



(86) **Date de dépôt PCT/PCT Filing Date:** 2014/05/30
(87) **Date publication PCT/PCT Publication Date:** 2014/12/04
(85) **Entrée phase nationale/National Entry:** 2015/11/27
(86) **N° demande PCT/PCT Application No.:** GB 2014/000206
(87) **N° publication PCT/PCT Publication No.:** 2014/191710
(30) **Priorité/Priority:** 2013/05/30 (GB1309654.0)

(51) **Cl.Int./Int.Cl. A61K 31/485** (2006.01),
A61P 23/00 (2006.01)

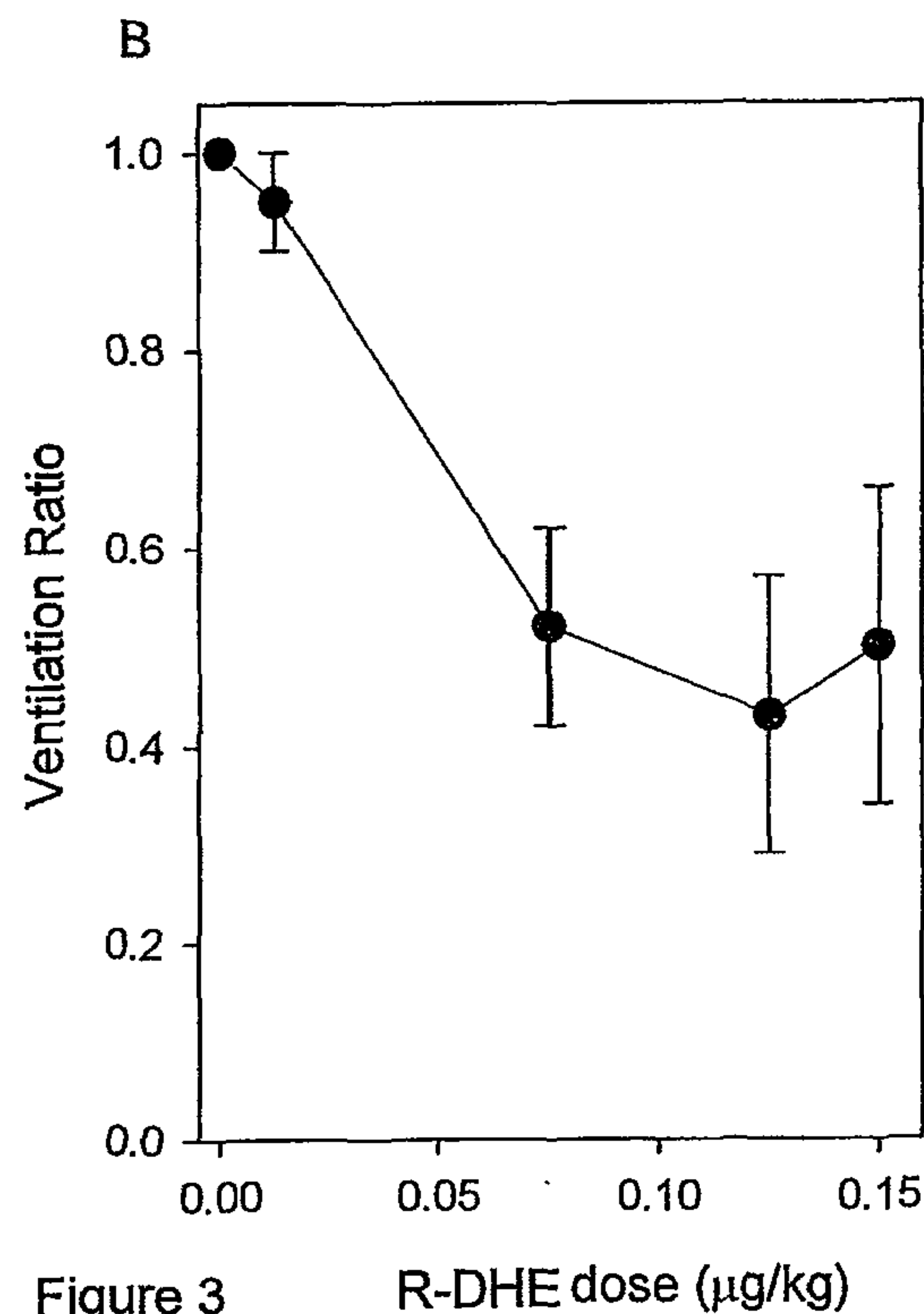
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(54) **Titre : DIHYDROETORPHINE POUR LE SOULAGEMENT DE LA DOULEUR ET L'ANESTHESIE**

(54) **Title: DIHYDROETORPHINE FOR THE PROVISION OF PAIN RELIEF AND ANAESTHESIA**



(57) **Abrégé/Abstract:**

The present invention provides a method of providing pain relief in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose of at least 0.01 µg/kg, preferably at least 0.05 µg/kg, and the level of respiratory depression in said subject is 65 or less % relative to the baseline level pre-administration of (R)-dihydroetorphine.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau(10) International Publication Number
WO 2014/191710 A1(43) International Publication Date
4 December 2014 (04.12.2014)

(51) International Patent Classification:

A61K 31/485 (2006.01) *A61P 23/00* (2006.01)

(21) International Application Number:

PCT/GB2014/000206

(22) International Filing Date:

30 May 2014 (30.05.2014)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

1309654.0 30 May 2013 (30.05.2013) GB

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,

[Continued on next page]

