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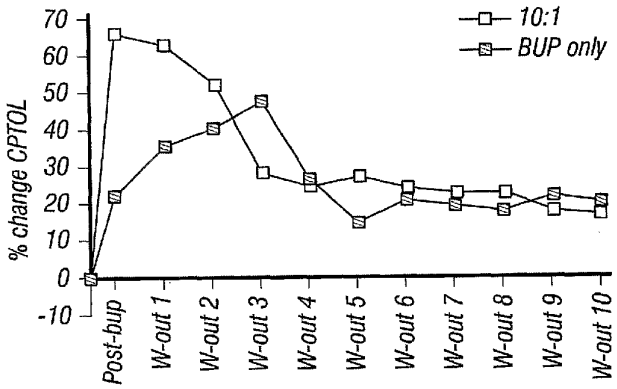

FIG. 3

(57) Abstract: A composition, in parenteral unit dosage form or in a unit dosage form suitable for delivery via the dermis or mucosa, comprises buprenorphine and an amount of naloxone such that the ratio by weight of buprenorphine to naloxone delivered to or reaching the plasma of a patient is in the range of from 7.5:1 to 12.4:1. The analgesic action of the buprenorphine is potentiated by the low dose of naloxone, which also serves to reduce the likelihood of abuse of the composition by drug addicts. Also provided are a method of treatment of pain and the use of naloxone and buprenorphine for the manufacture of a medicament.

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IMPROVEMENTS IN AND RELATING TO MEDICINAL COMPOSITIONS

The present invention relates to medicinal compositions containing buprenorphine in combination with naloxone; as well as to their use in the manufacture of such compositions and in clinical practice, as analgesics.

Whilst opioids are particularly effective in the management of moderate to severe pain their use is limited by unpleasant and potentially dangerous adverse effects. Such adverse effects can include sedation, respiratory depression, nausea and gastrointestinal problems. Thus efforts have been made to minimise adverse effects.

There are many opioids and some produce more significant adverse effects than others. Accordingly, careful selection of the opioid employed in an analgesic composition may itself reduce the incidence and severity of adverse effects. One particularly suitable opioid is buprenorphine which has been shown to have both agonist (morphine-like) and antagonist properties without producing significant physical dependence.

Buprenorphine (International Non-proprietary Name for N-cyclopropylmethyl-7[alpha]-[1-(S)-hydroxy-1,2,2-trimethyl-propyl]6,14-endoethano-6,7,8,14-tetrahydronoroöripavine) is a potent opiate partial agonist analgesic lacking the psychotomimetic effects found with other opiate analgesics. However, buprenorphine suffers from side effects typical of opiate agonists such as nausea and vomiting, constipation and respiratory depression in some patients, although there is a ceiling to its effects on

respiratory depression as a direct consequence of its partial agonist properties.

Attempts have also been made to enhance the analgesic effect of opioids while minimising the incidence and severity of adverse effects by combining opioid treatment with other drugs.

One approach is the addition of a non-opioid analgesic to the opioid treatment. The rationale here is that lower levels of opioid should be required to achieve antinociception and thus there should be a reduction of adverse effects.

Another approach is the co-administration of an opioid agonist and low doses of an opioid antagonist.

Given the potent blockade of opioid binding associated with administration of an opioid antagonist it would classically be expected that the use of such an agent would provide no improvement to pain relief and could conceivably increase pain through partial blockage effects of the agonist it is combined with. However it has been found that in some instances antinociception may be potentiated by co-administration of an antagonist.

One such antagonist is naloxone (International Non-proprietary Name for 1-N-allyl-14-hydroxynorhydro morphinone) which is a narcotic antagonist.

In GB 2150832A there is disclosed an analgesic composition in parenteral or sublingual form comprising an active dose of buprenorphine and an amount of naloxone sufficient to

prove aversive to a narcotic addict by parenteral administration but insufficient to compromise the analgesic action of the buprenorphine. The parenteral dosage form may contain buprenorphine and naloxone within the weight ratio of 3:1 to 1:1 and the sublingual form within the ratio 1:2 to 2:1. The testing in GB-A-2150832 was on rats.

