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Buprenorphine maintenance subjects are hyperalgesic and have no antinociceptive response to a very high morphine dose

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Buprenorphine maintenance subjects are hyperalgesic and have no

antinociceptive response to a very high morphine dose

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Running Title: Buprenorphine, hyperalgesia, antinociception, maintenance subjects

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Abstract

Objective. Acute pain management in opioid dependent persons is complicated because of tolerance and opioid-induced-hyperalgesia. Very high doses of morphine are ineffective in overcoming opioid-induced-hyperalgesia and providing antinociception to methadone maintained patients in an experimental setting. Whether the same occurs in buprenorphine maintained subjects is unknown.

Design. Randomised double blind placebo controlled. Subjects were tested on two occasions, at least five days apart; once with intravenous morphine and once with intravenous saline. Subjects were tested at about the time of putative trough plasma buprenorphine concentrations.

Setting. Ambulatory.

Subjects. Twelve buprenorphine maintained subjects: once daily sublingual dose (range 2-22 mg); no dose change for 1.5-12 months. Ten healthy controls.

Methods. Intravenous morphine bolus and infusions administered over 2 hours to achieve two separate pseudo-steady state plasma concentrations one hour apart. Pain tolerance assessed by application of nociceptive stimuli (cold pressor (seconds) and electrical stimulation (volts)). Ten blood samples collected for assay of plasma morphine, buprenorphine and norbuprenorphine concentrations until 3 hours after the end of last infusion; pain tolerance and respiration rate measured to coincide with blood sampling times.

Results. Cold pressor responses (seconds): baseline: control 34±6 versus

buprenorphine 17±2 (P=0.009); morphine infusion-end: control 52±11(P=0.04),

buprenorphine 17±2 (P>0.5); electrical stimulation responses (volts): baseline:

control 65±6 versus buprenorphine 53±5 (P=0.13); infusion-end: control 74±5

(P=0.007), buprenorphine 53±5 (P>0.98). Respiratory rate (breaths per minute):

baseline: control 17 versus buprenorphine 14 (P=0.03); infusion-end: control 15

(P=0.09), buprenorphine 12 (P<0.01). Infusion-end plasma morphine concentrations

(ng/mL): control 23±1, buprenorphine 136±10.

Conclusions. Buprenorphine subjects, compared with controls, were: hyperalgesic

(cold pressor test); did not experience antinociception, despite high plasma morphine

concentrations; experienced respiratory depression. Clinical implications are

discussed.

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Introduction

The prevalence of opioid dependence is growing worldwide. Dependence has traditionally been the result of illicit opioid abuse. However, it is increasingly associated with legally prescribed long-term use of opioids for the management of chronic pain [1]. Between 28 and 38.5 million people abuse opioids worldwide. In 2015, 2 million had a substance use disorder involving prescription pain relievers and 591,000 had a substance use disorder involving heroin [2]. Approximately 1% of the Australian population is opioid dependent and half of these are in opioid substitution treatment (OST) programs [3]. Of these, two-thirds receive methadone and one third buprenorphine (alone or with naloxone) but this difference is declining.

The management of acute pain in opioid dependent patients is complicated because of two major factors: tolerance, which can generally be overcome by dose increase but may be compromised by adverse effects, and the under recognized phenomenon of opioid-induced-hyperalgesia (OIH) characterized as paradoxical pain sensitization [4] which cannot be overcome by dose increase. Although there are no formal guidelines for the clinician, Macintyre et al [5] and Huxtable et al [6] advise, that in the clinical setting, the daily OST dose should be maintained and additional opioid used for acute pain management, titrated until satisfactory analgesia is achieved or an adverse effect (e.g. sedation or respiratory depression) occurs. Such an approach requires stringent observation such as admission to hospital.

Opioid-induced hyperalgesia occurs in opioid (e.g. heroin) addicted subjects prior to entry into methadone and buprenorphine treatments [7], chronic non-cancer pain

patients [8], and slow release morphine, methadone and buprenorphine maintained

subjects [9, 10, 11, 12]. Clinically used and very high doses of morphine are

ineffective in overcoming OIH and providing antinociception to methadone

maintained patients [11, 13] in an experimental setting. Whether the same occurs in

buprenorphine maintained subjects is unknown.

Buprenorphine, a semi-synthetic 4,5-epoxymorphinan opioid shows partial agonist

properties for some responses at the mu opioid receptor and variable effects at

the kappa and delta receptors [14]. Its major metabolite norbuprenorphine is also

active [15], although there is conjecture whether it crosses the blood-brain barrier

[16]. Opioid agonists such as morphine, over plasma concentration ranges that

produce dose-related increases in analgesia, also produce concentration-

dependent respiratory depression without any plateau in healthy human

volunteers [17]. In contrast, buprenorphine shows dose-dependent increases in

analgesia with a limited extent of respiratory depression [17, 18]. As a partial

agonist, under appropriate conditions, buprenorphine may act as an agonist or

antagonist at opioid receptors [19] and has shown antihyperalgesic effects in

healthy subjects using a model of intradermal electric stimulation [20]. Therefore,

buprenorphine may be unique in its ability to treat acute pain and possibly

attenuate OIH.

Previously we showed that methadone maintained subjects on doses of 2-120 mg

per day, under identical experimental conditions that will be described in this study,

experienced no antinociception with 55 mg of intravenous morphine but showed a

significant reduction in respiratory rate [13]. To date, no studies have examined the

effect of different daily buprenorphine doses on the antinociceptive and respiratory

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responses to morphine.

The aims of the study in buprenorphine maintained subjects were to: 1. Confirm the presence of OIH; 2. Ascertain whether very high intravenous morphine doses produce antinociceptive and respiratory depression effects and 3. Determine any relationship between buprenorphine dose and these effects. Our hypothesis is that buprenorphine maintained subjects are hyperalgesic and, that in contrast to methadone maintained subjects, experience antinociception with high morphine doses.

Methods

Ethics

The Research Ethics Committee of the Royal Adelaide Hospital, Adelaide, South Australia, Australia (RAH Protocol no: 010222) and the Institutional Review Board, Friends Research Institute, Los Angeles, California, USA (FRI IRB no: 00-03-057-02) approved the study. Both bodies adhere to the ethical standards set by the Helsinki Declaration (2008). The study was supported by National Institutes of Drug Abuse (NIDA) grant R01 DA 13706-02. This study was not registered on clinicaltrials.gov as this study was carried out before the requirement for registration. Subjects provided written informed consent, were paid for their involvement in the study and were free to withdraw at any time.

Subjects

Twelve buprenorphine maintained subjects comprising 7 men and 5 women with ages between 24 and 42 years (mean 35 years) were recruited. Their weights

ranged between 49 and 97 kg (mean 71 kg). They had been receiving sublingual

buprenorphine (Subutex ® Reckitt Benckiser, West Ryde, New South Wales,

Australia) for between 1.5 and 12 months (mean 4 months) with no dose change.

They had been enrolled in a buprenorphine maintenance program for a period

ranging between 2 and 22 months with a mean of 10 months. The group was

stratified according to dose, with four subjects in each of the dose ranges of 2 to 8

mg, 9 to 15 mg and 16 to 22 mg per day. Subjects were recruited if they self-

reported intravenous heroin use at least once in the previous month. It was

considered more ethical to administer morphine to individuals who continued to use

illicit heroin, rather than to those who used no opioids, apart from their prescribed

buprenorphine. Ten healthy control subjects (5 men and 5 women; aged between

21 and 41(mean 31) years); weight 59 and 102 (mean 80) kg) were selected.

These subjects were not taking any prescribed medications. They have been

described previously [13].

Exclusion criteria

Exclusion criteria for all subjects included pregnancy or lactation, use of

antiretroviral drugs, significant medical or psychiatric illness that required ongoing

treatment (except opioid addiction for buprenorphine subjects), daily alcohol

consumption exceeding 40 g for men and 20 g for women, severe liver impairment

(serum aspartate aminotransferase and alanine aminotransferase concentrations

greater than 3 times the upper limit of normal range and albumin concentrations

less than 33 grams per litre) or haemoglobin counts outside the normal range.

Healthy control subjects were excluded if they had any personal or family history of

addictive behaviours.

Study design

The study utilized a double blind placebo controlled design with four groups of

subjects (healthy controls, once daily buprenorphine dose of 2 to 8, 9 to 15 and,

16 to 22 mg). Subjects were tested on two occasions, at least five days apart;

once with morphine and once with saline. The order of administration was

randomised. Buprenorphine subjects were tested at about the time of putative

trough plasma concentrations of buprenorphine (approximately 20 hours after

the previous buprenorphine dose).

Procedure

Subjects were asked not to use any analgesics or illicit substances for twenty-four

hours prior to testing. A urine sample was collected on each study day for the

detection of opioids, benzodiazepines, sympathomimetic amines, cannabinoids and

barbiturates. Analysis of these samples confirmed that control subjects had not taken

any of these psychoactive substances. Subjects were excluded from the study if they

presented on study or screening days showing any signs of intoxication from any

substance.

Testing was conducted under constant ambient temperature (24L C) and constant

illumination (70 lux). Each session commenced at approximately 8 am and lasted 8

hours. Two indwelling catheters (Insyte Autoguard, Becton Dickenson, Sandy, Utah,

USA) were inserted into peripheral veins on opposite arms. The catheter in the

dominant arm served for drug infusion; the catheter in the non-dominant arm for

blood sampling. On each testing day, saline was infused at 2 ml/min for 30 min prior to morphine or saline administration for familiarisation.

Morphine administration

Morphine sulphate (David Bull Laboratories, Melbourne, Australia) infusions of 1 mg/ml were administered intravenously in two sixty-minute stages to achieve two consecutive target pseudo-steady-state plasma concentrations [11] using a syringe driver infusion pump (3100 Graseby Syringe Pump, Watford, Hertfordshire, UK). Buprenorphine subjects received an initial bolus of 15.2 mg of morphine sulphate followed by a constant infusion of 8.3 mg/hr for one hour to achieve a target pseudo steady-state plasma concentration of 80 ng/ml (Morphine 1). They were then administered an additional bolus of 15.2 mg of morphine sulphate followed by a constant infusion of 16.5 mg/hr for one hour to achieve the second target pseudo steady-state plasma concentration of 180 ng/ml (Morphine 2). The prescribed buprenorphine dose was administered 1 hour after infusions ceased. Control subjects were administered an initial bolus of 2.2 mg morphine sulphate followed by a constant infusion of 1.2 mg/hr for one hour to achieve a target pseudo steady-state plasma concentration of 11 ng/ml (Morphine 1). They were then administered 4.95 mg of morphine sulphate followed by a constant infusion of 3.6 mg/hr to achieve the second target pseudo steady-state plasma concentration of 33 ng/ml (Morphine 2) [11].

Blood sampling and assessment times

Seven millilitre blood samples were taken at the following times: prior to the thirty

minute saline familiarisation infusion, ten minutes prior to end of this infusion

(designated as baseline) and ten minutes prior to the end of each of the two

morphine or placebo saline infusions. Further blood samples were taken at 0.25,

0.5, 0.75, 1.0, 2.0, and 3 hours after the end of the last infusion. The blood samples

were centrifuged immediately and the plasma stored at –20 L C until assay.

Respiration rate was measured and nociceptive tests (see below) were

administered immediately after the collection of each blood sample except at 0.25,

0.50 and 0.75 hours after the last infusion.

Nociceptive tests, physiological responses and safety monitoring

Two nociceptive tests were administered: the cold pressor using the non-dominant

arm, and electrical stimulation using the earlobe. These tests have been described

previously [10]. Cold pressor involves the immersion of the non-dominant arm in

0.5–1.5 L C water and the response metric is seconds. Electrical stimulation

involves the transmission of an electrical pulse through the earlobe and is

measured in volts. One nociceptive marker was used which was pain tolerance,

when the participant verbally indicated that they could no longer tolerate the pain

and removed their arm from the water or requested that the electrical stimulation

cease.