(54) Title: DIHYDROETORPHINE FOR THE PROVISION OF PAIN RELIEF AND ANAESTHESIA

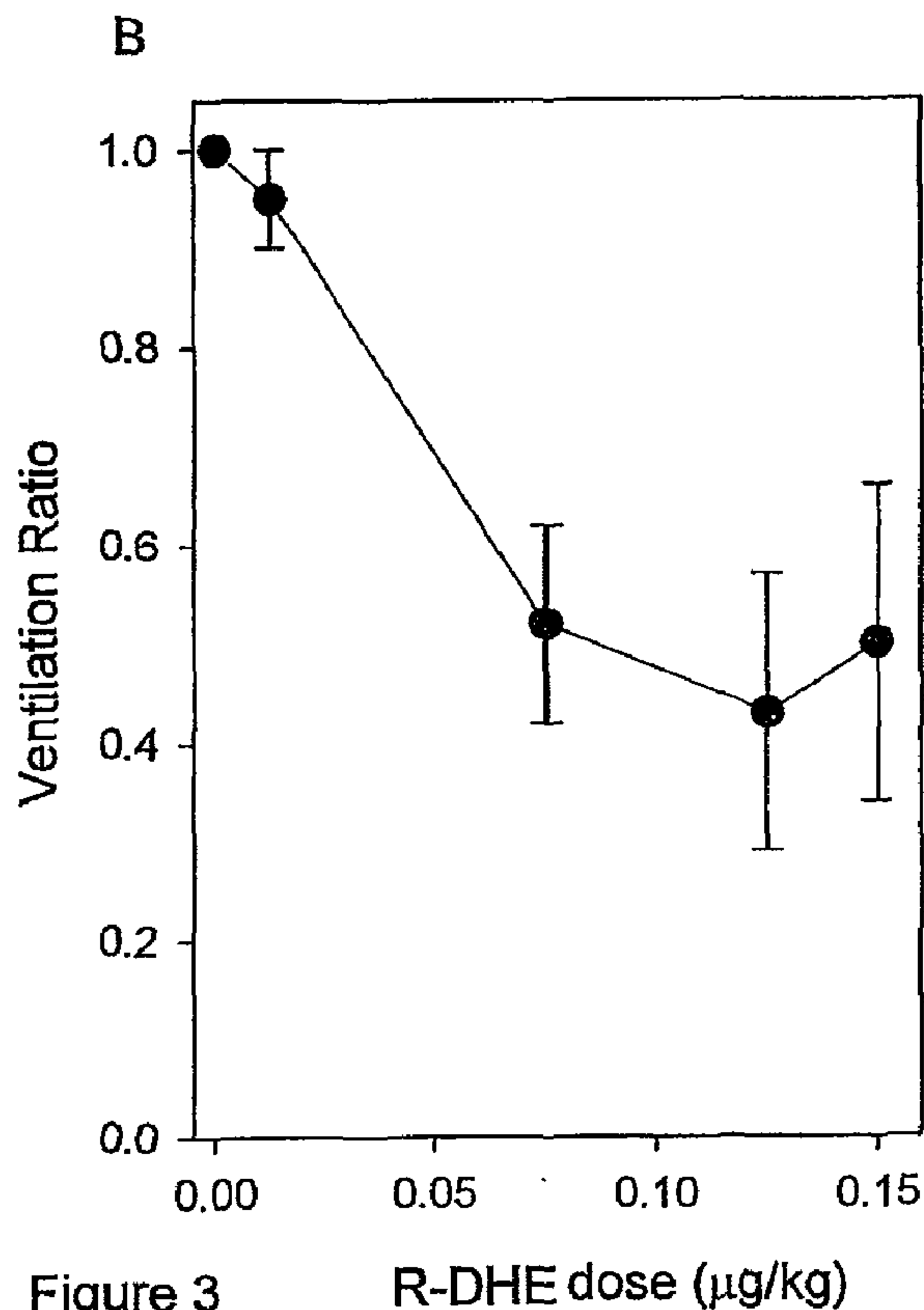


Figure 3

R-DHE dose (μg/kg)

(57) Abstract: The present invention provides a method of providing pain relief in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose of at least 0.01 μg/kg, preferably at least 0.05 μg/kg, and the level of respiratory depression in said subject is 65 or less % relative to the baseline level pre-administration of (R)-dihydroetorphine.

WO 2014/191710 A1

MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,

LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

DIHYDROETORPHINE FOR THE PROVISION OF PAIN RELIEF AND ANAESTHESIA

FIELD OF INVENTION

5 The present invention relates to a method of providing pain relief and anaesthesia in a human subject comprising administering (R)-dihydroetorphine. More specifically the invention relates to methods of providing analgesia or anaesthesia with reduced opioid-related side effects and in particular respiratory depression.

BACKGROUND

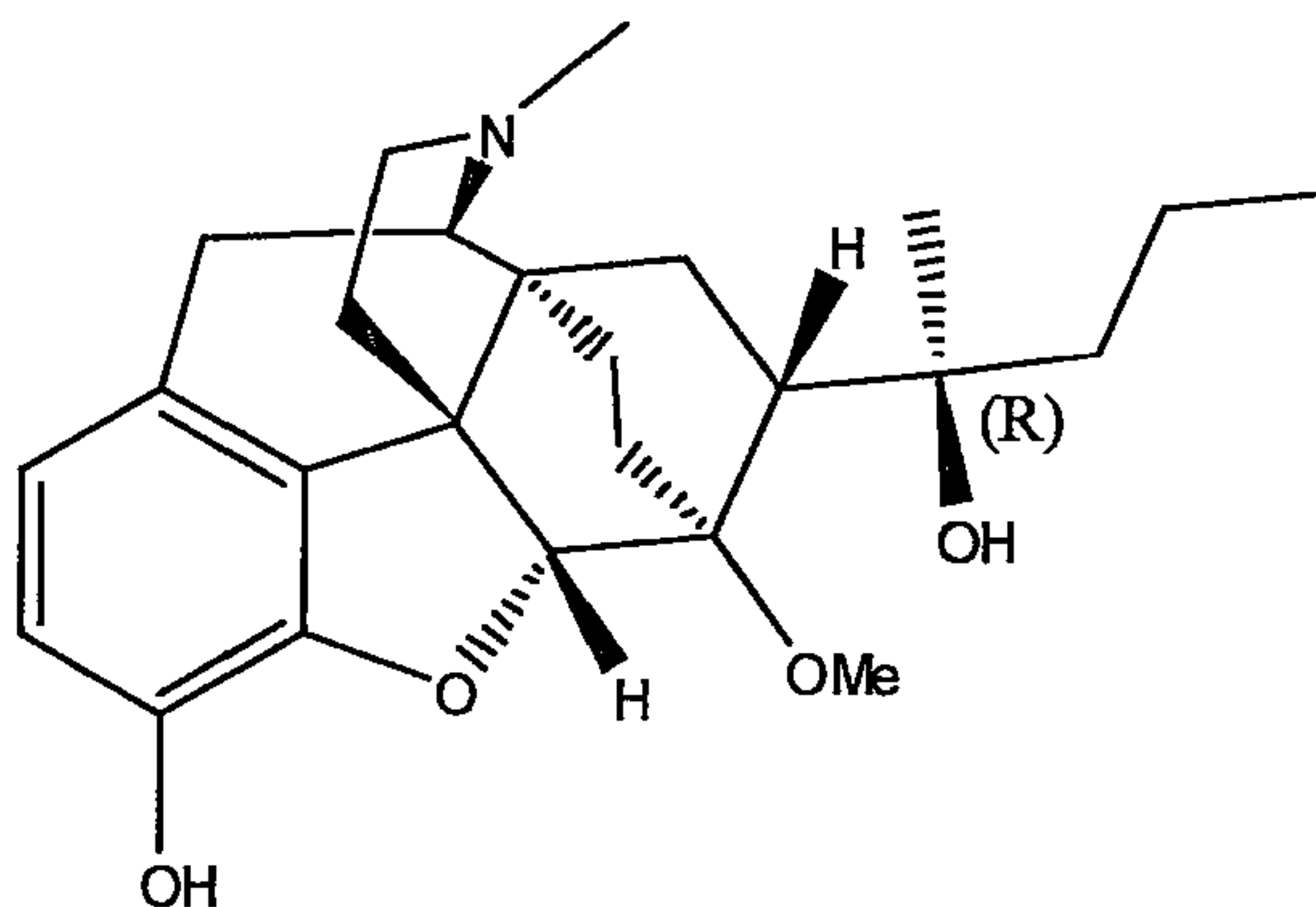
10 Pain is the most common symptom for which patients seek medical advice and treatment. Pain can be acute or chronic. While acute pain is usually self-limited, chronic pain persists for 3 months or longer and can lead to significant changes in a patient's personality, lifestyle, functional ability and overall quality of life (K. M. Foley, Pain, in Cecil Textbook of Medicine 100-107 (J. C. Bennett and F. Plum eds., 20th ed.
15 1996)). Pain can also be classified into different acute, subacute and chronic types including nociceptive, inflammatory, neuropathic or mixed pain. This includes visceral, somatic, radicular, neuralgic, central pain, pain associated with amputation, complex regional pain syndromes and fibromyalgia.