In EP 1242087A it is disclosed that parenteral and sublingual levels of buprenorphine are potentiated and enhanced by low doses of naloxone. Based on testing on rats, there is stated a suitable ratio by weight of buprenorphine to naloxone of 12.5:1 to 27.5:1, preferably 15:1 to 20:1.

Human studies have now been carried out and have generated new findings for the combined use of buprenorphine, as opioid agonist, and naloxone, as opioid antagonists. These new findings extend our understanding of the therapeutic doses which will give effective analgesia in humans.

According to a first aspect of the present invention there is provided an analgesic composition, in parenteral unit dosage form or in a unit dosage form suitable for delivery via the mucosa or dermis, the composition comprising buprenorphine and an amount of naloxone such that the ratio by weight of buprenorphine to naloxone delivered to or reaching the plasma of a patient is in the range of from 7.5:1 to 12.4:1.

It is believed that the analgesic action of buprenorphine is potentiated by the relatively small amount of naloxone.

It is to be understood that the terms buprenorphine and naloxone as used herein are intended to cover simple related, pharmaceutically acceptable, compounds such as esters, bases and salts, for example acid addition salts. Particularly preferred salts are the hydrochlorides. However the ratios and weights referred to herein refer to buprenorphine and naloxone *per se*, not salts, bases or esters.

The term parenteral is intended to encompass administration of the compositions by any way other than through the alimentary tract.

The term mucosa is intended to encompass any mucous membrane and includes oral mucosa, rectal mucosa, vaginal mucosa and nasal mucosa. The term dermis denotes non-mucosal skin.

Administration may take a few minutes, depending on its nature. Preferably it takes over a period of at least one minute, preferably at least two minutes, preferably at least three minutes. Preferably it take place over a period of up to ten minutes, preferably up to seven minutes, preferably up to five minutes.

Transdermal administration may encompass any mode of administration trough the dermis. Transmucosal administration may encompass any mode of administration trough the mucosa, and sites of administration may include, for example, vaginal and rectal mucosa and, preferably, mucosa of the oral-nasal cavity, for example

nasal, throat, buccal and, sublingual sites. Nasal and sublingual administration is especially preferred.

Preferably the defined ratio of buprenorphine to naloxone is achieved within sixty minutes after administration being completed; that is, preferably at some time within sixty minutes of administration being completed, the defined drug ratio in the plasma is achieved.

The composition may comprise buprenorphine and naloxone such that the ratio by weight of buprenorphine to naloxone delivered to or reaching the plasma of the patient is at least X:1 (X to 1) where X is 8.0, preferably 9.0, preferably 9.5, preferably 10.0, preferably 10.5, preferably 11.0.

The composition may comprise buprenorphine and naloxone such that the ratio by weight of buprenorphine to naloxone delivered to or reaching the plasma of the patient is no greater than Y:1 (Y to 1) where Y is 12.3, preferably 12.2 preferably 12.0, preferably 11.5.

Surprisingly, it has been found that although the relative amount of naloxone to buprenorphine is higher in the present invention than in EP 1242087B, the antagonist action of naloxone does not "win out" and naloxone in fact potentiates the agonist action of buprenorphine.

The composition may comprise a parenteral unit dosage form and the ratio of buprenorphine to naloxone within the parenteral composition may be substantially the same as that reaching or delivered to the plasma of a patient upon application. Thus the parenteral dosage form may comprise

buprenorphine and naloxone in the weight ratio 7.5:1 to 12.4:1, with preferred upper and lower limits of the ratio being as stated above for buprenorphine and naloxone in the plasma.

In a human being, as stated in EP 1242087B dosages of about 40 µg of buprenorphine per kilogram of body weight are suitably required to obtain satisfactory pain relief in the absence of potentiation. Thus for typical body weights of 50 to 80 kg, the buprenorphine dosage would be from 2 mg to 3.2 mg of buprenorphine per day. This would conveniently be administered as four unit doses.
The amounts of buprenorphine which are required to be effective in the compositions of the invention are less than the amounts which are required to be effective in the absence of the potentiating effects of naloxone.