Respiration rate was measured over one minute by observation without the

subjects' awareness. Safety was monitored and recorded throughout the study

by means of continuous pulse oximetry, continuous ECG waveform, categorical

nausea scale [21] and categorical sedation scale [22].

Plasma opioid quantification

The quantification of plasma buprenorphine and norbuprenorphine was by high performance liquid chromatography coupled to mass spectrometry as previously described [23]. The assay had a limit of quantification of 0.125 ng/ml for both analytes and all variability in accuracies and precision had coefficients of variation for buprenorphine and nor-buprenorphine of less than 15%. The quantification of plasma morphine was by high-performance liquid chromatography (HPLC) with coulometric detection as previously described [11]. The assay had a lower limit of quantification of 1 ng/ml and all variability in accuracies and precision had coefficients of variation below 7%.

Data analysis

Data are presented as mean ± SEM (with 95% confidence intervals (95% CI)). One-way ANOVA was used to compare outcome variables (cold pressor tolerance, electrical stimulation tolerance, respiration rate) between the buprenorphine dose groups. One-way ANOVA was also used to compare each outcome variable across treatments for the buprenorphine dose groups, combined buprenorphine subjects and the control subjects with 95% CI of differences. Unpaired samples t-tests were used to compare baseline values between the combined buprenorphine subjects and the control subjects. The Pearson product-moment correlation coefficient (Pearson's *r*) was used to measure the linear correlation between individual buprenorphine daily doses and plasma morphine concentrations. Bonferroni's and Dunnet's tests were used for post-hoc analyses as appropriate. Data for both studies were analysed using GraphPad Prism 4.2 for

Windows, GraphPad Software, San Diego, California, USA and P<0.05 was considered significant.

Results

Nociceptive tests

There were no significant differences (P>0.45) in pain tolerance responses between the three buprenorphine dose groups from baseline to morphine infusion 1 or morphine infusion 2. Hence, the data from the groups were combined.

Cold pressor responses

Pain tolerance responses at baseline and morphine infusion 2 for control subjects and the buprenorphine subjects are shown in Figure 1 (upper panel) and absolute values and ranges for all treatments in Table 1. Pain tolerance values for the buprenorphine subjects remained unchanged between baseline and the two morphine infusions. Pain tolerance values for the buprenorphine subjects were significantly lower than for control subjects at baseline (ANOVA P=0.009; 95% CI -5 to -30). Within group comparisons revealed that pain tolerance values for control subjects increased significantly (P=0.04) from baseline to morphine infusion 2 (P<0.05; 95% CI 2 to 34), but not baseline to morphine infusion 1 (P>0.05; 95% CI -12 to 20).

Electrical stimulation responses

Pain tolerance responses at baseline and morphine infusion 2 for control subjects and the buprenorphine subjects are shown in Figure 1 (middle panel) and absolute

values with ranges given in Table 1. Pain tolerance values for the buprenorphine

subjects were not significantly different to controls (ANOVA P=0.13) at baseline.

Within-group comparisons revealed that pain tolerance values for control subjects

increased significantly (P=0.007) from baseline to morphine infusion 2 (P<0.01;

95% CI 3 to 16), but not baseline to morphine infusion 1 (P>0.05; 95% CI -2.8 to

10). There was no significant change (P=0.98) in pain tolerance values for

combined buprenorphine subjects from baseline to morphine infusion 1 or

morphine infusion 2.

Respiration rates

Respiration rates (breaths per minute) relative to baseline and morphine infusion 2

are shown in Figure 1 (lower panel) and absolute values with ranges in Table 1.

Respiration rates for the buprenorphine subjects were significantly lower than for

control subjects at baseline (ANOVA P=0.03; 95% CI -0.25 to -4.9). Within group

comparisons revealed that the respiration rates for control subjects did not decrease

significantly (P=0.09) from baseline to morphine infusion 1 or morphine infusion 2.

Respiration rates for the buprenorphine subjects decreased significantly (ANOVA

P=0.006) from baseline to morphine infusion 2 (P<0.01; 95% CI -0.9 to -4.4) but not

morphine infusion 1 (P>0.05; 95% CI -2.8 to 10).

Buprenorphine dose group comparisons demonstrated significant changes in

respiration rates as follows. Group 2-8 mg daily: (ANOVA P=0.024) from baseline to

morphine infusion 1 (P<0.05; 95% CI -0.56 to -7.4) and baseline to morphine

infusion 2 (P<0.05; 95% CI -0.56 to - 7.4); group 9-15 mg daily: (ANOVA P=0.004)

between baseline and morphine infusion 2 (P<0.01; 95% CI –1.48 to-5.52), but not

morphine infusion 1 (P>0.05; 95% CI -2.02 to 2.02); group 16 to 22 mg daily: (ANOVA P=0.016) between both baseline and morphine infusion 1 (P<0.05; 95% CI -0.72 to -4.28) and baseline and morphine infusion 2 (P<0.05; 95% CI -0.22 to -3.78). There were no significant differences in respiration rate between the groups at baseline (P=0.90) or morphine infusion 2 (P=0.67). The lowest recorded respiration rates were ten breaths per minute in the control group and nine breaths per minute in the buprenorphine subjects.

Adverse events

There were no serious adverse events. Buprenorphine subjects did not experience nausea or vomiting, but seven control subjects required one dose of intramuscular metoclopramide hydrochloride 10 mg (Pfizer, Perth, Australia) with good effect for mild vomiting.

Plasma morphine, buprenorphine and norbuprenorphine concentrations

Pseudo steady-state plasma morphine concentrations for morphine 1 and 2 infusions are shown in Table 2A. Target pseudo steady-state plasma morphine concentration for the buprenorphine recipients were 80 ng/ml (Morphine 1) and 180 mg/ml (Morphine 2). Target pseudo steady-state plasma concentration for control subjects were 11 ng/ml (Morphine 1) and 33 mg/ml (Morphine 2). Pseudo state plasma morphine concentrations were lower than the desired target in both groups at morphine 1 and 2. Plasma morphine concentrations are also shown for the individual daily buprenorphine dose groups 2-8, 9-15 and 16-22 mg/day. There was no significant correlation (p=0.08) between individual buprenorphine doses and

plasma morphine concentrations at morphine infusion 1. However, there was a

significant inverse relationship between individual buprenorphine doses and plasma

morphine concentrations at morphine infusion 2 (Pearson's r =-0.74, p=0.006; slope

95% CI - 0.92 to -0.28).

There were no significant differences between combined mean plasma

buprenorphine concentrations (Table 2B), or for the three dose groups, at baseline

(P=0.64), morphine infusion 1 (P=0.71) or morphine infusion 2 (P=0.51). Likewise,

there were no significant differences between combined mean plasma

norbuprenorphine concentrations (Table 2C), or for the three dose groups, at

baseline, morphine infusion 1 or morphine infusion 2. At baseline on the saline

administration day, plasma buprenorphine and norbuprenorphine concentrations

were correlated to the buprenorphine dose (r^2=0.36 and 0.58, respectively;

Supplementary Tables 3A, 3B).

Discussion

To our knowledge, this is the first study to have examined the effect of added

morphine to buprenorphine OST subjects who were pain-free at the time of study,

using an experiment pain model. Buprenorphine subjects were hyperalgesic in the

cold pressor test in comparison with controls. Very high doses of morphine (55 mg)

produced high plasma concentrations (92 to 201 ng/ml) that failed to provide

antinociception in either the electrical stimulation or cold pressor tests, irrespective

of maintenance buprenorphine dose. In contrast, in control subjects, considerably

lower morphine doses (12 mg), achieving much lower concentrations (19 to 32

ng/ml), provided antinociception in both tests.

Our choice of using the cold pressor response to study opioid induced-hyperalgesia has been validated by others. Compton et al [13] examined hyperalgesia in opioid dependent subjects and found that these subjects, prior to induction and following stabilisation on either methadone or buprenorphine, were similarly hyperalgesic in the cold pressor test and did not exhibit hyperalgesia in the electrical stimulation test. Krishnan et al [12] compared the detection of hyperalgesia in opioid-substitution subjects maintained either on methadone or buprenorphine and healthy controls using the following pain stimuli: cold pain, electrical stimulation, mechanical pressure, and ischemic pain. They found that cold pain was the most suitable of the methods tested to detect opioid-induced hyperalgesia.

While the buprenorphine maintained subjects were tolerant to the antinociceptive effects of the high doses of morphine and plasma concentrations to which they were exposed, complete cross-tolerance to the respiratory depressant effects of morphine did not occur. Respiration rates dropped significantly across all dose groups, but by a limited amount (approximately 1.5 breaths per minute), which may not be clinically significant. In healthy volunteer subjects who received a single intravenous dose (0.2 mg/kg) of morphine, over a plasma concentration range (approximating 3-13 ng/mL) that produced a systematic increase in analgesia, morphine produced significant respiratory depression [24]. In contrast, in healthy adult volunteers who had experience with opioids but who were not physically dependent on opioids, Walsh and co-workers [18] demonstrated that respiratory depression increased with single buprenorphine single doses over a range of 1 to 4

mg (approximately 4 breaths per minute decrease), but that this dose effect began

to plateau at higher doses, with no difference between a 16 and 32 mg dose. In the

present study, with subjects chronically maintained on buprenorphine, high doses

of added morphine had a limited respiratory depressant effect at all buprenorphine

doses. It is, however, possible that higher doses of morphine might produce

respiratory depression if such doses are needed to achieve anti-nociception, given

that the lowest respiratory rate recorded was nine breaths per minute. Macintyre et

al [25] showed increased sedation score (a surrogate for respiratory depression) in

buprenorphine-maintained patients who received higher doses of morphine

equivalents following surgery than in this study.

Hyperalgesia is likely to be present, to a lesser or greater degree, in opioid

recipients for whatever indication. Non-cancer pain patients, maintained on either

methadone or slow release oral morphine for the treatment of that pain, were

shown to exhibit hyperalgesia in the cold pressor test [8], similar to that seen in

methadone [13] and buprenorphine subjects (this study) in opioid substitution

programs. Chakrabarti et al [26] (2010) found that people with a greater reported

experience of pain prior to induction onto buprenorphine maintenance required

greater daily doses. The present study found that there was no difference in the

degree of hyperalgesia experienced at baseline between the three dose ranges.

There was also no difference between the three dose ranges in terms of cross-

tolerance to the antinociceptive effects of very high dose morphine.

The most widely used drugs in opioid substitution programmes worldwide are

methadone and buprenorphine, with the latter gaining increasing prominence.

Methadone maintained subjects were examined under conditions identical [13] to those for the buprenorphine subjects in this study. The cold pressor test at baseline revealed that the combined methadone subjects were similarly hyperalgesic to the combined buprenorphine subjects. Furthermore, both groups were cross-tolerant to the antinociceptive effects of very high plasma morphine concentrations and both groups experienced similar decreases in respiration rate with the addition of very high plasma morphine concentrations. While buprenorphine has been used increasingly across the world because of its purported limited effect on respiratory depression and greater safety profile than other opioids such as morphine and methadone [17, 27, 28], our findings suggest that supplementary opioids for the management of pain in subjects in opioid substitution programs should be added cautiously under adequate supervision to avoid clinically significant respiratory depression.

Koppert et al [20], in a mechanical hyperalgesia model found that acutely, buprenorphine had a pronounced antihyperalgesic effect and suggested this may have clinical advantages in the management of chronic pain. In observational studies of chronic pain patients who were switched from high dose full opioid agonists to sublingual buprenorphine, [29, 30], the switch resulted in meaningful reduction in pain scores. Buprenorphine was more effective than full opioid agonists. The authors postulated that these findings may have resulted from buprenorphine's antihyperalgesic action [29]. However, Ravn and coworkers [31], using a multimodal testing technique, could not demonstrate any significant differences between morphine and buprenorphine in the profiles of antihyperalgesia and analgesia in healthy volunteers. The present study shows

that buprenorphine, a partial mu opioid receptor agonist and kappa receptor

antagonist, when used as a maintenance agent, produces similar respiratory

depression and hyperalgesia to methadone (a mu opioid receptor agonist) in

opioid maintained subjects tested under the same experimental conditions [13].