Pain has been traditionally managed by administering non-opioid analgesics,
20 such as acetylsalicylic acid, choline magnesium trisalicylate, acetaminophen, ibuprofen, fenoprofen, diflusal, and naproxen; or opioid analgesics, including morphine, hydromorphone, methadone, levorphanol, fentanyl, oxycodone, and oxymorphone.

Opioid analgesics form the cornerstone of contemporary treatment of moderate
25 to severe (acute and chronic) pain. Pain relief occurs in different clinical settings. Pain treatment is critical in the management and treatment of many diseases wherein pain is experienced as a symptom and/or as a side effect. Pain treatment is also critical during anaesthesia. Opioids, however, come with a series of side effects of which opioid-induced respiratory depression (OIRD) is potentially life threatening. In recent
30 years the number of lethal opioid-related respiratory complications has increased significantly, mainly due to the increase in opioid use, misuse or abuse of legally prescribed opioids for moderate to severe non-chronic cancer pain (most importantly lower back pain). Opioids produce respiratory depression via activation of the μ -opioid receptors (MORs) expressed on pontine neurons involved in the ventilatory control.

A wide range of opioid analgesics are known. Opioid agonists include, for example, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphine, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, hydrocodone, hydromorphone, hydromorphodone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacymorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, pantopon, papavereturn, paregoric, pentazocine, phenadoxone, phendimetrazine, phendimetrazone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, propylhexedrine, sufentanil, tilidine, tramadol, pharmaceutically acceptable salts thereof, and mixtures of any two or more of the foregoing.

Another known opioid analgesic is (R)-dihydroetorphine (R-DHE) shown below.



Compared to other opioid analgesics its properties have been investigated to a far lesser extent. Clinically it has only been used in humans in China in injectable and more recently sublingual form.

Fentanyl is currently the most commonly used opioid analgesic for the treatment of moderate to severe pain in clinical settings. It is usually administered intravenously (as a bolus or infusion). Low doses, e.g. 50-200 μg and low infusion rates, e.g. 0.05-0.08 $\mu\text{g}/\text{kg}/\text{minutes}$ are necessary if spontaneous ventilation is to be maintained because fentanyl produces a dose dependent respiratory depression with apnoea at high dose.

Fentanyl, and other members of the fentanyl family, is also the most commonly used opioid analgesic in anaesthesia. Following intravenous administration in a non-premedicated adult patient, fentanyl is expected to provide adequate analgesia for 10 – 20 minutes in surgical procedures involving low pain intensity. A bolus of fentanyl is expected to provide analgesia for about one hour and the analgesia produced is generally adequate for surgery involving moderate pain intensity. Administration of 50 microgram/kg will provide intense analgesia for some four to six hours for surgery associated with intense stimulation. Ventilated patients may be given a loading dose as a fast infusion of approximately 1 microgram/kg/minute for the first 10 minutes, followed by an infusion of approximately 0.1 microgram/kg/minute. Alternatively, the loading dose may be administered as a bolus. Due to the dose dependent respiratory depression associated with fentanyl, patients receiving fentanyl require careful and close monitoring during administration of the drug and for a prolonged period thereafter. The SPC for fentanyl also confirms that it should only be given in an environment where the airway can be controlled, resuscitation equipment is available and opioid antagonists are readily available.

Fentanyl additionally causes a number of other undesirable effects including, for example, nausea, vomiting, dizziness, mental clouding, dysphoria, pruritus, constipation, increased biliary tract pressure, urinary retention and hypotension. The development of tolerance to fentanyl and the risk of dependence and abuse for fentanyl is another undesirable effect.

As a result there is a continuing need for analgesic medications able to provide high efficacy pain relief while reducing the extent of undesired side effects.

SUMMARY OF INVENTION

Viewed from a first aspect the present invention provides a method of providing pain relief in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose of at least 0.01 µg/kg, more preferably at least 0.05 µg/kg, and the level of respiratory depression in said subject is 65 or less % relative to the baseline level pre-administration of (R)-dihydroetorphine and/or the level of respiration (e.g. as characterised by respiration minute volume and measured as described herein) is 35 to 100% relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides a method of providing pain relief in a human subject in need thereof comprising administering (R)-

dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose of at least 0.01 $\mu\text{g/kg}$, preferably at least 0.05 $\mu\text{g/kg}$, and the peak respiratory depression in said subject is 20 to 80 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

5 Viewed from a further aspect the present invention provides a method of providing analgesia in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose of at least 0.01 $\mu\text{g/kg}$, preferably at least 0.05 $\mu\text{g/kg}$, and the ventilation ratio in said subject is at least 0.3.

10 Viewed from a further aspect the present invention provides a method of providing pain relief in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose greater than the ED_{75} dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

15 Viewed from a further aspect the present invention provides a method of providing pain relief in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose greater than the ED_{50} dose and less than the ED_{75} dose and the level of respiratory depression in said subject is 50 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

20 Viewed from a further aspect the present invention provides a method of providing pain relief in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose greater than the ED_{75} dose and less than the ED_{95} dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

25 Viewed from a further aspect the present invention provides a method of providing pain relief to a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose that increases the pain threshold value relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.2 times and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

30 Viewed from a further aspect the present invention provides a method of providing pain relief in a human subject in need thereof whilst minimising risk of apnoea

35

comprising administering a dose of (R)-dihydroetorphine that provides dose dependent pain relief and dose-independent respiratory depression.

Viewed from a further aspect the present invention provides a method of providing maximum pain relief in a human subject in need thereof whilst minimising risk of apnoea comprising administering a dose of (R)-dihydroetorphine which causes a E_{MIN} in ventilation of 30-50 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides a method of treating pain in a human subject comprising administering to said subject an effective dose of (R)-dihydroetorphine, wherein during said treating at least one opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

Viewed from a further aspect the present invention provides a method of treating pain in a human subject comprising administering to said subject an effective dose of (R)-dihydroetorphine, wherein during said treating opioid-related respiratory depression is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine and at least one of the following criteria defining the levels of opioid-related side effects is satisfied in the 7.5 hours post administration of (R)-dihydroetorphine:

average NAS score for dizziness of less than 50

average NAS score for euphoria of less than 60

average NAS score for nausea of less than 40

average NAS score for sedation of less than 60

average NAS score for dysphoria of less than 40.