Importantly when equal doses of buprenorphine with and without the potentiating effect of naloxone are compared, the magnitude and duration of analgesia achieved by the former compositions (i.e. also containing naloxone), are markedly increased. Therefore the same analgesic performance can be achieved with a lower buprenorphine dose when combined with naloxone. It is proposed that an increased analgesic effect can be achieved and/or reduced concentration of buprenorphine can be used, within or across the therapeutic range.

Suitably, unit doses of the compositions of the present invention (containing naloxone) contain buprenorphine in an amount which is below that required to obtain corresponding pain relief in a unit dose of buprenorphine without naloxone.

Suitably, the compositions of the present invention comprise at least 10 µg of buprenorphine per unit dose, preferably at least 15 µg, preferably at least 20 µg, preferably at least 30 µg, and most preferably at least 40 µg. These values reflect the benefit of the invention in achieving analgesia at low dosages.

Suitably, the compositions of the present invention may contain any amount of buprenorphine, up to the upper end of conventional clinical practice. Suitably, they may contain up to 32 mg buprenorphine per unit dose, preferably up to 16 mg, preferably up to 8 mg, preferably up to 4 mg, preferably up to 2 mg, preferably up to 1 mg, preferably up to 600 µg, preferably up to 400 µg, preferably up to 200 µg, preferably up to 160 µg, and most preferably up to 100 µg.

Suitably, in accordance with the present invention, a patient is administered at least 0.25 µg of buprenorphine per kg (of body weight) per 24 hours. Preferably the amount is at least 0.5 µg, preferably at least 1 µg, preferably at least 1.5 µg and most preferably at least 2 µg.

Suitably, in accordance with the present invention, a patient is administered up to 640 µg of buprenorphine per kg per 24 hours. Preferably the amount is up to 320 µg, preferably up to 160 µg, preferably up to 80 µg, preferably up to 40 µg, preferably up to 20 µg, preferably up to 16 µg, and preferably up to 12 µg. Most preferably the amount is not greater than 8 µg.

Suitably by use of compositions of the present invention the amount of buprenorphine administered to a patient for the purpose of achieving relief from pain is at least 40 µg per 24 hours, preferably at least 60 µg, preferably at least 80 µg, preferably at least 120 µg, and most preferably at least 160 µg.

Suitably by use of compositions of the present invention the amount of buprenorphine administered to a patient for the purpose of achieving relief from pain is up to 32 mg, preferably up to 16 mg, preferably up to 8 mg, preferably up to 4 mg, preferably up to 2 mg, preferably up to 1 mg, preferably up to 800 µg, preferably up to 600 µg, preferably up to 400 µg, preferably up to 200 µg, preferably up to 160 µg, preferably up to 100 µg.

Suitably, the composition comprises at least 1 µg of naloxone per unit dose, preferably at least 1.5 µg, preferably at least 2 µg, and most preferably at least 4 µg.

Suitably, the composition comprises up to 4 mg of naloxone per unit dose, preferably up to 2 mg, preferably up to 1 mg, preferably up to 500 µg, preferably up to 300 µg, preferably up to 200 µg, preferably up to 100 µg, preferably up to 80 µg, and most preferably up to 50 µg.

Suitably the amount of naloxone administered is at least 0.025 µg naloxone per kg of body weight per 24 hours. Preferably the amount is at least 0.05 µg, preferably at least 0.1 µg, preferably at least 0.15 µg, preferably at least 0.2 µg, preferably at least 0.25 µg, preferably at least 0.4 µg.

Suitably the amount of naloxone administered is up to 320 µg naloxone per kg of body weight per 24 hours. Preferably the amount is up to 160 µg, preferably up to 80 µg, preferably up to 40 µg, preferably up to 20 µg, preferably up to 10 µg, preferably up to 8 µg, and preferably up to 6 µg. Preferably the amount is not greater than 4 µg per kg per 24 hours.

Suitably the amount of naloxone administered is at least 5 µg per 24 hours, preferably at least 8 µg, preferably at least 10 µg, preferably at least 15 µg, and most preferably at least 20 µg.

Suitably the amount of naloxone administered is up to 16 mg µg per 24 hours, preferably up to 8 mg, preferably up to 4 mg, preferably up to 2 mg, preferably up to 1 mg, preferably up to 500 µg, preferably up to 400 µg, preferably up to 300 µg, and most preferably up to 200 µg.