These results suggest that, at the buprenorphine doses to which our subjects

were exposed, antihyperalgesia could not be demonstrated with the cold pressor

test.

Macintyre and colleagues [25] examined retrospectively pain relief and opioid

requirements in the first 24 hours after surgery in patients taking buprenorphine

(dose range was similar to that in the present study) and methadone as OST.

Outcomes in the two patient groups were similar. The post-operative 24-hour

analgesia requirement, provided as patient controlled analgesia, was defined as

morphine dose equivalents. Buprenorphine maintained patients required an

average of 200 mg; methadone maintained patients required 221 mg. Pain

scores were similar across both groups. Sedation scores of 2 or greater occurred

in 22.7% and 24.1% of buprenorphine and methadone maintained patients

respectively. This important clinical study was not designed to determine

possible mechanisms for the outcomes. Our findings, in an experimental setting

in OST pain-free patients, complement the findings of this clinical study: very

large morphine equivalent doses result in insignificant analgesia and the

development of respiratory depression, albeit small, given the relatively small

(compared to the PCA doses in the clinical study) dose of morphine provided to

our subjects. Our findings strongly suggest that hyperalgesia is a likely

mechanism for the findings of Macintyre and colleagues [25], in addition to

tolerance. It is pertinent that buprenorphine and methadone maintained patients behaved almost identically, suggesting that buprenorphine had no antihyperalgesic properties.

We measured plasma concentrations of morphine, buprenorphine and norbuprenorphine to more accurately assess the extent of exposure by the subject to these analytes, rather than relying simply on the given doses. While there were no significant differences between plasma buprenorphine concentrations for the three dose groups at baseline, there was considerable variability in the range of concentrations. Hyperalgesia occurred across the whole range of plasma concentrations. The lowest individual plasma buprenorphine concentration was 0.16 ng/ml (in the 2-8 mg/day dose group).

Transdermal buprenorphine patches are increasingly used for the management of chronic pain. In Australia, they are available in various strengths, ranging from 10-40 mg, which deliver 10 to 40 ug/h and are generally applied once a week, likely for prolonged periods. When 10 ug/h patches were administered to healthy volunteers once a week for 3 doses the average plasma concentrations were between 0.155 and 0.172 ng/ml across the 3 periods [32]; 20 ug/h patches administered to healthy volunteers as a single dose yielded mean maximum plateau plasma concentrations of about 0.25 ng/ml between 48 and 96 hours after application [33]; single applications of 35 and 70 ug/h patches yielded mean maximum plasma concentrations of 0.31 and 0.62 ng/ml respectively [34]. These values fall within the range of plasma concentrations described in the present study that were associated with hyperalgesia. Thus, it would be reasonable to

assume that some patients receiving buprenorphine for the management of chronic pain could be hyperalgesic. Kress [34] reviewed several trials/reports of the efficacy of transdermal buprenorphine (varying doses) in patients with cancer and noncancer pain with the minimum duration of observation of three months. In most of the studies, satisfactory pain relief occurred in at least 50% of subjects, suggesting that hyperalgesia may not be universal in patients suffering from pain rather than those who receive opioids as substitution treatment.

There are several limitations to this study. The sample size is small and not driven by a formal power calculation. However, we based our population size on the results of Doverty et al [11], who showed highly significant differences in cold pressor tolerance between 16 healthy controls (n=16) and 16 methadone maintenance subjects. Despite the smaller sample size in this study, significant differences were seen between buprenorphine recipients and the controls. Plasma buprenorphine concentrations were measured only at the putative peak. However, given the long half-life of buprenorphine and that the subjects would have been at steady state, we considered the sampling regimen justified.

What might be the best strategy to improve pain relief in buprenorphine maintained patients who experience acute pain, such as following surgery or trauma? Reviews from Huxtable et al [6] and Schug et al [5] state that in the clinical setting, for the opioid maintained population, opioid dose should be increased until analgesia is achieved or sedation occurs and that the dose of the maintenance opioid should be continued without interruption [25]. The purpose of this study was to provide the evidence for opioid dose escalation that would provide antinociception without

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respiratory depression in the buprenorphine maintained population. This study

demonstrates that buprenorphine maintained subjects are hyperalgesic at baseline

and that very high morphine doses result in limited respiratory depression, but not

antinociception. There is a need to explore alternative strategies for providing acute

pain relief in buprenorphine (and methadone) maintained patients. For example,

Huxtable [6] and Schug et al [5] recommend that an adjuvant analgesic alone, or in

combination with morphine, may overcome the limitations of cross-tolerance and

side effects to provide pain management in the buprenorphine and methadone

maintained population.

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Figure Legend

Figure 1. Cold pressor pain tolerance responses (upper panel), electrical stimulation

pain tolerance responses (middle panel) and respiration rate (lower panel) mean (±

SEM) pain in 10 healthy control and 12 buprenorphine subjects at baseline (B) and

morphine infusion 2 (M2). † $P<0.05$; †† $P<0.01$ between groups; * $P<0.05$; ** $P<0.01$

between treatments. Note: different morphine concentrations between buprenorphine

and control subjects.

Table 1. Cold pressor and electrical stimulation responses, and respiration rates for 12 buprenorphine maintained and 10 control subjects on morphine administration days.

Response	Group	Baseline	Morphine 1[1]	Morphine 2[2]
Cold Pressor (seconds)	Control	34±6††	38±7	52±11*
		(4 to 73)	(5 to 64)	(7 to 23)
	Combined	17±2	17±2	17±2
	Buprenorphine[3]	(9 to 18)	(4 to 29)	(4 to 27)
Electrical Stimulation (volts)	Control	65±6	68±5	74±5**
		(38 to 100)	(48 to 100)	(60 to 100)
	Combined	53±5	53±4	53±5
	Buprenorphine[3]	(24 to 92)	(24 to 72)	(34 to 96)
Respiration Rate (breaths per minute)	Control	17	16.5	15
		(14 to 22)	(13 to 19)	(10 to 19)
	Combined	14†	12.5	12**
	Buprenorphine[3]	(9 to 20)	(12 to 17)	(9 to 15)
	2-8 mg (P=0.024)[4]	15.5±1.6	11.5±0.9*	11.5±1.3*
		(13-20)	(10-13)	(9-15)

9-15 mg (P=0.004)[4]	15±1.2	15±1.1	11.5±0.6**
	(12-17)	(12-17)	(10-13)
16-22 mg (P=0.016)[4]	14.8±0.5	12.3±0.6*	12.8±1.3*
	(14-16)	(11-14)	(10-16)

[1] For buprenorphine maintained subjects Morphine 1 was initial 15.2 mg bolus of morphine sulphate followed by 8.3 mg/hr constant infusion for one hour. [2]Morphine 2 was 15.2 mg bolus of morphine sulphate followed by 16.5 mg constant infusion for one hour. For controls Morphine 1 was initial bolus of 2.2 mg morphine sulphate followed by 1.2 mg/hr constant infusion for one hour. Morphine 2 was 4.95 bolus of morphine sulphate followed by constant infusion of 3.6 mg/hr for one hour. Data for the nociceptive responses are mean±SEM (range) and for respiration rates median (range). [3]The results for the three buprenorphine dose groups are combined.

[4]ANOVA P values comparing baseline to Morphine 1 and Morphine 2.

† P<0.05, †† P<0.01 buprenorphine versus control; * P<0.05, ** P<0.01 morphine 2 versus control.

Table 2A. Plasma morphine concentrations (ng/ml) on morphine administration days in 12

buprenorphine maintained and 10 healthy control subjects**.**

	Morphine 1	**Morphine 2**
Control Subjects	7.0±0.4	23±1
All buprenorphine Subjects	62±4 (42 to 87)	136±10 (92 to 201)
Buprenorphine Subjects 2-8 mg/day	70±8 (49 to 91)	175±15 (119 to 201)
Buprenorphine Subjects 9-15 mg/day	60±4 (48 to 71)	129±9 (48 to 108)
Buprenorphine Subjects 16-22 mg/day	57±4 (52 to 71)	109±8 (92 to 129)

The infusion regimens for buprenorphine maintained subjects and healthy control subjects on

Morphine 1 and Morphine 2 days are described in the methods. Data are mean±SEM (range).

Table 2B. Plasma buprenorphine concentrations (ng/ml) at baseline and on morphine

administration days in 12 buprenorphine maintained subjects.

	Baseline	**Morphine 1**	**Morphine 2**
All Buprenorphine Subjects	1.2±0.3 (0.23 to 3.3)	0.95±0.19 (0.16 to 0.23)	1.03±0.23 (0.16 to 3.0)
Buprenorphine Subjects 2-8 mg/day	0.71±0.23 (0.42 to 1.17)	0.46±0.12 (0.16 to 0.76)	0.45±0.10 (0.16 to 0.58)
Buprenorphine Subjects 9-15 mg/day	1.45±0.45 (0.21 to 2.20)	1.14±0.36 (0.90 to 1.75)	1.40±0.53 (0.26 to 2.7)
Buprenorphine Subjects 16-22 mg/day	1.17±0.28 (0.8 to 1.98)	1.23±0.24 (0.79 to 1.79)	1.33±0.22 (0.79 to1.87)

The morphine infusion regimens on Morphine 1 and Morphine 2 days are described in

the methods. Data are mean±SEM (range).

Table 2C. Plasma norbuprenorphine concentrations (ng/ml) at baseline and on morphine

administration days in 12 buprenorphine maintained subjects.

	Baseline	**Morphine 1**	**Morphine 2**
All Buprenorphine Subjects	1.7±0.3 (0.30-3.62)	1.61±0.33 (0.31-3.72)	1.85±0.40 (0.34-3.53)

The morphine infusion regimens on Morphine 1 and Morphine 2 days are described in

the methods. Data are mean±SEM (range).

Cold Pressor

Electrical Stimulation

Respiration Rate
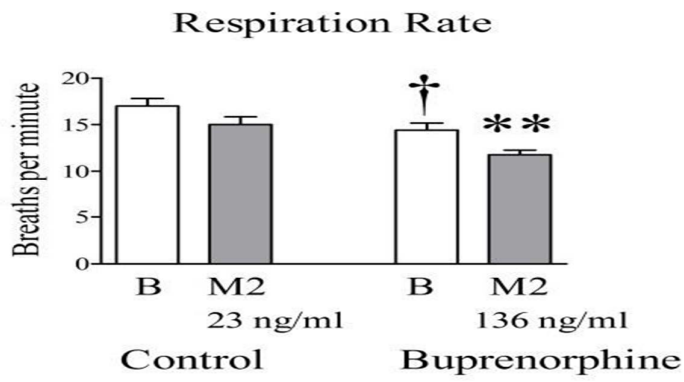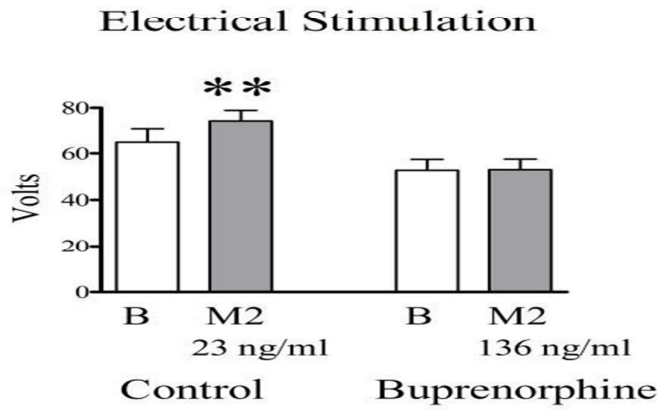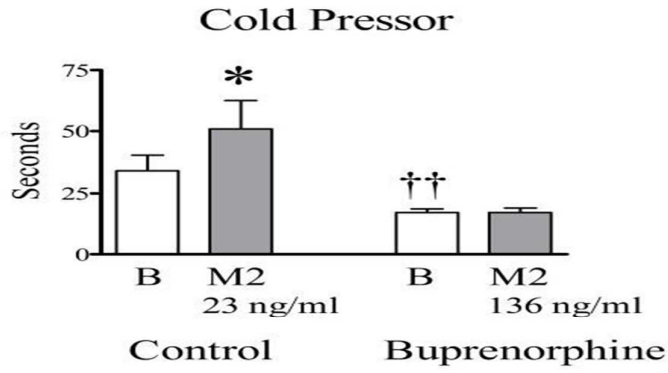
Supplementary Table. Plasma concentrations of buprenorphine (A) and norbuprenorphine (B) in 12 buprenorphine maintained subjects on saline infusion days.