Viewed from a further aspect the present invention provides a method of providing anaesthesia in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose of at least 0.15 $\mu\text{g/kg}$ and the level of respiratory depression in said subject is 65 or less % relative to the baseline level pre-administration of (R)-dihydroetorphine and/or the level of respiration (e.g. as characterised by respiration minute volume and measured as described herein) is 35 to 100% relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides a method of providing anaesthesia in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered

in a dose of at least 0.15 $\mu\text{g/kg}$ and the peak respiratory depression in said subject is 20 to 80 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides a method of providing anaesthesia in a human subject in need thereof comprising administering
5 (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose of at least 0.15 $\mu\text{g/kg}$ and the resulting ventilation ratio in said subject is at least 0.3.

Viewed from a further aspect the present invention provides a method of providing anaesthesia in a human subject in need thereof comprising administering
10 (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose greater than the ED_{75} dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides a method of providing anaesthesia in a human subject in need thereof comprising administering
15 (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose greater than the ED_{50} dose and less than the ED_{75} dose and the level of respiratory depression in said subject is 50 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides a method of providing anaesthesia in a human subject in need thereof comprising administering
20 (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose greater than the ED_{75} dose and less than the ED_{95} dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.
25

Viewed from a further aspect the present invention provides a method of providing anaesthesia to a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose that increases the pain threshold value relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.5 times and the level of respiratory
30 depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides a method of providing anaesthesia in a human subject in need thereof whilst minimising risk of

apnoea comprising administering a dose of (R)-dihydroetorphine that provides dose dependent pain relief and dose-independent respiratory depression.

Viewed from a further aspect the present invention provides a method of providing maximum anaesthesia in a human subject in need thereof whilst minimising risk of apnoea comprising administering a dose of (R)-dihydroetorphine which causes a E_{MIN} in ventilation of 30-50 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides a method of providing anaesthesia in a human subject comprising administering to said subject an effective dose of (R)-dihydroetorphine, wherein during said treating at least one opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

Viewed from a further aspect the present invention provides a method of providing anaesthesia in a human subject comprising administering to said subject an effective dose of (R)-dihydroetorphine, wherein during said treating opioid-related respiratory depression is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine and at least one of the following criteria defining the levels of opioid-related side effects is satisfied in the 7.5 hours post administration of (R)-dihydroetorphine:

average NAS score for dizziness of 0 to 50
average NAS score for euphoria of 0 to 60
average NAS score for nausea of 0 to 40
average NAS score for sedation of 0 to 60
average NAS score for dysphoria of 0 to 40.

Viewed from a further aspect the present invention provides a method of providing pain relief or anaesthesia in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose of 0.20 to 0.5 $\mu\text{g/kg}$ and the level of respiratory depression in said subject is 85 or less % relative to the baseline level pre-administration of (R)-dihydroetorphine and/or the level of respiration (e.g. as characterised by respiration minute volume and measured as described herein) is 15 to 100% relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides a method of providing pain relief or anaesthesia in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine

is administered in a dose of 0.20 to 0.5 $\mu\text{g/kg}$ and the peak respiratory depression in said subject is 15 to 80 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

5 Viewed from a further aspect the present invention provides a method of providing pain relief or anaesthesia in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose of 0.20 to 0.5 $\mu\text{g/kg}$ and the resulting ventilation ratio in said subject is at least 0.15.

10 Viewed from a further aspect the present invention provides (R)-dihydroetorphine for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of at least 0.01 $\mu\text{g/kg}$, preferably at least 0.05 $\mu\text{g/kg}$, and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

15 Viewed from a further aspect the present invention provides (R)-dihydroetorphine for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of at least 0.01 $\mu\text{g/kg}$, preferably at least 0.05 $\mu\text{g/kg}$, and the peak respiratory depression in said subject is 20 to 80 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

20 Viewed from a further aspect the present invention provides (R)-dihydroetorphine for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of at least 0.01 $\mu\text{g/kg}$, preferably at least 0.05 $\mu\text{g/kg}$, and the ventilation ratio in said subject is at least 0.3.

25 Viewed from a further aspect the present invention provides (R)-dihydroetorphine for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{75} dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

30 Viewed from a further aspect the present invention provides (R)-dihydroetorphine for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{50} dose and less than the ED_{75} dose and the level of respiratory depression in said subject is 50 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides (R)-dihydroetorphine for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{75} dose and less than

the ED₉₅ dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides (R)-dihydroetorphine for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose that increases the pain threshold value relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.2 times and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides (R)-dihydroetorphine for the treatment of pain whilst minimising risk of apnoea, wherein during said treatment a dose of (R)-dihydroetorphine that provides dose dependent pain relief and dose-independent respiratory depression is administered.

Viewed from a further aspect the present invention provides (R)-dihydroetorphine for the treatment of pain whilst minimising risk of apnoea, wherein during said treatment a dose of (R)-dihydroetorphine which causes a E_{MIN} in ventilation of 30-50 % relative to the baseline level pre-administration of (R)-dihydroetorphine is administered.

Viewed from a further aspect the present invention provides (R)-dihydroetorphine for the treatment of pain, wherein during said treatment at least one opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

Viewed from a further aspect the present invention provides (R)-dihydroetorphine for the treatment of pain, wherein during said treatment opioid-related respiratory depression is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine and at least one of the following criteria is satisfied in the 7.5 hours post administration of (R)-dihydroetorphine:

- average NAS score for dizziness of less than 50
- average NAS score for euphoria of less than 60
- average NAS score for nausea of less than 40
- average NAS score for sedation of less than 60
- average NAS score for dysphoria of less than 40.

Viewed from a further aspect the present invention provides (R)-dihydroetorphine for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of at least 0.15 µg/kg and the level of

respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides (R)-dihydroetorphine for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of at least 0.15 $\mu\text{g/kg}$ and the peak
5 respiratory depression in said subject is 20 to 80 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides (R)-dihydroetorphine for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of at least 0.15 $\mu\text{g/kg}$ and the ventilation
10 ratio in said subject is at least 0.3.

Viewed from a further aspect the present invention provides (R)-dihydroetorphine for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{75} dose and the level of
15 respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides (R)-dihydroetorphine for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{50} dose and less than
20 the ED_{75} dose and the level of respiratory depression in said subject is 50 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides (R)-dihydroetorphine for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{75} dose and less than
25 the ED_{95} dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides (R)-dihydroetorphine for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose that increases the pain threshold value
30 relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.5 times and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides (R)-dihydroetorphine for providing anaesthesia whilst minimising risk of apnoea, wherein

during said treatment a dose of (R)-dihydroetorphine that provides dose dependent pain relief and dose-independent respiratory depression is administered.