References above to the amounts of compounds which may be administered to a patient are with reference to an adult patient.

Whatever the absolute amounts of buprenorphine and naloxone administered, the definition(s) stated herein of the ratio of buprenorphine to naloxone must be satisfied.

It is preferable to formulate the compositions in unit dosage forms i.e. physically discrete units containing the appropriate amounts of buprenorphine and naloxone, together with pharmaceutically acceptable diluents and/or carriers. Such unit dosage forms for parenteral

administration are suitably in the form of ampoules. The unit dosage form for transdermal or transmucosal administration may, for example, be a tablet, film, spray, patch, rub-in composition or lozenge. Administration, which will be further described in the second aspect, may comprise the delivery of a medicament comprising buprenorphine and naloxone, preferably in such a form.

Compositions of the invention may contain a buffer system, for example an organic acid and a salt thereof, such as citric acid and sodium citrate.

Compositions in the form of sublingual dosage forms suitably contain soluble excipients selected from materials such as lactose, mannitol, dextrose, sucrose or mixtures thereof. They suitably also contain granulating and disintegrating agents selected from materials such as starch, binding agents such as povidone or hydroxypropyl-methyl cellulose and lubricating agents such as magnesium stearate.

Compositions intended for parenteral administration may comprise an isotonic solution of buprenorphine and naloxone in sterile water. Conveniently the solution may be made isotonic by use of dextrose and sterilised by autoclaving or by filtration through a membrane filter. The compositions may be administered intramuscularly, intradermally, intraperitonealy, intravenously, intraarterially, subcutaneously or by the epidural route.

The compositions for parenteral administration, or for delivery via the mucosa, such as by sublingual administration, as detailed above, may be prepared by

manufacturing techniques which are well known to those skilled in the art.

According to a second aspect the present invention there is provided a method for the treatment of pain in a human patient, which method comprises the administration to a human patient, by a parenteral or dermal or mucosal route, of buprenorphine and naloxone such that the ratio by weight of buprenorphine to naloxone delivered to or reaching the plasma of the patient is in the range from 7.5:1 to 12.4:1.

Preferred ratios of buprenorphine to naloxone are as defined above with respect to the first aspect.

Suitably, the method comprises delivery via the mucosa. The method may comprise delivery in a sublingual unit dosage form.

Suitably, the method comprises the administration of buprenorphine and an amount of naloxone for the purpose of potentiating the analgesic action of the buprenorphine and in particular to optimising the balance between the analgesic action of the buprenorphine and the anti-abuse presence of the naloxone. It will be appreciated that this balance is extremely important. The medicament must be a potent analgesic for it to fulfil its intended function. At the same time in the present day it is vitally important that opioid medicaments discourage abuse by addicts. It is believed that the present invention is extremely effective in these respects.

Separate administration of buprenorphine and of naloxone is not excluded in the method. Suitably, however, the method comprises administering a composition comprising buprenorphine and naloxone, to a human. Suitably, the method employs a composition according to the first aspect. The definitions given above in relation to the first aspect apply to the second aspect, noting however that the buprenorphine and naloxone may in principle be administered separately in the second aspect.

Suitably, the method comprises administering to the human or animal from 0.25 µg to 20 µg per kilogram of body weight of buprenorphine per day.

The method may comprise administering a dose of buprenorphine which would, if administered alone, produce minimal or no antinociception. The method may comprise administering to the human amounts of buprenorphine and naloxone as stated above in relation to the first aspect of the invention.

The method may comprise any feature as described in relation to the first aspect.

According to a third aspect of the present invention there is provided the use of naloxone and buprenorphine in the manufacture of a medicament for the treatment of pain, wherein the naloxone and buprenorphine are used in an amount such that the medicament is delivered to the patient or reaches, in the plasma of a patient, a ratio by weight of buprenorphine to naloxone in the range of from 7.5:1 to 12.4:1.

Suitably the use comprises the use of buprenorphine and naloxone in the manufacture of a medicament for the treatment of pain, wherein buprenorphine is used for its analgesic effect, but at a lower level than would be needed, for a given analgesic effect against a given pain in a given patient, in the absence of naloxone. Thus the naloxone potentiates the analgesic effect of buprenorphine. Further, it renders the medicament less attractive (and preferably entirely unattractive) to drug addicts.