A. Plasma buprenorphine (ng/ml)

	Baseline	Saline 1	Saline 2
All Buprenorphine Subjects	1.2±0.3	1.01±0.26	1.18±0.29
Buprenorphine Subjects 2-8 mg/day	0.38±0.10 (0.15 to 0.64)	0.30±0.006 (0.15 to	0.33±0.08 (0.15 to
Buprenorphine Subjects 9-15 mg/day	1.59±0.68 (0.23 to 3.30)	1.16±0.46 (0.24 to	1.3±0.6 (0.19 to
Buprenorphine Subjects 16-22 mg/day	1.84±0.76 (0.69 to 4.07)	1.6±0.59 (0.61 to 3.31)	1.81±0.53 (0.63 to 3.03)

The infusion regimens are described in the methods. Data are mean±SEM (range).

B. Plasma Norbuprenorphine (ng/ml)

	Baseline	Saline 1	Saline 2
All Buprenorphine	1.78±0.34	1.68±0.3	1.93±0.42
Subjects	(0.29-3.9)	(0.29-3.4)	(0.24-4.7)

The infusion regimens are described in the methods. Data are mean±SEM (range).

Buprenorphine maintenance subjects are hyperalgesic and have no

antinociceptive response to a very high morphine dose

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Running Title: Buprenorphine, hyperalgesia, antinociception, maintenance subjects

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Abstract

Objective. Acute pain management in opioid dependent persons is complicated because of tolerance and opioid-induced-hyperalgesia. Very high doses of morphine are ineffective in overcoming opioid-induced-hyperalgesia and providing antinociception to methadone maintained patients in an experimental setting. Whether the same occurs in buprenorphine maintained subjects is unknown.

Design. Randomised double blind placebo controlled. Subjects were tested on two occasions, at least five days apart; once with intravenous morphine and once with intravenous saline. Subjects were tested at about the time of putative trough plasma buprenorphine concentrations.

Setting. Ambulatory.

Subjects. Twelve buprenorphine maintained subjects: once daily sublingual dose (range 2-22 mg); no dose change for 1.5-12 months. Ten healthy controls.

Methods. Intravenous morphine bolus and infusions administered over 2 hours to achieve two separate pseudo-steady state plasma concentrations one hour apart. Pain tolerance assessed by application of nociceptive stimuli (cold pressor (seconds) and electrical stimulation (volts)). Ten blood samples collected for assay of plasma morphine, buprenorphine and norbuprenorphine concentrations until 3 hours after the end of last infusion; pain tolerance and respiration rate measured to coincide with blood sampling times.

Results. Cold pressor responses (seconds): baseline: control 34±6 versus

buprenorphine 17±2 (P=0.009); morphine infusion-end: control 52±11(P=0.04),

buprenorphine 17±2 (P>0.5); electrical stimulation responses (volts): baseline:

control 65±6 versus buprenorphine 53±5 (P=0.13); infusion-end: control 74±5

(P=0.007), buprenorphine 53±5 (P>0.98). Respiratory rate (breaths per minute):

baseline: control 17 versus buprenorphine 14 (P=0.03); infusion-end: control 15

(P=0.09), buprenorphine 12 (P<0.01). Infusion-end plasma morphine concentrations

(ng/mL): control 23±1, buprenorphine 136±10.

Conclusions. Buprenorphine subjects, compared with controls, were: hyperalgesic

(cold pressor test); did not experience antinociception, despite high plasma morphine

concentrations; experienced respiratory depression. Clinical implications are

discussed.

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Introduction

The prevalence of opioid dependence is growing worldwide. Dependence has traditionally been the result of illicit opioid abuse. However, it is increasingly associated with legally prescribed long-term use of opioids for the management of chronic pain [1]. Between 28 and 38.5 million people abuse opioids worldwide. In 2015, 2 million had a substance use disorder involving prescription pain relievers and 591,000 had a substance use disorder involving heroin [2]. Approximately 1% of the Australian population is opioid dependent and half of these are in opioid substitution treatment (OST) programs [3]. Of these, two-thirds receive methadone and one third buprenorphine (alone or with naloxone) but this difference is declining.

The management of acute pain in opioid dependent patients is complicated because of two major factors: tolerance, which can generally be overcome by dose increase but may be compromised by adverse effects, and the under recognized phenomenon of opioid-induced-hyperalgesia (OIH) characterized as paradoxical pain sensitization [4] which cannot be overcome by dose increase. Although there are no formal guidelines for the clinician, Macintyre et al [5] and Huxtable et al [6] advise, that in the clinical setting, the daily OST dose should be maintained and additional opioid used for acute pain management, titrated until satisfactory analgesia is achieved or an adverse effect (e.g. sedation or respiratory depression) occurs. Such an approach requires stringent observation such as admission to hospital.

Opioid-induced hyperalgesia occurs in opioid (e.g. heroin) addicted subjects prior to entry into methadone and buprenorphine treatments [7], chronic non-cancer pain

patients [8], and slow release morphine, methadone and buprenorphine maintained

subjects [9, 10, 11, 12]. Clinically used and very high doses of morphine are

ineffective in overcoming OIH and providing antinociception to methadone

maintained patients [11, 13] in an experimental setting. Whether the same occurs in

buprenorphine maintained subjects is unknown.

Buprenorphine, a semi-synthetic 4,5-epoxymorphinan opioid shows partial agonist

properties for some responses at the mu opioid receptor and variable effects at

the kappa and delta receptors [14]. Its major metabolite norbuprenorphine is also

active [15], although there is conjecture whether it crosses the blood-brain barrier

[16]. Opioid agonists such as morphine, over plasma concentration ranges that

produce dose-related increases in analgesia, also produce concentration-

dependent respiratory depression without any plateau in healthy human

volunteers [17]. In contrast, buprenorphine shows dose-dependent increases in

analgesia with a limited extent of respiratory depression [17, 18]. As a partial

agonist, under appropriate conditions, buprenorphine may act as an agonist or

antagonist at opioid receptors [19] and has shown antihyperalgesic effects in

healthy subjects using a model of intradermal electric stimulation [20]. Therefore,

buprenorphine may be unique in its ability to treat acute pain and possibly

attenuate OIH.

Previously we showed that methadone maintained subjects on doses of 2-120 mg

per day, under identical experimental conditions that will be described in this study,

experienced no antinociception with 55 mg of intravenous morphine but showed a

significant reduction in respiratory rate [13]. To date, no studies have examined the

effect of different daily buprenorphine doses on the antinociceptive and respiratory

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responses to morphine.

The aims of the study in buprenorphine maintained subjects were to: 1. Confirm the presence of OIH; 2. Ascertain whether very high intravenous morphine doses produce antinociceptive and respiratory depression effects and 3. Determine any relationship between buprenorphine dose and these effects. Our hypothesis is that buprenorphine maintained subjects are hyperalgesic and, that in contrast to methadone maintained subjects, experience antinociception with high morphine doses.

Methods

Ethics

The Research Ethics Committee of the Royal Adelaide Hospital, Adelaide, South Australia, Australia (RAH Protocol no: 010222) and the Institutional Review Board, Friends Research Institute, Los Angeles, California, USA (FRI IRB no: 00-03-057-02) approved the study. Both bodies adhere to the ethical standards set by the Helsinki Declaration (2008). The study was supported by National Institutes of Drug Abuse (NIDA) grant R01 DA 13706-02. This study was not registered on clinicaltrials.gov as this study was carried out before the requirement for registration. Subjects provided written informed consent, were paid for their involvement in the study and were free to withdraw at any time.

Subjects

Twelve pain-free buprenorphine maintained subjects comprising 7 men and 5 women with ages between 24 and 42 years (mean 35 years) were recruited. Their

weights ranged between 49 and 97 kg (mean 71 kg). They had been receiving

sublingual buprenorphine (Subutex ® Reckitt Benckiser, West Ryde, New South

Wales, Australia) for between 1.5 and 12 months (mean 4 months) with no dose

change. They had been enrolled in a buprenorphine maintenance program for a

period ranging between 2 and 22 months with a mean of 10 months. The group

was stratified according to prescribed and efficacious maintenance dose, with four

subjects in each of the dose ranges of 2 to 8 mg, 9 to 15 mg and 16 to 22 mg per

day. Subjects were recruited if they self-reported intravenous heroin use at least

once in the previous month. It was considered more ethical to administer morphine

to individuals who continued to use illicit heroin, rather than to those who used no

opioids, apart from their prescribed buprenorphine. Ten healthy control subjects (5

men and 5 women; aged between 21 and 41(mean 31) years); weight 59 and 102

(mean 80) kg) were selected. These subjects were not taking any prescribed

medications. They have been described previously [13].

Exclusion criteria

Exclusion criteria for all subjects included pregnancy or lactation, use of

antiretroviral drugs, significant medical or psychiatric illness that required ongoing

treatment (except opioid addiction for buprenorphine subjects), daily alcohol

consumption exceeding 40 g for men and 20 g for women, severe liver impairment

(serum aspartate aminotransferase and alanine aminotransferase concentrations

greater than 3 times the upper limit of normal range and albumin concentrations

less than 33 grams per litre) or haemoglobin counts outside the normal range.

Healthy control subjects were excluded if they had any personal or family history of

addictive behaviours.

Study design

The study utilized a double blind placebo controlled design with four groups of

subjects (healthy controls, once daily buprenorphine dose of 2 to 8, 9 to 15 and,

16 to 22 mg). Subjects were tested on two occasions, at least five days apart;

once with morphine and once with saline. The order of administration was

randomised. Buprenorphine subjects were tested at about the time of putative

trough plasma concentrations of buprenorphine (approximately 20 hours after

the previous buprenorphine dose).

Procedure

Subjects were asked not to use any analgesics or illicit substances for twenty-four

hours prior to testing. A urine sample was collected on each study day for the

detection of opioids, benzodiazepines, sympathomimetic amines, cannabinoids and

barbiturates. Analysis of these samples confirmed that control subjects had not taken

any of these psychoactive substances. Subjects were excluded from the study if they

presented on study or screening days showing any signs of intoxication from any

substance.

Testing was conducted under constant ambient temperature (24L C) and constant

illumination (70 lux). Each session commenced at approximately 8 am and lasted 8

hours. Two indwelling catheters (Insyte Autoguard, Becton Dickenson, Sandy, Utah,

USA) were inserted into peripheral veins on opposite arms. The catheter in the

dominant arm served for drug infusion; the catheter in the non-dominant arm for

blood sampling. On each testing day, saline was infused at 2 ml/min for 30 min prior to morphine or saline administration for familiarisation.

Morphine administration

Morphine sulphate (David Bull Laboratories, Melbourne, Australia) infusions of 1 mg/ml were administered intravenously in two sixty-minute stages to achieve two consecutive target pseudo-steady-state plasma concentrations [11] using a syringe driver infusion pump (3100 Graseby Syringe Pump, Watford, Hertfordshire, UK). Buprenorphine subjects received an initial bolus of 15.2 mg of morphine sulphate followed by a constant infusion of 8.3 mg/hr for one hour to achieve a target pseudo steady-state plasma concentration of 80 ng/ml (Morphine 1). They were then administered an additional bolus of 15.2 mg of morphine sulphate followed by a constant infusion of 16.5 mg/hr for one hour to achieve the second target pseudo steady-state plasma concentration of 180 ng/ml (Morphine 2). The prescribed buprenorphine dose was administered 1 hour after infusions ceased. Control subjects were administered an initial bolus of 2.2 mg morphine sulphate followed by a constant infusion of 1.2 mg/hr for one hour to achieve a target pseudo steady-state plasma concentration of 11 ng/ml (Morphine 1). They were then administered 4.95 mg of morphine sulphate followed by a constant infusion of 3.6 mg/hr to achieve the second target pseudo steady-state plasma concentration of 33 ng/ml (Morphine 2) [11].