Viewed from a further aspect the present invention provides (R)-dihydroetorphine for providing anaesthesia whilst minimising risk of apnoea, wherein
5 during said treatment a dose of (R)-dihydroetorphine which causes a E_{MIN} in ventilation of 30-50 % relative to the baseline level pre-administration of (R)-dihydroetorphine is administered.

Viewed from a further aspect the present invention provides (R)-dihydroetorphine for providing anaesthesia, wherein during said treatment at least one
10 opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

Viewed from a further aspect the present invention provides (R)-dihydroetorphine for providing anaesthesia, wherein during said treatment opioid-related respiratory depression is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine and at least one of the following criteria is
15 satisfied in the 7.5 hours post administration of (R)-dihydroetorphine:

average NAS score for dizziness of 0 to 50

average NAS score for euphoria of 0 to 60

average NAS score for nausea of 0 to 40

20 average NAS score for sedation of 0 to 60

average NAS score for dysphoria of 0 to 40.

Viewed from a further aspect the present invention provides (R)-dihydroetorphine for providing pain relief or anaesthesia, wherein said (R)-dihydroetorphine is administered in a dose of 0.20 to 0.5 $\mu\text{g/kg}$ and the level of
25 respiratory depression in the subject is 85 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides (R)-dihydroetorphine for providing pain relief or anaesthesia, wherein said (R)-dihydroetorphine is administered in a dose of 0.20 to 0.5 $\mu\text{g/kg}$ and the peak
30 respiratory depression in the subject is 15 to 80 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides (R)-dihydroetorphine for providing pain relief or anaesthesia, wherein said (R)-dihydroetorphine is administered in a dose of 0.20 to 0.5 $\mu\text{g/kg}$ and the ventilation ratio
35 in the subject is at least 0.15.

Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of at least 0.01 $\mu\text{g/kg}$, preferably at least 0.05 $\mu\text{g/kg}$, and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during treatment said (R)-dihydroetorphine is administered in a dose of at least 0.01 $\mu\text{g/kg}$, preferably at least 0.05 $\mu\text{g/kg}$, and the peak respiratory depression in said subject is 20 to 80 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of at least 0.01 $\mu\text{g/kg}$, preferably at least 0.05 $\mu\text{g/kg}$ and the ventilation ratio in said subject is at least 0.3.

Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{75} dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{50} dose and less than the ED_{75} dose and the level of respiratory depression in said subject is 50 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{75} dose and less than the ED_{95} dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose that increases the pain threshold value relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.2 times and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during said treatment a dose of (R)-dihydroetorphine that provides dose dependent pain relief and dose-independent respiratory depression is administered.

Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during said treatment a dose of (R)-dihydroetorphine which causes a E_{MIN} in ventilation of 30-50 % relative to the baseline level pre-administration of (R)-dihydroetorphine is administered.

Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during said treatment at least one opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during said treatment opioid-related respiratory depression is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine and at least one of the following criteria is satisfied in the 7.5 hours post administration of (R)-dihydroetorphine:

average NAS score for dizziness of less than 50
average NAS score for euphoria of less than 60
average NAS score for nausea of less than 40
average NAS score for sedation of less than 60
average NAS score for dysphoria of less than 40.

Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of at

least 0.15 $\mu\text{g/kg}$ and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during treatment said (R)-dihydroetorphine is administered in a dose of at least 0.15 $\mu\text{g/kg}$ and the peak respiratory depression in said subject is 20 to 80 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of at least 0.15 $\mu\text{g/kg}$ and the ventilation ratio in said subject is at least 0.3.

Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{75} dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{50} dose and less than the ED_{75} dose and the level of respiratory depression in said subject is 50 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{75} dose and less than the ED_{95} dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose that increases the pain threshold value relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.5 times and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during said treatment a dose of (R)-dihydroetorphine that provides dose dependent pain relief and dose-independent respiratory depression is administered.

5 Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during said treatment a dose of (R)-dihydroetorphine which causes a E_{MIN} in ventilation of 30-50 % relative to the baseline level pre-administration of (R)-dihydroetorphine is administered.

10 Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during said treatment at least one opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

15 Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during said treatment opioid-related respiratory depression is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine and at least one of the following criteria is satisfied in the 7.5 hours post administration of (R)-dihydroetorphine:

20 average NAS score for dizziness of 0 to 50
average NAS score for euphoria of 0 to 60
average NAS score for nausea of 0 to 40
average NAS score for sedation of 0 to 60
average NAS score for dysphoria of 0 to 40.

25 Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain or anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of 0.20 to 0.5 $\mu\text{g/kg}$ and the level of respiratory depression in said subject is 85 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

30 Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain or anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of 0.20 to 0.5 $\mu\text{g/kg}$ and the peak respiratory depression in said subject is 15 to 80 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

Viewed from a further aspect the present invention provides use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain or anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of 0.20 to 0.5 $\mu\text{g/kg}$ and the ventilation ratio in said subject is at least 0.3.

5

DEFINITIONS

As used herein the term "pain" refers to an unpleasant feeling that is conveyed to the brain by sensory neurons called nociceptors.

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As used herein the term "nociceptive pain" refers to pain caused by tissue injury detected by nociceptors at the site of injury. After the injury, the site becomes a source of ongoing pain and tenderness.

15

As used herein the terms "pain relief" and "analgesia" refer to the removal and/or reduction in pain resulting from the action of a drug. The terms are used herein synonymously.

As used herein the term "anaesthesia" means a loss of consciousness, sensation, or awareness resulting from pharmacological depression of nerve function.

As used herein the term "sedation" refers to the calming of mental excitement or abatement of physiological function by administration of a drug called a sedative.

20

As used herein, the term "effective amount" means the amount of drug needed to reach an analgesic effect.

As used herein the term "opioid" refers to natural, semi-synthetic and synthetic drugs that have opioid-like effects similar to morphine.

25

As used herein the term "side effect" refers to an effect of a drug, e.g. opioid, that is not the intended therapeutic effect. The term "opioid-related side effect" refers to non-therapeutic effects caused by opioids. Respiratory depression is an example of an opioid-related side effect.

30

As used herein the terms "respiration" and "ventilation" are used to refer to the flow of air into the lungs. Generally the terms are used herein interchangeably. Respiration may be characterised by respiration minute volume (or minute ventilation) which is the volume of gas inhaled or exhaled from the lungs per minute. Unless otherwise specified the term respiration refers to average respiration.