The use of buprenorphine and naloxone in the manufacture of a medicament according to the third aspect may comprise any feature as described in relation to the first or second aspect.

Suitably, the use of buprenorphine and naloxone in the manufacture of a medicament comprises the manufacture of a medicament comprising a composition according to the first aspect. However the use of buprenorphine and naloxone in the manufacture of a medicament having two dosage units, containing buprenorphine and naloxone respectively, is not excluded.

The present invention will now be illustrated by way of example with reference to the accompanying drawings in which:

Figure 1 is a graph of pain tolerance results for a buprenorphine and naloxone combination;

Figure 2 is a graph of pain tolerance results for buprenorphine alone; and

Figure 3 is a comparative graph.

Methods

Nociceptive testing

The cold pressor (CP) test was used to assess antinociception of buprenorphine and buprenorphine and naloxone combinations. The compound forms were buprenorphine HCl and naloxone HCl dihydrate. The CP test utilised two plastic cylindrical containers, one of which was filled with warm water and the other with a combination of water and crushed ice to achieve a "slushy" consistency. The subject immersed the non-dominant forearm and hand into the warm water for exactly 2 minutes. At 1 minute 45 seconds, a blood pressure cuff on the immersed arm was inflated to a pressure 20 mmHg below the diastolic blood pressure. The blood pressure cuff minimised the role of blood flow in determining the reaction to cold. At exactly 2 minutes, the forearm was transferred from the warm water to the cold water bath. The subject's eyes were covered for the entire procedure to minimise distraction and cues for time. Upon immersion of the limb in the cold water bath, subjects were asked to indicate when they first experienced pain (pain threshold, CPTHR), then asked to leave their arm submerged until they can no longer tolerate the pain (pain tolerance, CPTOL). Pain threshold and tolerance times were recorded in seconds from immersion in cold. An undisclosed cut-off of 180 seconds was imposed, after which time pain tolerance can no longer be accurately assessed due to numbness. Pain

tolerance (CPTOL) is the reported pain response parameter in the current investigations.

For the present tests nociceptive testing was conducted in the same environment, with minimal background noise, audible voices and no clock with audible ticking. Ambient room temperature and lighting was consistent. At no time did the experimenter discuss with the subject his/her performance on the test, or answer any questions related to the average pain tolerance time or any previous results.

Screening

Before testing subjects were screened according to the inclusion and exclusion criteria based upon such factors as previous medical conditions and drug abuse.

Test Procedure

Suitable screened subjects were tested according to the following procedure. Subjects provided a urine sample upon arrival on the day of testing, which was tested for drugs of abuse (opioids, cannabinoids, benzodiazepines and sympathomimetic amines) and, for female subjects, pregnancy. A 22 gauge indwelling venous catheter was inserted into the best available forearm vein on each arm (above the CP immersion line for the non-dominant arm). A male luer lock adaptor injection site was attached to each catheter. One catheter was used for blood sampling throughout the testing day, and the other for infusions. The participant was then connected to a monitor, which was

set to continuously monitor physiological parameters for the duration of the testing session.

On each testing day, subjects received a 30 minute unblinded intravenous infusion of saline, followed by one or more 30 minute drug (or placebo) infusions. The purpose of the initial saline infusion was two-fold: to establish whether any changes in pain or physiological parameters would occur as a response to the infusion process itself, and to ensure that there was no obstruction to venous access via the catheter and the infusion pump was operating correctly.

Infusions were administered using a syringe pump. Drugs and saline were prepared in 30ml BD Plastipak syringes. Infusions were run at a rate of 20ml per hour for 30 minutes. Each syringe was attached to a minimum volume extension set (150cm tubing, female luer lock, male luer lock, 0.5mL/30cm). The male luer lock was attached to a lever lock cannula. The extension set was primed with the drug/saline, and inserted into the injection site. In buprenorphine:antagonist ratio studies, BUP and antagonist were administered simultaneously. For the simultaneous infusion of two drugs (via one cannula), a Y-type catheter extension set with two injection sites was attached to the catheter, and the lever lock cannulas (connected via the minimum volume extension set to each syringe) were inserted in each of the injection sites.