Blood sampling and assessment times

Seven millilitre blood samples were taken at the following times: prior to the thirty

minute saline familiarisation infusion, ten minutes prior to end of this infusion

(designated as baseline) and ten minutes prior to the end of each of the two

morphine or placebo saline infusions. Further blood samples were taken at 0.25,

0.5, 0.75, 1.0, 2.0, and 3 hours after the end of the last infusion. The blood samples

were centrifuged immediately and the plasma stored at –20 L C until assay.

Respiration rate was measured and nociceptive tests (see below) were

administered immediately after the collection of each blood sample except at 0.25,

0.50 and 0.75 hours after the last infusion.

Nociceptive tests, physiological responses and safety monitoring

Two nociceptive tests were administered: the cold pressor using the non-dominant

arm, and electrical stimulation using the earlobe. These tests have been described

previously [10]. Cold pressor involves the immersion of the non-dominant arm in

0.5–1.5 L C water and the response metric is seconds. Electrical stimulation

involves the transmission of an electrical pulse through the earlobe and is

measured in volts. One nociceptive marker was used which was pain tolerance,

when the participant verbally indicated that they could no longer tolerate the pain

and removed their arm from the water or requested that the electrical stimulation

cease.

Respiration rate was measured over one minute by observation without the

subjects' awareness. Safety was monitored and recorded throughout the study

by means of continuous pulse oximetry, continuous ECG waveform, categorical

nausea scale [21] and categorical sedation scale [22].

Plasma opioid quantification

The quantification of plasma buprenorphine and norbuprenorphine was by high performance liquid chromatography coupled to mass spectrometry as previously described [23]. The assay had a limit of quantification of 0.125 ng/ml for both analytes and all variability in accuracies and precision had coefficients of variation for buprenorphine and nor-buprenorphine of less than 15%. The quantification of plasma morphine was by high-performance liquid chromatography (HPLC) with coulometric detection as previously described [11]. The assay had a lower limit of quantification of 1 ng/ml and all variability in accuracies and precision had coefficients of variation below 7%.

Data analysis

Data are presented as mean ± SEM (with 95% confidence intervals (95% CI)). One-way ANOVA was used to compare outcome variables (cold pressor tolerance, electrical stimulation tolerance, respiration rate) between the buprenorphine dose groups. One-way ANOVA was used to compare each outcome variable across treatments for the buprenorphine dose groups, combined buprenorphine subjects and the control subjects with 95% CI of differences. Unpaired samples t-tests were used to compare baseline values between the combined buprenorphine subjects and the control subjects. The Pearson product-moment correlation coefficient (Pearson's *r*) was used to measure the linear correlation between individual buprenorphine daily doses and plasma morphine concentrations. Bonferroni's and Dunnet's tests were used for post-hoc analyses as appropriate. Data for both studies were analysed using GraphPad Prism 4.2 for

Windows, GraphPad Software, San Diego, California, USA and P<0.05 was

considered significant.

Results

Nociceptive tests

There were no significant differences (P>0.45) in pain tolerance responses between

the three buprenorphine dose groups from baseline to morphine infusion 1 or

morphine infusion 2. Hence, the data from the groups were combined.

Cold pressor responses

Pain tolerance responses at baseline and morphine infusion 2 for control subjects

and the buprenorphine subjects are shown in Figure 1 (upper panel) and absolute

values and ranges for all treatments in Table 1. Pain tolerance values for the

buprenorphine subjects remained unchanged between baseline and the two

morphine infusions. Pain tolerance values for the buprenorphine subjects were

significantly lower than for control subjects at baseline (ANOVA P=0.009; 95% CI -

5 to -30). Within group comparisons revealed that pain tolerance values for control

subjects increased significantly (P=0.04) from baseline to morphine infusion 2

(P<0.05; 95% CI 2 to 34), but not baseline to morphine infusion 1 (P>0.05; 95% CI

-12 to 20).

Electrical stimulation responses

Pain tolerance responses at baseline and morphine infusion 2 for control subjects

and the buprenorphine subjects are shown in Figure 1 (middle panel) and absolute

values with ranges given in Table 1. Pain tolerance values for the buprenorphine

subjects were not significantly different to controls (ANOVA P=0.13) at baseline.

Within-group comparisons revealed that pain tolerance values for control subjects

increased significantly (P=0.007) from baseline to morphine infusion 2 (P<0.01;

95% CI 3 to 16), but not baseline to morphine infusion 1 (P>0.05; 95% CI -2.8 to

10). There was no significant change (P=0.98) in pain tolerance values for

combined buprenorphine subjects from baseline to morphine infusion 1 or

morphine infusion 2.

Respiration rates

Respiration rates (breaths per minute) relative to baseline and morphine infusion 2

are shown in Figure 1 (lower panel) and absolute values with ranges in Table 1.

Respiration rates for the buprenorphine subjects were significantly lower than for

control subjects at baseline (ANOVA P=0.03; 95% CI -0.25 to -4.9). Within group

comparisons revealed that the respiration rates for control subjects did not decrease

significantly (P=0.09) from baseline to morphine infusion 1 or morphine infusion 2.

Respiration rates for the buprenorphine subjects decreased significantly (ANOVA

P=0.006) from baseline to morphine infusion 2 (P<0.01; 95% CI -0.9 to -4.4) but not

morphine infusion 1 (P>0.05; 95% CI -2.8 to 10).

Buprenorphine dose group comparisons demonstrated significant changes in

respiration rates as follows. Group 2-8 mg daily: (ANOVA P=0.024) from baseline to

morphine infusion 1 (P<0.05; 95% CI -0.56 to -7.4) and baseline to morphine

infusion 2 (P<0.05; 95% CI -0.56 to - 7.4); group 9-15 mg daily: (ANOVA P=0.004)

between baseline and morphine infusion 2 (P<0.01; 95% CI –1.48 to-5.52), but not

morphine infusion 1 (P>0.05; 95% CI -2.02 to 2.02); group 16 to 22 mg daily: (ANOVA P=0.016) between both baseline and morphine infusion 1 (P<0.05; 95% CI -0.72 to -4.28) and baseline and morphine infusion 2 (P<0.05; 95% CI -0.22 to -3.78). There were no significant differences in respiration rate between the groups at baseline (P=0.90) or morphine infusion 2 (P=0.67). The lowest recorded respiration rates were ten breaths per minute in the control group and nine breaths per minute in the buprenorphine subjects.

Adverse events

There were no serious adverse events. Buprenorphine subjects did not experience nausea or vomiting, but seven control subjects required one dose of intramuscular metoclopramide hydrochloride 10 mg (Pfizer, Perth, Australia) with good effect for mild vomiting.

Plasma morphine, buprenorphine and norbuprenorphine concentrations

Pseudo steady-state plasma morphine concentrations for morphine 1 and 2 infusions are shown in Table 2A. Target pseudo steady-state plasma morphine concentration for the buprenorphine recipients were 80 ng/ml (Morphine 1) and 180 mg/ml (Morphine 2). Target pseudo steady-state plasma concentration for control subjects were 11 ng/ml (Morphine 1) and 33 mg/ml (Morphine 2). Pseudo state plasma morphine concentrations were lower than the desired target in both groups at morphine 1 and 2. Plasma morphine concentrations are also shown for the individual daily buprenorphine dose groups 2-8, 9-15 and 16-22 mg/day. There was no significant correlation (p=0.08) between individual buprenorphine doses and

plasma morphine concentrations at morphine infusion 1. However, there was a

significant inverse relationship between individual buprenorphine doses and plasma

morphine concentrations at morphine infusion 2 (Pearson's r =-0.74, p=0.006; slope

95% CI - 0.92 to -0.28).

There were no significant differences between combined mean plasma

buprenorphine concentrations (Table 2B), or for the three dose groups, at baseline

(P=0.64), morphine infusion 1 (P=0.71) or morphine infusion 2 (P=0.51). Likewise,

there were no significant differences between combined mean plasma

norbuprenorphine concentrations (Table 2C), or for the three dose groups, at

baseline, morphine infusion 1 or morphine infusion 2. At baseline on the saline

administration day, plasma buprenorphine and norbuprenorphine concentrations

were correlated to the buprenorphine dose (r^2=0.36 and 0.58, respectively;

Supplementary Tables 3A, 3B).

Discussion

To our knowledge, this is the first study to have examined the effect of added

morphine to buprenorphine OST subjects who were pain-free at the time of study,

using an experiment pain model. Buprenorphine subjects were hyperalgesic in the

cold pressor test in comparison with controls. Very high doses of morphine (55 mg)

produced high plasma concentrations (92 to 201 ng/ml) that failed to provide

antinociception in either the electrical stimulation or cold pressor tests, irrespective

of maintenance buprenorphine dose. In contrast, in control subjects, considerably

lower morphine doses (12 mg), achieving much lower concentrations (19 to 32

16

ng/ml), provided antinociception in both tests.

Our choice of using the cold pressor response to study opioid induced-hyperalgesia has been validated by others. Compton et al [13] examined hyperalgesia in opioid dependent subjects and found that these subjects, prior to induction and following stabilisation on either methadone or buprenorphine, were similarly hyperalgesic in the cold pressor test and did not exhibit hyperalgesia in the electrical stimulation test. Krishnan et al [12] compared the detection of hyperalgesia in opioid-substitution subjects maintained either on methadone or buprenorphine and healthy controls using the following pain stimuli: cold pain, electrical stimulation, mechanical pressure, and ischemic pain. They found that cold pain was the most suitable of the methods tested to detect opioid-induced hyperalgesia.

While the buprenorphine maintained subjects were tolerant to the antinociceptive effects of the high doses of morphine and plasma concentrations to which they were exposed, complete cross-tolerance to the respiratory depressant effects of morphine did not occur. Respiration rates dropped significantly across all dose groups, but by a limited amount (approximately 1.5 breaths per minute), which may not be clinically significant. In healthy volunteer subjects who received a single intravenous dose (0.2 mg/kg) of morphine, over a plasma concentration range (approximating 3-13 ng/mL) that produced a systematic increase in analgesia, morphine produced significant respiratory depression [24]. In contrast, in healthy adult volunteers who had experience with opioids but who were not physically dependent on opioids, Walsh and co-workers [18] demonstrated that respiratory

depression increased with single buprenorphine single doses over a range of 1 to 4 mg (approximately 4 breaths per minute decrease), but that this dose effect began to plateau at higher doses, with no difference between a 16 and 32 mg dose. In the present study, with subjects chronically maintained on buprenorphine, high doses of added morphine had a limited respiratory depressant effect at all buprenorphine doses. It is, however, possible that higher doses of morphine might produce respiratory depression if such doses are needed to achieve anti-nociception, given that the lowest respiratory rate recorded was nine breaths per minute. Macintyre et al [25] showed increased sedation score (a surrogate for respiratory depression) in buprenorphine-maintained patients who received higher doses of morphine equivalents following surgery than in this study.

Hyperalgesia is likely to be present, to a lesser or greater degree, in opioid recipients for whatever indication. Non-cancer pain patients, maintained on either methadone or slow release oral morphine for the treatment of that pain, were shown to exhibit hyperalgesia in the cold pressor test [8], similar to that seen in methadone [13] and buprenorphine subjects (this study) in opioid substitution programs. Chakrabarti et al [26] (2010) found that people with a greater reported experience of pain prior to induction onto buprenorphine maintenance required greater daily doses. The present study found that there was no difference in the degree of hyperalgesia experienced at baseline between the three dose ranges. There was also no difference between the three dose ranges in terms of cross-tolerance to the antinociceptive effects of very high dose morphine.