35

As used herein the term "respiratory depression" refers to a decrease in the respiration minute volume. Respiratory depression may manifest as shortness of breath and/or a slowing in rate of breathing. A respiratory depression of 100%

indicates apnoea. A respiratory depression of 40% indicates that the respiration minute volume is 60 % of the baseline value. Respiratory depression may be measured by different techniques as described below. Unless specified otherwise, the term respiratory depression refers to average respiratory depression. As used herein
5 the term “peak respiratory depression” refers to the maximum level of respiratory depression that is detected during measurement of respiration over a period of time, e.g. 1 hour.

As used herein the term “ventilation ratio” refers to the ratio of the average level of respiration or ventilation post-administration of drug to the average level of
10 respiration or ventilation pre-administration of drug, e.g. as determined according to the method set out in the examples herein. A value of less than 1 therefore indicates a decrease in ventilation, i.e. respiratory depression.

As used herein the term “dizziness” refers to a sensation of unsteadiness, often accompanied by a feeling of movement within the head.

15 As used herein the term “euphoria” refers to a feeling of elation or well being.

As used herein the term “nausea” refers to the sensation of being about to vomit.

As used herein the term “sedation” refers to a decrease in attention, mental awareness, focus, and state of consciousness and manifests in a lack of physical
20 strength (muscle fatigue), lack of voluntary activity, lethargy, drowsiness, and sleep.

As used here the term “dysphoria” refers to an emotional state characterised by anxiety, depression and restlessness.

As used herein the term “apnoea” refers to the cessation of rhythmic breathing for 60 seconds or more.

25 As used herein the term “equianalgesic” refers to a dose of drug that provides substantially the same level of analgesia as a given amount of another drug. The amounts of each drug may be different, but the level of analgesia provided is the same.

As used herein the term “ceiling effect” refers to the achievement of a maximum effect regardless of an increase in drug dose. In other words the effect plateaus. This
30 means that increasing the drug dose further will not increase the effect that has a ceiling any further.

As used herein the term “dose-independent respiratory depression” refers to the occurrence of a ceiling effect or plateauing in respiratory depression that does not cause apnoea. This means that further increases in the drug dose will not increase the
35 respiratory depression any further.

As used herein the term " E_{MIN} " refers to the asymptotic minimum in respiration or ventilation.

As used herein the term " ED_{50} " refers to the dose causing a 50% reduction in respiration or ventilation relative to the baseline value pre-administration of the drug. Analogously the terms " ED_{75} ", " ED_{85} " and " ED_{90} " refers to the dose causing a 75 %, 85 % and 90% reduction in ventilation relative to the baseline value pre-administration of the drug respectively.

As used herein the NAS score is on a scale of 0 to 100 where 0 is no effect and 100 is worst imaginable effect.

10

DETAILED DESCRIPTION OF THE INVENTION

The present invention generally relates to methods of treating pain or providing analgesia. The methods of the invention may alleviate pain or may reduce the level of pain. Preferably the methods of the invention alleviate or remove pain. The methods of the present invention include treating pain or providing analgesia during anaesthesia.

In the methods of the invention, pain relief or analgesia, whether during anaesthesia or not, is treated by administering (R)-dihydroetorphine, which is an opioid, whilst controlling respiratory depression and minimising other side effects conventionally associated with opioid treatment. The common occurrence of side effects during opioid treatment is disadvantageous for several reasons. In some cases side effects, e.g. respiratory depression, can endanger a subject's life and in extreme cases lead to fatality. More commonly side effects (e.g. nausea, dysphoria) negatively impact either physically and/or psychologically on subjects and in almost all cases side effects reduce patient compliance to a treatment regime.

It has been surprisingly found that the level of respiratory depression associated with methods of treating pain by administering (R)-dihydroetorphine exhibits a ceiling effect. In other words the level of respiratory depression associated with administration of (R)-dihydroetorphine reaches a maximum and further increases in the dose of (R)-dihydroetorphine administered do not impact on the level of respiratory depression observed. Even more significantly the ceiling effect is achieved in the analgesic window. This means that the treatment of pain by administration of (R)-dihydroetorphine, e.g. in certain doses, is significantly safer and less likely to result in opioid-induced respiratory depression, than treatment with other opioids such as

fentanyl. This is particularly advantageous when the treatment of pain is during anaesthesia wherein the highest doses of (R)-dihydroetorphine tend to be used.

The level of respiratory depression associated with an opioid, e.g. (R)-dihydroetorphine, treatment may be quantified versus the baseline respiration level, i.e. the respiration level pre administration of the drug. Preferably the average level of respiratory depression is determined by measuring the average level of respiration pre and post administration of the opioid, e.g. as described in the examples. A respiratory depression of 0% means that the levels of respiration pre and post administration of the opioid are identical. A respiratory depression of 100% means that post administration of the opioid apnoea occurs. A respiratory depression of 30% means that post administration of the drug the level of respiration is reduced by 30% and the level of respiration is 70% of the pre administration level. Respiratory depression is therefore the level of reduction in respiration relative to the pre administration level. Preferably the pre administration average respiratory function is measured for 1 hour prior to administration of the drug.

In the methods of the present invention the average and peak respiratory depression is preferably measured under iso-hypercapnic conditions for, e.g. 1 hour following administration of said (R)-dihydroetorphine. Preferably the (R)-dihydroetorphine is administered intravenously. Preferably the dose of (R)-dihydroetorphine is administered over 10 minutes. The 1 hour over which measurement is made commences following the administration of (R)-dihydroetorphine.

The measurement of average respiratory depression is preferably carried out by the end-tidal forcing technique wherein end-tidal PCO_2 and end tidal PO_2 are forced to follow a specific pattern over time. Advantageously this ensures that the ventilatory response of the test opioid is independent of effects of confounding changes in arterial CO_2 and independent of the speed of administration of the drug. Preferably the level of respiratory depression is measured as described in the examples herein. Particularly preferably the average respiratory depression is measured under iso-hypercapnic conditions for 10 to 120 minutes, more preferably 30 to 90 minutes and still more preferably 1 hour post-administration of (R)-dihydroetorphine with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of $20 \pm 2\text{L/min}$. Preferably the end tidal carbon dioxide level is clamped at 50 mmHg. Preferably the level of respiration or ventilation is measured continuously.

In some preferred methods of the invention, the average respiratory depression, e.g. as measured under the above conditions, is 0 to 65%, more preferably 0 to 60 %, still more preferably 0 to 50 %, yet more preferably 0 to 45 % and even more preferably 0 to 35 % relative to the baseline level prior to administration of the (R)-dihydroetorphine. In further preferred methods of the invention, the average respiratory depression e.g. as measured under the above conditions, is 20 to 65 %, more preferably 40 to 65 % and still more preferably 50 to 65 % relative to the baseline level prior to administration of (R)-dihydroetorphine. A smaller % of respiratory depression is advantageous, with a value of 0% indicating that no respiratory depression occurs as a result of administration of the drug.