Testing sessions were conducted on numerous occasions during each testing day. Each testing session consisted of the following measures in the order listed: nausea and sedation recorded, blood sample taken, physiological

parameters recorded (pulse, oxygen saturation and blood pressure), nociceptive testing (as detailed above) completed, and respiration recorded (breaths per minute counted for one full minute during warm water component of CP).

Testing sessions were conducted at set intervals throughout each testing day. These were as follows: 1. Prior to the commencement of infusions; 2. Twenty minutes after the commencement of the 30 minute saline infusion; 3. Twenty minutes after the commencement of the 30 minute drug infusion, and hourly following the cessation of the (last) drug infusion. This is referred to as the washout period. The purpose of conducting the testing session 20 minutes after commencing each 30 minute infusion was to allow time for the testing to be completed before starting the subsequent infusion.

Comparison of results

As baseline values were different between conditions, CPTOL data were expressed as percent change from baseline in order to compare the effect associated with different drug combinations. Each participant's response at each time point for each condition was expressed as a percent change from baseline response according to the equation below. Data are expressed as the mean (±SEM) of these values at each post-drug testing session for each condition.

$$\frac{\text{Post-drug latency - baseline latency}}{\text{baseline latency}} * 100$$

This provides a value for percentage change CPTOL.

Examples

Example 1

Eight healthy Caucasian volunteers (4 male, 4 female) were enrolled in the study. Data from one 37 year old male was excluded from analyses due to an opioid positive urine on the BUP only testing day. The final sample (n=7), then, comprised 3 males and 4 females, with a mean age of 25.14 (±1.02, range 21-37) and mean CPTOL at screening of 43.00 (±6.73, range 29-80). There were no significant differences between males and females in terms of age (p=0.265) or CPTOL at screening (0.764).

Subjects were administered buprenorphine and Naloxone in a ratio of 10:1 by IV infusion with buprenorphine administered at a dose of 0.5 µg/kg body weight. The washout monitoring was performed for a period of 10 hours. The CPTOL results are presented in Figure 1. No adverse effects causing concern were noted.

Example 2 - comparative

As a comparative example the same subjects from Example 1 were administered, on a separate day, buprenorphine and saline (referred to subsequently as "BUP only") by IV infusion. Buprenorphine was again administered at a dose of 0.5 µg/kg body weight and the washout monitoring performed over 10 hours. The CPTOL results are presented in Figure 2.

Comparison of examples

The percentage change for CPTOL from the baseline was calculated for Examples 1 and 2 and the results are presented in Figure 3. It may be seen that in the early hours of the test there was a benefit of the buprenorphine and naloxone combination compared to buprenorphine alone.

Example 3 – parenteral composition

A parenteral formulation having the following composition:

	mg/ml.
Buprenorphine as HCl salt	0.05
Naloxone as HCl salt	0.005
Anhydrous dextrose	50.0
Hydrochloric acid to pH 4.0	
Water for injection to 1.0 ml	

was prepared by dissolving dextrose, buprenorphine hydrochloride and naloxone hydrochloride in that order with stirring, in about 95% batch volume of water for injection. The acidity of the solution was adjusted to pH 4.0 by the addition of 0.1M hydrochloric acid, and the solution was made up to volume with water for injection. The solution was filtered through a membrane filter and transferred to sterilised 2 ml glass ampoules containing 2 ml of the solution. The ampoules were sealed and the product sterilised by autoclaving.

Example 4 - sublingual composition

A sublingual tablet having the following composition:

	mg/tablet
Buprenorphine as HCl salt	0.04
Naloxone as HCl salt	0.006
Mannitol	18.0
Maize starch	9.0
Povidone	1.2
Magnesium stearate	0.45
Lactose	to 60.0

was prepared by screening all the materials with the exception of the magnesium stearate through a 750 µm sieve and blending them together. The mixed powders were then subjected to an aqueous granulation procedure and dried at 50°C. The resulting granules were forced through a 750 µm sieve and blended with magnesium stearate (pre-sieved through a 500 µm sieve). The tablet granules were compressed to yield tablets of 5.56 mm diameter and weight 60 mg.