The most widely used drugs in opioid substitution programmes worldwide are

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methadone and buprenorphine, with the latter gaining increasing prominence.

Methadone maintained subjects were examined under conditions identical [13] to

those for the buprenorphine subjects in this study. The cold pressor test at

baseline revealed that the combined methadone subjects were similarly

hyperalgesic to the combined buprenorphine subjects. Furthermore, both groups

were cross-tolerant to the antinociceptive effects of very high plasma morphine

concentrations and both groups experienced similar decreases in respiration rate

with the addition of very high plasma morphine concentrations. While

buprenorphine has been used increasingly across the world because of its

purported limited effect on respiratory depression and greater safety profile than

other opioids such as morphine and methadone [17, 27, 28], our findings suggest

that supplementary opioids for the management of pain in subjects in opioid

substitution programs should be added cautiously under adequate supervision to

avoid clinically significant respiratory depression.

Koppert et al [20], in a mechanical hyperalgesia model found that acutely,

buprenorphine had a pronounced antihyperalgesic effect and suggested this may

have clinical advantages in the management of chronic pain. In observational

studies of chronic pain patients who were switched from high dose full opioid

agonists to sublingual buprenorphine, [29, 30], the switch resulted in meaningful

reduction in pain scores. Buprenorphine was more effective than full opioid

agonists. The authors postulated that these findings may have resulted from

buprenorphine's antihyperalgesic action [29]. However, Ravn and coworkers [31],

using a multimodal testing technique, could not demonstrate any significant

differences between morphine and buprenorphine in the profiles of

antihyperalgesia and analgesia in healthy volunteers. The present study shows

that buprenorphine, a partial mu opioid receptor agonist and kappa receptor

antagonist, when used as a maintenance agent, produces similar respiratory

depression and hyperalgesia to methadone (a mu opioid receptor agonist) in

opioid maintained subjects tested under the same experimental conditions [13].

These results suggest that, at the buprenorphine doses to which our subjects

were exposed, antihyperalgesia could not be demonstrated with the cold pressor

test.

Macintyre and colleagues [25] examined retrospectively pain relief and opioid

requirements in the first 24 hours after surgery in patients taking buprenorphine

(dose range was similar to that in the present study) and methadone as OST.

Outcomes in the two patient groups were similar. The post-operative 24-hour

analgesia requirement, provided as patient controlled analgesia, was defined as

morphine dose equivalents. Buprenorphine maintained patients required an

average of 200 mg; methadone maintained patients required 221 mg. Pain

scores were similar across both groups. Sedation scores of 2 or greater occurred

in 22.7% and 24.1% of buprenorphine and methadone maintained patients

respectively. This important clinical study was not designed to determine

possible mechanisms for the outcomes. Our findings, in an experimental setting

in OST pain-free patients, complement the findings of this clinical study: very

large morphine equivalent doses result in insignificant analgesia and the

development of respiratory depression, albeit small, given the relatively small

(compared to the PCA doses in the clinical study) dose of morphine provided to

our subjects. Our findings strongly suggest that hyperalgesia is a likely

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mechanism for the findings of Macintyre and colleagues [25], in addition to

tolerance. It is pertinent that buprenorphine and methadone maintained patients

behaved almost identically, suggesting that buprenorphine had no

antihyperalgesic properties.

We measured plasma concentrations of morphine, buprenorphine and

norbuprenorphine to more accurately assess the extent of exposure by the

subject to these analytes, rather than relying simply on the given doses. While

there were no significant differences between plasma buprenorphine

concentrations for the three dose groups at baseline, there was considerable

variability in the range of concentrations. Hyperalgesia occurred across the

whole range of plasma concentrations. The lowest individual plasma

buprenorphine concentration was 0.16 ng/ml (in the 2-8 mg/day dose group).

Transdermal buprenorphine patches are increasingly used for the management

of chronic pain. In Australia, they are available in various strengths, ranging from

10-40 mg, which deliver 10 to 40 ug/h and are generally applied once a week,

likely for prolonged periods. When 10 ug/h patches were administered to healthy

volunteers once a week for 3 doses the average plasma concentrations were

between 0.155 and 0.172 ng/ml across the 3 periods [32]; 20 ug/h patches

administered to healthy volunteers as a single dose yielded mean maximum

plateau plasma concentrations of about 0.25 ng/ml between 48 and 96 hours

after application [33]; single applications of 35 and 70 ug/h patches yielded mean

maximum plasma concentrations of 0.31 and 0.62 ng/ml respectively [34]. These

values fall within the range of plasma concentrations described in the present

study that were associated with hyperalgesia. Thus, it would be reasonable to assume that some patients receiving buprenorphine for the management of chronic pain could be hyperalgesic. Kress [34] reviewed several trials/reports of the efficacy of transdermal buprenorphine (varying doses) in patients with cancer and noncancer pain with the minimum duration of observation of three months. In most of the studies, satisfactory pain relief occurred in at least 50% of subjects, suggesting that hyperalgesia may not be universal in patients suffering from pain rather than those who receive opioids as substitution treatment.

There are several limitations to this study. The sample size is small and not driven by a formal power calculation. However, we based our population size on the results of Doverty et al [11], who showed highly significant differences in cold pressor tolerance between 16 healthy controls (n=16) and 16 methadone maintenance subjects. Despite the smaller sample size in this study, significant differences were seen between buprenorphine recipients and the controls. Plasma buprenorphine concentrations were measured only at the putative peak. However, given the long half-life of buprenorphine and that the subjects would have been at steady state, we considered the sampling regimen justified.

What might be the best strategy to improve pain relief in buprenorphine maintained patients who experience acute pain, such as following surgery or trauma? Reviews from Huxtable et al [6] and Schug et al [5] state that in the clinical setting, for the opioid maintained population, opioid dose should be increased until analgesia is achieved or sedation occurs and that the dose of the maintenance opioid should be continued without interruption [25]. The purpose of this study was to provide the

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evidence for opioid dose escalation that would provide antinociception without respiratory depression in the buprenorphine maintained population. This study demonstrates that buprenorphine maintained subjects are hyperalgesic at baseline and that very high morphine doses result in limited respiratory depression, but not antinociception. There is a need to explore alternative strategies for providing acute pain relief in buprenorphine (and methadone) maintained patients. For example, Huxtable [6] and Schug et al [5] recommend that an adjuvant analgesic alone, or in combination with morphine, may overcome the limitations of cross-tolerance and side effects to provide pain management in the buprenorphine and methadone maintained population.

Acknowledgements

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Figure Legend

Figure 1. Cold pressor pain tolerance responses (upper panel), electrical stimulation pain tolerance responses (middle panel) and respiration rate (lower panel) mean (± SEM) pain in 10 healthy control and 12 buprenorphine subjects at baseline (B) and morphine infusion 2 (M2). † $P<0.05$; †† $P<0.01$ between groups; * $P<0.05$; ** $P<0.01$ between treatments. Note: different morphine concentrations between buprenorphine and control subjects.

Buprenorphine maintenance subjects are hyperalgesic and have no antinociceptive response to a very high morphine dose

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Running Title: Buprenorphine, hyperalgesia, antinociception, maintenance subjects

2

Abstract

Objective. Acute pain management in opioid dependent persons is complicated because of tolerance and opioid-induced-hyperalgesia. Very high doses of morphine are ineffective in overcoming opioid-induced-hyperalgesia and providing antinociception to methadone maintained patients in an experimental setting. Whether the same occurs in buprenorphine maintained subjects is unknown.

Design. Randomised double blind placebo controlled. Subjects were tested on two occasions, at least five days apart; once with intravenous morphine and once with intravenous saline. Subjects were tested at about the time of putative trough plasma buprenorphine concentrations.

Setting. Ambulatory.

Subjects. Twelve buprenorphine maintained subjects: once daily sublingual dose (range 2-22 mg); no dose change for 1.5-12 months. Ten healthy controls.

Methods. Intravenous morphine bolus and infusions administered over 2 hours to achieve two separate pseudo-steady state plasma concentrations one hour apart. Pain tolerance assessed by application of nociceptive stimuli (cold pressor (seconds) and electrical stimulation (volts)). Ten blood samples collected for assay of plasma morphine, buprenorphine and norbuprenorphine concentrations until 3 hours after the end of last infusion; pain tolerance and respiration rate measured to coincide with blood sampling times.

Results. Cold pressor responses (seconds): baseline: control 34±6 versus

buprenorphine 17±2 (P=0.009); morphine infusion-end: control 52±11(P=0.04),

buprenorphine 17±2 (P>0.5); electrical stimulation responses (volts): baseline:

control 65±6 versus buprenorphine 53±5 (P=0.13); infusion-end: control 74±5

(P=0.007), buprenorphine 53±5 (P>0.98). Respiratory rate (breaths per minute):

baseline: control 17 versus buprenorphine 14 (P=0.03); infusion-end: control 15

(P=0.09), buprenorphine 12 (P<0.01). Infusion-end plasma morphine concentrations

(ng/mL): control 23±1, buprenorphine 136±10.

Conclusions. Buprenorphine subjects, compared with controls, were: hyperalgesic

(cold pressor test); did not experience antinociception, despite high plasma morphine

concentrations; experienced respiratory depression. Clinical implications are

discussed.

4

Introduction

The prevalence of opioid dependence is growing worldwide. Dependence has

traditionally been the result of illicit opioid abuse. However, it is increasingly

associated with legally prescribed long-term use of opioids for the management of

chronic pain [1]. Between 28 and 38.5 million people abuse opioids worldwide. In

2015, 2 million had a substance use disorder involving prescription pain relievers

and 591,000 had a substance use disorder involving heroin [2]. Approximately 1% of

the Australian population is opioid dependent and half of these are in opioid

substitution treatment (OST) programs [3]. Of these, two-thirds receive methadone

and one third buprenorphine (alone or with naloxone) but this difference is declining.

The management of acute pain in opioid dependent patients is complicated

because of two major factors: tolerance, which can generally be overcome by dose

increase but may be compromised by adverse effects, and the under recognized

phenomenon of opioid-induced-hyperalgesia (OIH) characterized as paradoxical

pain sensitization [4] which cannot be overcome by dose increase. Although there

are no formal guidelines for the clinician, Macintyre et al [5] and Huxtable et al [6]

advise, that in the clinical setting, the daily OST dose should be maintained and

additional opioid used for acute pain management, titrated until satisfactory

analgesia is achieved or an adverse effect (e.g. sedation or respiratory depression)

occurs. Such an approach requires stringent observation such as admission to

hospital.

Opioid-induced hyperalgesia occurs in opioid (e.g. heroin) addicted subjects prior to

entry into methadone and buprenorphine treatments [7], chronic non-cancer pain

patients [8], and slow release morphine, methadone and buprenorphine maintained

subjects [9, 10, 11, 12]. Clinically used and very high doses of morphine are

ineffective in overcoming OIH and providing antinociception to methadone

maintained patients [11, 13] in an experimental setting. Whether the same occurs in

buprenorphine maintained subjects is unknown.

Buprenorphine, a semi-synthetic 4,5-epoxymorphinan opioid shows partial agonist

properties for some responses at the mu opioid receptor and variable effects at

the kappa and delta receptors [14]. Its major metabolite norbuprenorphine is also

active [15], although there is conjecture whether it crosses the blood-brain barrier

[16]. Opioid agonists such as morphine, over plasma concentration ranges that

produce dose-related increases in analgesia, also produce concentration-

dependent respiratory depression without any plateau in healthy human

volunteers [17]. In contrast, buprenorphine shows dose-dependent increases in

analgesia with a limited extent of respiratory depression [17, 18]. As a partial

agonist, under appropriate conditions, buprenorphine may act as an agonist or

antagonist at opioid receptors [19] and has shown antihyperalgesic effects in

healthy subjects using a model of intradermal electric stimulation [20]. Therefore,

buprenorphine may be unique in its ability to treat acute pain and possibly

attenuate OIH.