Thus in preferred methods of the invention the level of respiration, e.g. as characterised by respiration minute volume and measured as described above, is 35 to 100%, more preferably 40 to 100 %, still more preferably 50 to 100%, yet more preferably 55 to 100% and even more preferably 65 to 100 % relative to the baseline respiration level prior to administration of the (R)-dihydroetorphine. In further preferred methods of the invention, the average respiration, e.g. as characterised by respiration minute volume and measured as described above, is 35 to 80%, more preferably 35 to 60% and still more preferably 35 to 50 % relative to the baseline respiration level prior to administration of the (R)-dihydroetorphine.

The peak respiratory depression may also be measured by the above-described technique. The measurement of peak respiratory depression is preferably carried out by the end-tidal forcing technique wherein end-tidal PCO_2 and end tidal PO_2 are forced to follow a specific pattern over time. The peak respiratory depression is the highest level of respiratory depression measured under iso-hypercapnic conditions for 10 to 120 minutes, more preferably 30 to 90 minutes and still more preferably 1 hour post-administration of (R)-dihydroetorphine with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of $20 \pm 2\text{L/min}$ as described above. Preferably the end tidal carbon dioxide level is clamped at 50 mmHg. When measuring peak respiratory depression, the level of respiration or ventilation is preferably measured continuously.

In some preferred methods of the invention, the peak respiratory depression is 20 to 80 %, more preferably 45 to 75 %, still more preferably 50 to 70 % and yet more preferably 60 to 70 % relative to the baseline level prior to administration of (R)-dihydroetorphine. In further preferred methods of the invention, the nadir in respiration level is 20 to 80%, more preferably 25 to 55 %, still more preferably 30 to 50 % and yet

more preferably 30 to 40 % relative to the baseline level prior to administration of (R)-dihydroetorphine.

5 Respiratory depression may alternatively be quantitated in terms of a ventilation ratio. The ventilation ratio is the ratio of average respiration in the 1 hour post administration of (R)-dihydroetorphine to the average respiration pre-administration of (R)-dihydroetorphine. The pre administration respiration is measured for 1 hour prior to administration of the drug. Thus a high ventilation ratio corresponds to a low level of respiratory depression. In preferred methods of the present invention the ventilation ratio in the subject is at least 0.3. More preferably the ventilation ratio in the subject is
10 between 0.3 and 0.6, still more preferably 0.35 to 0.55 and yet more preferably 0.4 to 0.45.

Preferably the ventilation ratio is determined by measuring respiration pre-administration of (R)-dihydroetorphine for 1 hour and for 1 hour post-administration of (R)-dihydroetorphine under iso-hypercapnic conditions. Particularly preferably the
15 ventilation ratio is determined by measuring respiration pre-administration of (R)-dihydroetorphine and for 10 to 120 minutes, more preferably 30 to 90 minutes and still more preferably 1 hour post-administration administration of (R)-dihydroetorphine under iso-hypercapnic conditions with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of $20 \pm$
20 2L/min. Yet more preferably the end tidal carbon dioxide level is clamped at 50 mmHg. Preferably respiration or ventilation is measured continuously.

The above-described methods for measuring peak and average respiratory depression are under forced conditions. Average respiratory depression may be alternatively measured in a physiological setting by measuring oxygen saturation levels
25 (SpO_2) prior to and post administration of (R)-dihydroetorphine. SpO_2 levels may be determined using an oximeter according to conventional procedures.

The pre administration level of SpO_2 is preferably measured for 1 hour prior to administration of the drug. The post administration SpO_2 is preferably measured for 1 hour following administration of the (R)-dihydroetorphine. The average respiratory
30 depression is the ratio of the average SpO_2 level post administration to the average SpO_2 level pre administration $\times 100$. Preferably the (R)-dihydroetorphine is administered intravenously. Preferably the dose of (R)-dihydroetorphine is administered over 10 minutes. The 1 hour over which measurement is made commences following the administration of (R)-dihydroetorphine.

When determined in a clinical setting using SpO₂ levels, the average respiratory depression is 0 to 10%, more preferably 0 to 7.5 %, still more preferably 0 to 5 %, yet more preferably 0 to 2.5 % and even more preferably 0 to 2 % relative to the baseline level prior to administration of the (R)-dihydroetorphine. In such preferred methods the average respiration, e.g. as characterised by respiration minute volume and measured using SpO₂ levels, is 90 to 100%, more preferably 92.5 to 100 %, still more preferably 95 to 100% and yet more preferably 98 to 100% relative to the baseline respiration level prior to administration of the (R)-dihydroetorphine.

In preferred methods of the invention, e.g. for providing pain relief or analgesia, (R)-dihydroetorphine is administered in a dose of 0.01 to 1 µg/kg, more preferably 0.02 to 0.75 µg/kg, still more preferably 0.03 to 0.5 µg/kg and yet more preferably 0.03 to 0.4 µg/kg. Particularly preferably the (R)-dihydroetorphine is administered in a dose of 0.04 to 0.25 µg/kg, more preferably 0.05 to 0.175 µg/kg, still more preferably 0.06 to 0.16 µg/kg and yet more preferably 0.075 to 0.15 µg/kg. Still more preferably the dose of (R)-dihydroetorphine is 0.075 µg/kg, 0.125 µg/kg, 0.15 µg/kg, 0.20 µg/kg or 0.25 µg/kg.

Especially preferably the (R)-dihydroetorphine is administered in a dose of 0.01 to 1 µg/kg/h, more preferably 0.02 to 0.75 µg/kg/h and still more preferably 0.03 to 0.5 µg/kg/h. Particularly preferably the (R)-dihydroetorphine is administered in a dose of 0.04 to 0.25 µg/kg/h, more preferably 0.05 to 0.175 µg/kg/h, still more preferably 0.06 to 0.16 µg/kg/h and yet more preferably 0.075 to 0.15 µg/kg/h. Still more preferably the (R)-dihydroetorphine is administered in a dose of 0.04 to 0.25 µg/kg/10 min, more preferably 0.05 to 0.175 µg/kg/10 min, still more preferably 0.06 to 0.16 µg/kg/10 min and yet more preferably 0.075 to 0.15 µg/kg/10 min.

At a dose of about 0.05 µg/kg or greater the dose response curve for analgesia is dose dependent but the dose response curve for respiratory depression or ventilation ratio is dose independent. In other words at a dose of about 0.05 µg/kg or greater the benefit from the ceiling effect in respiratory depression is realised. Thus in particularly preferred methods of the invention (R)-dihydroetorphine is administered in a dose of 0.05 to 0.175 µg/kg, more preferably 0.075 to 0.15 µg/kg, and the level of respiratory depression in the subject is between 50 and 65 % relative to the baseline level pre-administration of (R)-dihydroetorphine. In further particularly preferred methods of the invention (R)-dihydroetorphine is administered in a dose of 0.075 to 0.15 µg/kg and the ventilation ratio in the subject is 0.3 to 0.5. Doses below the ceiling effect, e.g. 0.0125

$\mu\text{g/kg}$, are, however, also advantageous as the level of respiratory depression associated with these may be, e.g. as low as less than 5%.