CLAIMS

1. An analgesic composition, in parenteral unit dosage form or in a unit dosage form suitable for delivery via the mucosa or dermis, the composition comprising buprenorphine and an amount of naloxone such that the ratio by weight of buprenorphine to naloxone delivered to or reaching the plasma of a patient is in the range of from 7.5:1 to 12.4:1.

2. A composition as claimed in claim 1, wherein said ratio is at least X:1 where X is 8.0 or 9.0 or 9.5 or 10.0 or 10.5 or 11.0.

3. A composition as claimed in claim 1 or 2, wherein said ratio is up to Y:1 where Y is 12.3 or 12.2 or 12.0 or 11.5.

4. A composition as claimed in claim 1 wherein the amount of buprenorphine in the unit dosage form is from 10 µg to 8 mg.

5. A method for the treatment of pain in a human patient, which method comprises the administration to a human patient, by a parenteral or dermal or mucosal route, of buprenorphine and naloxone such that the ratio by weight of buprenorphine to naloxone delivered to or reaching the plasma of the patient is in the range from 7.5:1 to 12.4:1.

6. The use of naloxone and buprenorphine in the manufacture of a medicament for the treatment of pain,

wherein the naloxone and buprenorphine are used in an amount such that the medicament is delivered to the patient or reaches, in the plasma of a patient, a ratio by weight of buprenorphine to naloxone in the range of from 7.5:1 to 12.4:1.

7. A method or use as claimed in claim 5 or 6, wherein the administration of buprenorphine is in the range 0.25 to 640 µg per kg of body weight per 24 hours.

8. A composition or method or use, substantially as hereinbefore described in accordance with the present invention.

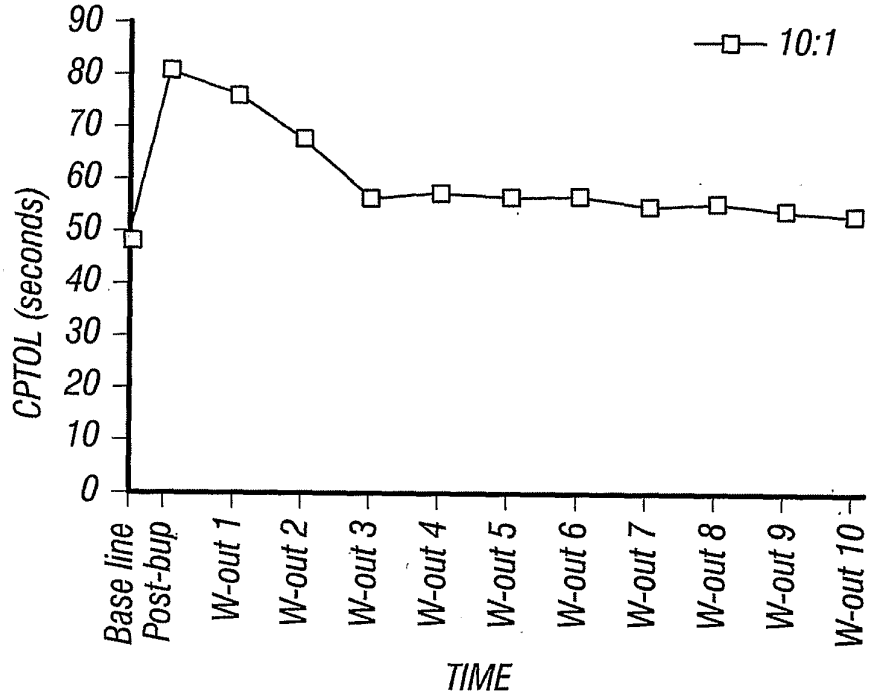
90
80
70
60
50
40
30
20
10
0
CPTOL (seconds)
10:1
Base line
Post-bup
W-out 1
W-out 2
W-out 3
W-out 4
W-out 5
W-out 6
W-out 7
W-out 8
W-out 9
W-out 10
TIME