Previously we showed that methadone maintained subjects on doses of 2-120 mg

per day, under identical experimental conditions that will be described in this study,

experienced no antinociception with 55 mg of intravenous morphine but showed a

significant reduction in respiratory rate [13]. To date, no studies have examined the

effect of different daily buprenorphine doses on the antinociceptive and respiratory

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responses to morphine.

The aims of the study in buprenorphine maintained subjects were to: 1. Confirm the presence of OIH; 2. Ascertain whether very high intravenous morphine doses produce antinociceptive and respiratory depression effects and 3. Determine any relationship between buprenorphine dose and these effects. Our hypothesis is that buprenorphine maintained subjects are hyperalgesic and, that in contrast to methadone maintained subjects, experience antinociception with high morphine doses.

Methods

Ethics

The Research Ethics Committee of the Royal Adelaide Hospital, Adelaide, South Australia, Australia (RAH Protocol no: 010222) and the Institutional Review Board, Friends Research Institute, Los Angeles, California, USA (FRI IRB no: 00-03-057-02) approved the study. Both bodies adhere to the ethical standards set by the Helsinki Declaration (2008). The study was supported by National Institutes of Drug Abuse (NIDA) grant R01 DA 13706-02. This study was not registered on clinicaltrials.gov as this study was carried out before the requirement for registration. Subjects provided written informed consent, were paid for their involvement in the study and were free to withdraw at any time.

Subjects

Twelve pain-free buprenorphine maintained subjects comprising 7 men and 5 women with ages between 24 and 42 years (mean 35 years) were recruited. Their

weights ranged between 49 and 97 kg (mean 71 kg). They had been receiving

sublingual buprenorphine (Subutex ® Reckitt Benckiser, West Ryde, New South

Wales, Australia) for between 1.5 and 12 months (mean 4 months) with no dose

change. They had been enrolled in a buprenorphine maintenance program for a

period ranging between 2 and 22 months with a mean of 10 months. The group

was stratified according to prescribed and efficacious maintenance dose, with four

subjects in each of the dose ranges of 2 to 8 mg, 9 to 15 mg and 16 to 22 mg per

day. Subjects were recruited if they self-reported intravenous heroin use at least

once in the previous month. It was considered more ethical to administer morphine

to individuals who continued to use illicit heroin, rather than to those who used no

opioids, apart from their prescribed buprenorphine. Ten healthy control subjects (5

men and 5 women; aged between 21 and 41(mean 31) years); weight 59 and 102

(mean 80) kg) were selected. These subjects were not taking any prescribed

medications. They have been described previously [13].

Exclusion criteria

Exclusion criteria for all subjects included pregnancy or lactation, use of

antiretroviral drugs, significant medical or psychiatric illness that required ongoing

treatment (except opioid addiction for buprenorphine subjects), daily alcohol

consumption exceeding 40 g for men and 20 g for women, severe liver impairment

(serum aspartate aminotransferase and alanine aminotransferase concentrations

greater than 3 times the upper limit of normal range and albumin concentrations

less than 33 grams per litre) or haemoglobin counts outside the normal range.

Healthy control subjects were excluded if they had any personal or family history of

addictive behaviours.

Study design

The study utilized a double blind placebo controlled design with four groups of

subjects (healthy controls, once daily buprenorphine dose of 2 to 8, 9 to 15 and,

16 to 22 mg). Subjects were tested on two occasions, at least five days apart;

once with morphine and once with saline. The order of administration was

randomised. Buprenorphine subjects were tested at about the time of putative

trough plasma concentrations of buprenorphine (approximately 20 hours after

the previous buprenorphine dose).

Procedure

Subjects were asked not to use any analgesics or illicit substances for twenty-four

hours prior to testing. A urine sample was collected on each study day for the

detection of opioids, benzodiazepines, sympathomimetic amines, cannabinoids and

barbiturates. Analysis of these samples confirmed that control subjects had not taken

any of these psychoactive substances. Subjects were excluded from the study if they

presented on study or screening days showing any signs of intoxication from any

substance.

Testing was conducted under constant ambient temperature (24L C) and constant

illumination (70 lux). Each session commenced at approximately 8 am and lasted 8

hours. Two indwelling catheters (Insyte Autoguard, Becton Dickenson, Sandy, Utah,

USA) were inserted into peripheral veins on opposite arms. The catheter in the

dominant arm served for drug infusion; the catheter in the non-dominant arm for

blood sampling. On each testing day, saline was infused at 2 ml/min for 30 min prior to morphine or saline administration for familiarisation.

Morphine administration

Morphine sulphate (David Bull Laboratories, Melbourne, Australia) infusions of 1 mg/ml were administered intravenously in two sixty-minute stages to achieve two consecutive target pseudo-steady-state plasma concentrations [11] using a syringe driver infusion pump (3100 Graseby Syringe Pump, Watford, Hertfordshire, UK). Buprenorphine subjects received an initial bolus of 15.2 mg of morphine sulphate followed by a constant infusion of 8.3 mg/hr for one hour to achieve a target pseudo steady-state plasma concentration of 80 ng/ml (Morphine 1). They were then administered an additional bolus of 15.2 mg of morphine sulphate followed by a constant infusion of 16.5 mg/hr for one hour to achieve the second target pseudo steady-state plasma concentration of 180 ng/ml (Morphine 2). The prescribed buprenorphine dose was administered 1 hour after infusions ceased. Control subjects were administered an initial bolus of 2.2 mg morphine sulphate followed by a constant infusion of 1.2 mg/hr for one hour to achieve a target pseudo steady-state plasma concentration of 11 ng/ml (Morphine 1). They were then administered 4.95 mg of morphine sulphate followed by a constant infusion of 3.6 mg/hr to achieve the second target pseudo steady-state plasma concentration of 33 ng/ml (Morphine 2) [11].

Blood sampling and assessment times

Seven millilitre blood samples were taken at the following times: prior to the thirty

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minute saline familiarisation infusion, ten minutes prior to end of this infusion

(designated as baseline) and ten minutes prior to the end of each of the two

morphine or placebo saline infusions. Further blood samples were taken at 0.25,

0.5, 0.75, 1.0, 2.0, and 3 hours after the end of the last infusion. The blood samples

were centrifuged immediately and the plasma stored at –20 L C until assay.

Respiration rate was measured and nociceptive tests (see below) were

administered immediately after the collection of each blood sample except at 0.25,

0.50 and 0.75 hours after the last infusion.

Nociceptive tests, physiological responses and safety monitoring

Two nociceptive tests were administered: the cold pressor using the non-dominant

arm, and electrical stimulation using the earlobe. These tests have been described

previously [10]. Cold pressor involves the immersion of the non-dominant arm in

0.5–1.5 L C water and the response metric is seconds. Electrical stimulation

involves the transmission of an electrical pulse through the earlobe and is

measured in volts. One nociceptive marker was used which was pain tolerance,

when the participant verbally indicated that they could no longer tolerate the pain

and removed their arm from the water or requested that the electrical stimulation

cease.

Respiration rate was measured over one minute by observation without the

subjects' awareness. Safety was monitored and recorded throughout the study

by means of continuous pulse oximetry, continuous ECG waveform, categorical

nausea scale [21] and categorical sedation scale [22].

Plasma opioid quantification

The quantification of plasma buprenorphine and norbuprenorphine was by high performance liquid chromatography coupled to mass spectrometry as previously described [23]. The assay had a limit of quantification of 0.125 ng/ml for both analytes and all variability in accuracies and precision had coefficients of variation for buprenorphine and nor-buprenorphine of less than 15%. The quantification of plasma morphine was by high-performance liquid chromatography (HPLC) with coulometric detection as previously described [11]. The assay had a lower limit of quantification of 1 ng/ml and all variability in accuracies and precision had coefficients of variation below 7%.

Data analysis

Data are presented as mean ± SEM (with 95% confidence intervals (95% CI)).. One-way ANOVA was used to compare each outcome variable across treatments for the buprenorphine combined subjects and the control subjects with 95% CI of differences. Unpaired samples t-tests were used to compare baseline values between the combined buprenorphine subjects and the control subjects. The Pearson product-moment correlation coefficient (Pearson's *r*) was used to measure the linear correlation between individual buprenorphine daily doses and plasma morphine concentrations. Bonferroni's and Dunnet's tests were used for post-hoc analyses as appropriate. Data for both studies were analysed using GraphPad Prism 4.2 for Windows, GraphPad Software, San Diego, California, USA and $P < 0.05$ was considered significant.

Results

Nociceptive tests

There were no significant differences (P>0.45) in pain tolerance responses between

the three buprenorphine dose groups from baseline to morphine infusion 1 or

morphine infusion 2. Hence, the data from the groups were combined.

Cold pressor responses

Pain tolerance responses at baseline and morphine infusion 2 for control subjects

and the buprenorphine subjects are shown in Figure 1 (upper panel) and absolute

values and ranges for all treatments in Table 1. Pain tolerance values for the

buprenorphine subjects remained unchanged between baseline and the two

morphine infusions. Pain tolerance values for the buprenorphine subjects were

significantly lower than for control subjects at baseline (ANOVA P=0.009; 95% CI -

5 to -30). Within group comparisons revealed that pain tolerance values for control

subjects increased significantly (P=0.04) from baseline to morphine infusion 2

(P<0.05; 95% CI 2 to 34), but not baseline to morphine infusion 1 (P>0.05; 95% CI

-12 to 20).

Electrical stimulation responses

Pain tolerance responses at baseline and morphine infusion 2 for control subjects

and the buprenorphine subjects are shown in Figure 1 (middle panel) and absolute

values with ranges given in Table 1. Pain tolerance values for the buprenorphine

subjects were not significantly different to controls (ANOVA P=0.13) at baseline.

Within-group comparisons revealed that pain tolerance values for control subjects

increased significantly (P=0.007) from baseline to morphine infusion 2 (P<0.01; 95% CI 3 to 16), but not baseline to morphine infusion 1 (P>0.05; 95% CI -2.8 to 10). There was no significant change (P=0.98) in pain tolerance values for combined buprenorphine subjects from baseline to morphine infusion 1 or morphine infusion 2.

Respiration rates

Respiration rates (breaths per minute) relative to baseline and morphine infusion 2 are shown in Figure 1 (lower panel) and absolute values with ranges in Table 1. Respiration rates for the buprenorphine subjects were significantly lower than for control subjects at baseline (ANOVA P=0.03; 95% CI -0.25 to -4.9). Within group comparisons revealed that the respiration rates for control subjects did not decrease significantly (P=0.09) from baseline to morphine infusion 1 or morphine infusion 2. Respiration rates for the buprenorphine subjects decreased significantly (ANOVA P=0.006) from baseline to morphine infusion 2 (P<0.01; 95% CI -0.9 to -4.4) but not morphine infusion 1 (P>0.05; 95% CI -2.8 to 10).

Buprenorphine dose group comparisons demonstrated significant changes in respiration rates as follows. Group 2-8 mg daily: (ANOVA P=0.024) from baseline to morphine infusion 1 (P<0.05; 95% CI -0.56 to -7.4) and baseline to morphine infusion 2 (P<0.05; 95% CI -0.56 to - 7.4); group 9-15 mg daily: (ANOVA P=0.004) between baseline and morphine infusion 2 (P<0.01; 95% CI –1.48 to-5.52), but not morphine infusion 1 (P>0.05; 95% CI -2.02 to 2.02); group 16 to 22 mg daily: (ANOVA P=0.016) between both baseline and morphine infusion 1 (P<0.05; 95% CI -0.72 to -4.28) and baseline and morphine infusion 2 (P<0.05; 95% CI -0.22 to -

3.78). There were no significant differences in respiration rate between the groups

at baseline (P=0.90) or morphine infusion 2 (P=0.67). The lowest recorded

respiration rates were ten breaths per minute in the control group and nine breaths

per minute in the buprenorphine subjects.

Adverse events

There were no serious adverse events. Buprenorphine subjects did not experience

nausea or vomiting, but seven control subjects required one dose of intramuscular

metoclopramide hydrochloride 10 mg (Pfizer, Perth, Australia) with good effect for

mild vomiting.

