**: 209–216

Davis, M. P. (2005) Buprenorphine in cancer pain. *Support. Care Cancer* **13**: 878–887

El-Kadi, A. O., Sharif, S. I. (1994) The influence of various experimental conditions on the expression of naloxone-induced withdrawal symptoms in mice. *Gen. Pharmacol*. **25**: 1505–1510

Janiri, L., Mannelli, P., Persico, A. M., Serretti, A., Tempesta, E. (1994) Opiate detoxification of methadone maintenance patients using lefetamine, clonidine and buprenorphine. *Drug Alcohol Depend*. **36**: 139–145

Kest, B., Palmese, C. A., Hopkins, E., Adler, M., Juni, A. (2001) Assessment of acute and chronic morphine dependence in male and female mice. *Pharmacol. Biochem. Behav*. **70**: 149–156

Kest, B., Palmese, C. A., Hopkins, E., Adler, M., Juni, A., Mogil, J. S. (2002) Naloxone-precipitated withdrawal jumping in 11 inbred mouse strains: evidence for common genetic mechanisms in acute and chronic morphine physical dependence. *Neuroscience* **115**: 463–469

Kosten, T. R. (2003) Buprenorphine for opioid detoxification: a brief review. *Addict. Disord. Treat*. **2**: 107–112

Law, F. D., Myles, J. S., Daglish, M. R. C., Nutt, D. J. (2004) The clinical use of buprenorphine in opiate addiction: evidence and practice. *Acta Neuropsychiatr*. **16**: 246–274

Lewis, J. W. (1985) Buprenorphine. *Drug Alcohol Depend*. **14**: 363–372

Liu, K. S., Hu, O. Y. P., Ho, S. T., Tzeng, J. I., Chen, Y. W., Wang J. J. (2004) Antinociceptive effect of a novel long-acting nalbuphine preparation. *Br. J. Anaesth*. **92**: 712–715

Nigam, A. K., Ray, R., Tripathi, B. M. (1993) Buprenorphine in opiate withdrawal: a comparison with clonidine. *J. Subst. Abuse Treat*. **10**: 391–394

Pick, C. G., Peter, Y., Schreiber, S., Weizman, R. (1997) Pharmacological characterization of buprenorphine, a mixed agonist-antagonist with κ_3 analgesia. *Brain Res*. **744**: 41–46

Roy, S. D., Roos, E., Sharma, K. (1994) Transdermal delivery of buprenorphine through cadaver skin. *J. Pharm. Sci*. **83**: 126–130

Sigmon, S. C., Wong, C. J., Chausmer, A. L., Liebson I. A., Bigelow, G. E. (2004) Evaluation of injection depot formulation of buprenorphine: placebo comparison. *Addiction* **99**: 1439–1449

Sobel, B. F. X., Sigmon, S. C., Walsh, S. L., Johnson, R. E., Liebson, I. A., Nuwayser, E. S., Kerrigan, J. H., Bigelow, G. E. (2004) Open-label trial of an injection depot formulation of buprenorphine in opioid detoxification. *Drug Alcohol Depend*. **73**: 11–22

Tornay, C. B., Favrat, B., Monnat, M., Daeppen, J. B., Schnyder, C., Bertschy, G. (2003) Ultra-rapid opiate detoxification using deep sedation and prior oral buprenorphine preparation: long-term results. *Drug Alcohol Depend*. **69**: 283–288

Umbricht, A., Montoya, I. D., Hoover, D. R., Demuth, K. L., Chiang, C. T., Preston, K. L. (1999) Naltrexone shortened opioid detoxification with buprenorphine. *Drug Alcohol Depend*. **56**: 181–190

Walsh, S. L., Preston, K. L., Bigelow, G. E., Stitzer, M. L. (1995) Acute administration of buprenorphine in humans: partial agonist and blockade effect. *J. Pharmacol. Exp. Ther*. **274**: 361–372