FIG. 1

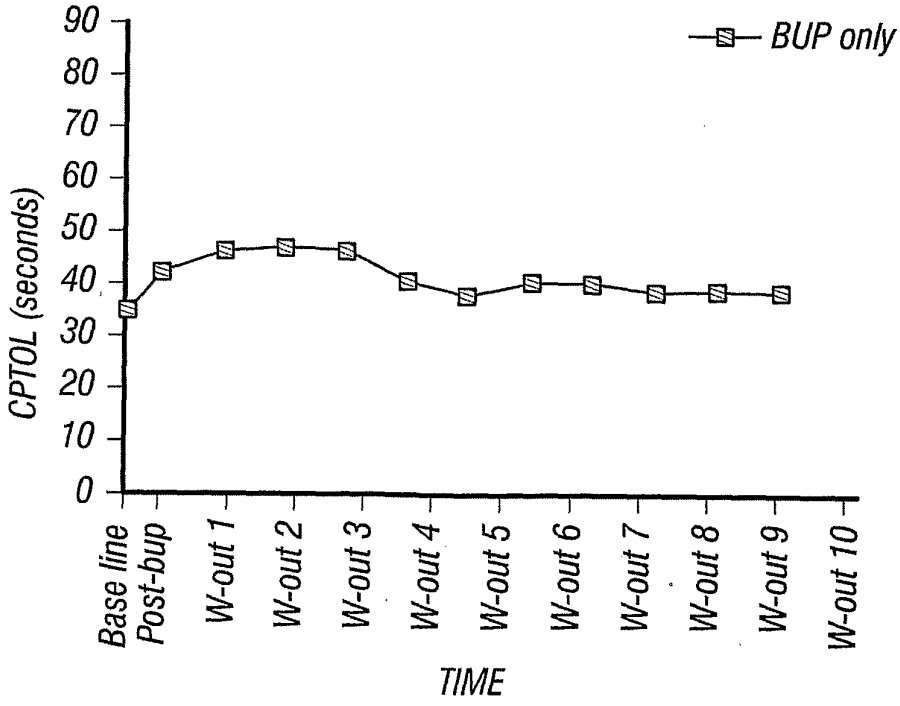
90
80
70
60
50
40
30
20
10
0
CPTOL (seconds)
BUP only
Base line
Post-bup
W-out 1
W-out 2
W-out 3
W-out 4
W-out 5
W-out 6
W-out 7
W-out 8
W-out 9
W-out 10
TIME

FIG. 2

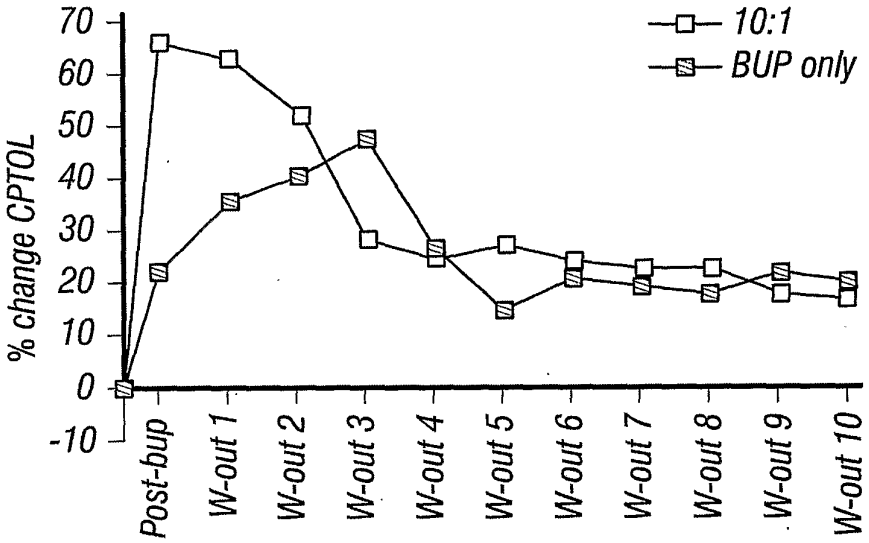
70
60
50
40
30
20
10
0
-10
% change CPTOL
10:1
BUP only
Post-bup
W-out 1
W-out 2
W-out 3
W-out 4
W-out 5
W-out 6
W-out 7
W-out 8
W-out 9
W-out 10

FIG. 3