Plasma morphine, buprenorphine and norbuprenorphine concentrations

Pseudo steady-state plasma morphine concentrations for morphine 1 and 2

infusions are shown in Table 2A. Target pseudo steady-state plasma morphine

concentration for the buprenorphine recipients were 80 ng/ml (Morphine 1) and 180

mg/ml (Morphine 2). Target pseudo steady-state plasma concentration for control

subjects were 11 ng/ml (Morphine 1) and 33 mg/ml (Morphine 2). Pseudo state

plasma morphine concentrations were lower than the desired target in both groups

at morphine 1 and 2. Plasma morphine concentrations are also shown for the

individual daily buprenorphine dose groups 2-8, 9-15 and 16-22 mg/day. There was

no significant correlation (p=0.08) between individual buprenorphine doses and

plasma morphine concentrations at morphine infusion 1. However, there was a

significant inverse relationship between individual buprenorphine doses and plasma

morphine concentrations at morphine infusion 2 (Pearson's r =-0.74, p=0.006; slope

95% CI - 0.92 to -0.28).

There were no significant differences between combined mean plasma

buprenorphine concentrations (Table 2B), or for the three dose groups, at baseline

(P=0.64), morphine infusion 1 (P=0.71) or morphine infusion 2 (P=0.51). Likewise,

there were no significant differences between combined mean plasma

norbuprenorphine concentrations (Table 2C), or for the three dose groups, at

baseline, morphine infusion 1 or morphine infusion 2. At baseline on the saline

administration day, plasma buprenorphine and norbuprenorphine concentrations

were correlated to the buprenorphine dose (r^2=0.36 and 0.58, respectively;

Supplementary Tables 3A, 3B).

Discussion

To our knowledge, this is the first study to have examined the effect of added

morphine to buprenorphine OST subjects who were pain-free at the time of study,

using an experiment pain model. Buprenorphine subjects were hyperalgesic in the

cold pressor test in comparison with controls. Very high doses of morphine (55 mg)

produced high plasma concentrations (92 to 201 ng/ml) that failed to provide

antinociception in either the electrical stimulation or cold pressor tests, irrespective

of maintenance buprenorphine dose. In contrast, in control subjects, considerably

lower morphine doses (12 mg), achieving much lower concentrations (19 to 32

ng/ml), provided antinociception in both tests.

Our choice of using the cold pressor response to study opioid induced-

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hyperalgesia has been validated by others. Compton et al [13] examined

hyperalgesia in opioid dependent subjects and found that these subjects, prior to

induction and following stabilisation on either methadone or buprenorphine, were

similarly hyperalgesic in the cold pressor test and did not exhibit hyperalgesia in the

electrical stimulation test. Krishnan et al [12] compared the detection of

hyperalgesia in opioid-substitution subjects maintained either on methadone or

buprenorphine and healthy controls using the following pain stimuli: cold pain,

electrical stimulation, mechanical pressure, and ischemic pain. They found that cold

pain was the most suitable of the methods tested to detect opioid-induced

hyperalgesia.

While the buprenorphine maintained subjects were tolerant to the antinociceptive

effects of the high doses of morphine and plasma concentrations to which they

were exposed, complete cross-tolerance to the respiratory depressant effects of

morphine did not occur. Respiration rates dropped significantly across all dose

groups, but by a limited amount (approximately 1.5 breaths per minute), which may

not be clinically significant. In healthy volunteer subjects who received a single

intravenous dose (0.2 mg/kg) of morphine, over a plasma concentration range

(approximating 3-13 ng/mL) that produced a systematic increase in analgesia,

morphine produced significant respiratory depression [24]. In contrast, in healthy

adult volunteers who had experience with opioids but who were not physically

dependent on opioids, Walsh and co-workers [18] demonstrated that respiratory

depression increased with single buprenorphine single doses over a range of 1 to 4

mg (approximately 4 breaths per minute decrease), but that this dose effect began

to plateau at higher doses, with no difference between a 16 and 32 mg dose. In the

present study, with subjects chronically maintained on buprenorphine, high doses

of added morphine had a limited respiratory depressant effect at all buprenorphine

doses. It is, however, possible that higher doses of morphine might produce

respiratory depression if such doses are needed to achieve anti-nociception, given

that the lowest respiratory rate recorded was nine breaths per minute. Macintyre et

al [25] showed increased sedation score (a surrogate for respiratory depression) in

buprenorphine-maintained patients who received higher doses of morphine

equivalents following surgery than in this study.

Hyperalgesia is likely to be present, to a lesser or greater degree, in opioid

recipients for whatever indication. Non-cancer pain patients, maintained on either

methadone or slow release oral morphine for the treatment of that pain, were

shown to exhibit hyperalgesia in the cold pressor test [8], similar to that seen in

methadone [13] and buprenorphine subjects (this study) in opioid substitution

programs. Chakrabarti et al [26] (2010) found that people with a greater reported

experience of pain prior to induction onto buprenorphine maintenance required

greater daily doses. The present study found that there was no difference in the

degree of hyperalgesia experienced at baseline between the three dose ranges.

There was also no difference between the three dose ranges in terms of cross-

tolerance to the antinociceptive effects of very high dose morphine.

The most widely used drugs in opioid substitution programmes worldwide are

methadone and buprenorphine, with the latter gaining increasing prominence.

Methadone maintained subjects were examined under conditions identical [13] to

those for the buprenorphine subjects in this study. The cold pressor test at

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baseline revealed that the combined methadone subjects were similarly

hyperalgesic to the combined buprenorphine subjects. Furthermore, both groups

were cross-tolerant to the antinociceptive effects of very high plasma morphine

concentrations and both groups experienced similar decreases in respiration rate

with the addition of very high plasma morphine concentrations. While

buprenorphine has been used increasingly across the world because of its

purported limited effect on respiratory depression and greater safety profile than

other opioids such as morphine and methadone [17, 27, 28], our findings suggest

that supplementary opioids for the management of pain in subjects in opioid

substitution programs should be added cautiously under adequate supervision to

avoid clinically significant respiratory depression.

Koppert et al [20], in a mechanical hyperalgesia model found that acutely,

buprenorphine had a pronounced antihyperalgesic effect and suggested this may

have clinical advantages in the management of chronic pain. In observational

studies of chronic pain patients who were switched from high dose full opioid

agonists to sublingual buprenorphine, [29, 30], the switch resulted in meaningful

reduction in pain scores. Buprenorphine was more effective than full opioid

agonists. The authors postulated that these findings may have resulted from

buprenorphine's antihyperalgesic action [29]. However, Ravn and coworkers [31],

using a multimodal testing technique, could not demonstrate any significant

differences between morphine and buprenorphine in the profiles of

antihyperalgesia and analgesia in healthy volunteers. The present study shows

that buprenorphine, a partial mu opioid receptor agonist and kappa receptor

antagonist, when used as a maintenance agent, produces similar respiratory

depression and hyperalgesia to methadone (a mu opioid receptor agonist) in

opioid maintained subjects tested under the same experimental conditions [13].

These results suggest that, at the buprenorphine doses to which our subjects

were exposed, antihyperalgesia could not be demonstrated with the cold pressor

test.

Macintyre and colleagues [25] examined retrospectively pain relief and opioid

requirements in the first 24 hours after surgery in patients taking buprenorphine

(dose range was similar to that in the present study) and methadone as OST.

Outcomes in the two patient groups were similar. The post-operative 24-hour

analgesia requirement, provided as patient controlled analgesia, was defined as

morphine dose equivalents. Buprenorphine maintained patients required an

average of 200 mg; methadone maintained patients required 221 mg. Pain

scores were similar across both groups. Sedation scores of 2 or greater occurred

in 22.7% and 24.1% of buprenorphine and methadone maintained patients

respectively. This important clinical study was not designed to determine

possible mechanisms for the outcomes. Our findings, in an experimental setting

in OST pain-free patients, complement the findings of this clinical study: very

large morphine equivalent doses result in insignificant analgesia and the

development of respiratory depression, albeit small, given the relatively small

(compared to the PCA doses in the clinical study) dose of morphine provided to

our subjects. Our findings strongly suggest that hyperalgesia is a likely

mechanism for the findings of Macintyre and colleagues [25], in addition to

tolerance. It is pertinent that buprenorphine and methadone maintained patients

behaved almost identically, suggesting that buprenorphine had no

antihyperalgesic properties.

We measured plasma concentrations of morphine, buprenorphine and norbuprenorphine to more accurately assess the extent of exposure by the subject to these analytes, rather than relying simply on the given doses. While there were no significant differences between plasma buprenorphine concentrations for the three dose groups at baseline, there was considerable variability in the range of concentrations. Hyperalgesia occurred across the whole range of plasma concentrations. The lowest individual plasma buprenorphine concentration was 0.16 ng/ml (in the 2-8 mg/day dose group).

Transdermal buprenorphine patches are increasingly used for the management of chronic pain. In Australia, they are available in various strengths, ranging from 10-40 mg, which deliver 10 to 40 ug/h and are generally applied once a week, likely for prolonged periods. When 10 ug/h patches were administered to healthy volunteers once a week for 3 doses the average plasma concentrations were between 0.155 and 0.172 ng/ml across the 3 periods [32]; 20 ug/h patches administered to healthy volunteers as a single dose yielded mean maximum plateau plasma concentrations of about 0.25 ng/ml between 48 and 96 hours after application [33]; single applications of 35 and 70 ug/h patches yielded mean maximum plasma concentrations of 0.31 and 0.62 ng/ml respectively [34]. These values fall within the range of plasma concentrations described in the present study that were associated with hyperalgesia. Thus, it would be reasonable to assume that some patients receiving buprenorphine for the management of chronic pain could be hyperalgesic. Kress [34] reviewed several trials/reports of

the efficacy of transdermal buprenorphine (varying doses) in patients with cancer

and noncancer pain with the minimum duration of observation of three months. In

most of the studies, satisfactory pain relief occurred in at least 50% of subjects,

suggesting that hyperalgesia may not be universal in patients suffering from pain

rather than those who receive opioids as substitution treatment.

There are several limitations to this study. The sample size is small and not driven

by a formal power calculation. However, we based our population size on the

results of Doverty et al [11], who showed highly significant differences in cold

pressor tolerance between 16 healthy controls (n=16) and 16 methadone

maintenance subjects. Despite the smaller sample size in this study, significant

differences were seen between buprenorphine recipients and the controls. Plasma

buprenorphine concentrations were measured only at the putative peak. However,

given the long half-life of buprenorphine and that the subjects would have been at

steady state, we considered the sampling regimen justified.

What might be the best strategy to improve pain relief in buprenorphine maintained

patients who experience acute pain, such as following surgery or trauma? Reviews

from Huxtable et al [6] and Schug et al [5] state that in the clinical setting, for the

opioid maintained population, opioid dose should be increased until analgesia is

achieved or sedation occurs and that the dose of the maintenance opioid should be

continued without interruption [25]. The purpose of this study was to provide the

evidence for opioid dose escalation that would provide antinociception without

respiratory depression in the buprenorphine maintained population. This study

demonstrates that buprenorphine maintained subjects are hyperalgesic at baseline

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and that very high morphine doses result in limited respiratory depression, but not antinociception. There is a need to explore alternative strategies for providing acute pain relief in buprenorphine (and methadone) maintained patients. For example, Huxtable [6] and Schug et al [5] recommend that an adjuvant analgesic alone, or in combination with morphine, may overcome the limitations of cross-tolerance and side effects to provide pain management in the buprenorphine and methadone maintained population.

Acknowledgements

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Figure Legend

Figure 1. Cold pressor pain tolerance responses (upper panel), electrical stimulation pain tolerance responses (middle panel) and respiration rate (lower panel) mean (± SEM) pain in 10 healthy control and 12 buprenorphine subjects at baseline (B) and morphine infusion 2 (M2). † P<0.05; †† P<0.01 between groups; * P<0.05; ** P<0.01 between treatments. Note: different morphine concentrations between buprenorphine and control subjects.