In preferred methods of the invention, e.g. for providing anaesthesia, (R)-dihydroetorphine is administered in a dose of 0.05 to 1 $\mu\text{g/kg}$, more preferably 0.075 to 0.75 $\mu\text{g/kg}$ and still more preferably 0.1 to 0.6 $\mu\text{g/kg}$. Particularly preferably the (R)-dihydroetorphine is administered in a dose of 0.15 to 0.6 $\mu\text{g/kg}$, more preferably 0.175 to 0.5 $\mu\text{g/kg}$ and still more preferably 0.2 to 0.45 $\mu\text{g/kg}$. Especially preferably the (R)-dihydroetorphine is administered in a dose of 0.05 to 1 $\mu\text{g/kg/h}$, more preferably 0.075 to 0.75 $\mu\text{g/kg/h}$ and still more preferably 0.1 to 0.6 $\mu\text{g/kg/h}$. Particularly preferably the (R)-dihydroetorphine is administered in a dose of 0.15 to 0.6 $\mu\text{g/kg/h}$, more preferably 0.175 to 0.5 $\mu\text{g/kg/h}$, still more preferably 0.2 to 0.45 $\mu\text{g/kg/h}$ and yet more preferably 0.3 to 0.4 $\mu\text{g/kg/h}$. Still more preferably the (R)-dihydroetorphine is administered in a dose of 0.15 to 0.6 $\mu\text{g/kg/10 min}$, more preferably 0.175 to 0.5 $\mu\text{g/kg/10 min}$, still more preferably 0.2 to 0.45 $\mu\text{g/kg/10 min}$ and yet more preferably 0.3 to 0.4 $\mu\text{g/kg/10 min}$. At these doses the dose response curve for analgesia is dose dependent but the dose response curve for respiratory depression or ventilation ratio is dose independent thus the benefit from the ceiling effect in respiratory depression is realised. Thus in particularly preferred methods of the invention (R)-dihydroetorphine is administered in a dose of 0.15 to 0.4 $\mu\text{g/kg}$, more preferably 0.2 to 0.3 $\mu\text{g/kg}$, and the level of respiratory depression in the subject is between 50 and 65 % relative to the baseline level pre-administration of (R)-dihydroetorphine. In further particularly preferred methods of the invention (R)-dihydroetorphine is administered in a dose of 0.15 to 0.4 $\mu\text{g/kg}$ and the ventilation ratio in the subject is 0.3 to 0.5.

In further preferred methods of the invention (R)-dihydroetorphine is administered in a dose greater than or equal to the ED_{75} dose, more preferably a dose greater than or equal to the ED_{85} dose and still more preferably a dose greater than or equal to the ED_{90} dose and the level of respiratory depression in the subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine. The ED_{75} , ED_{85} and ED_{90} doses may be determined by methods conventional in the art from the dose response curve, e.g. as described in the examples.

Particularly preferably (R)-dihydroetorphine is administered in a dose between the ED_{75} dose and the ED_{95} dose. Particularly preferably the level of respiratory depression in the subject is between 40 and 65 % relative to the baseline level pre-administration of (R)-dihydroetorphine. This highlights the dose-independence of (R)-dihydroetorphine on respiratory depression. As set out above the ED_{75} dose of (R)-

5 dihydroetorphine is the dose that causes a 75 % reduction in ventilation. Because respiratory depression reaches a ceiling at approximately the ED₅₀ dose, however, the level of ventilation at ED₇₅, ED₈₅ and ED₉₀ is fairly similar to that at ED₅₀ and is thus acceptable, e.g. around 35-50 % of the baseline level. This makes the use of (R)-dihydroetorphine, particularly at higher doses, much safer to use than other opioids such as fentanyl.

10 Thus in one particularly preferred method of the present invention (R)-dihydroetorphine is administered in a dose greater than the ED₅₀ dose and less than the ED₇₅ dose and the level of respiratory depression in the subject is 50 % or less, more preferably 45 % or less and still more preferably 40 % or less, relative to the baseline level pre-administration of (R)-dihydroetorphine.

15 In another particularly preferred method of the present invention (R)-dihydroetorphine is administered in a dose greater than the ED₇₅ dose and less than the ED₉₅ dose and the level of respiratory depression in the subject is 65 % or less, more preferably 60 % or less and still more preferably 55 % or less, relative to the baseline level pre-administration of (R)-dihydroetorphine.

20 A significant advantage of the methods of the present invention is that it enables a high level of pain relief, in some cases during anaesthesia, to be provided whilst minimising risk of apnoea and the corresponding risk of need for intervention and provision of assisted breathing. This is preferably achieved by administering a dose of (R)-dihydroetorphine that provides dose dependent pain relief and dose-independent respiratory depression. Preferably the dose of (R)-dihydroetorphine achieves a E_{MIN} in ventilation of 30 to 50 % $\pm$ 10%, more preferably 35 to 45 % $\pm$ 10% and still more preferably 35 to 45 % $\pm$ 5%, relative to the baseline level pre-administration of (R)-dihydroetorphine. At such a dose, respiratory depression is dose-independent, but pain relief is still dose dependent. Preferably such a dose is in the range 0.075 to 0.175 μ g/kg.

30 Preferred methods of the invention provide a level of analgesia which, as measured by the cold pressor test, is at least a -20 % change, preferably at least a -40 % change, more preferably at least a -50% change and yet more preferably at least a -70 %, compared to baseline level, e.g. pre-administration of R-dihydroetorphine. Particularly preferred methods of the invention provide a level of analgesia which, as measured by the cold pressor test, is a -20 to -90 % change, more preferably a -25 to -85% change and still more preferably a -30 to -80% change compared to baseline level, e.g. pre-administration of R-dihydroetorphine. Preferably these changes are

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achieved at 10 minutes, 30 minutes, 1 hour and/or 2 hours following administration of (R)-dihydroetorphine. The changes are “-” because they indicate that less pain is experienced relative to baseline level. Preferably the cold pressor test is carried out as described in the examples.

5 Further preferred methods of the invention increase the pain threshold level in a subject relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.2 times and preferably at least 1.5 times. Further preferred methods of the invention increase the pain threshold level in the subject relative to the baseline level pre-administration of (R)-dihydroetorphine by 1.2 to 3.0 times. Preferably the pain
10 threshold levels are measured by applying pain using a transcutaneous electrical stimulus to the skin over the tibial bone and increasing the electrical stimulus at a rate of 0.5 mA per 2s, e.g. as described in the examples. Although respiratory depression is the most dangerous side effect associated with opioid pain relief treatment and anaesthesia, other side effects are also common and problematic. A
15 benefit of the use of (R)-dihydroetorphine in the treatment of pain and provision of anaesthesia is that the spectrum of side effects associated with the treatment is minimised. In preferred methods of the invention the opioid-related side effects that are minimised. Particularly preferably the opioid related side effects are reduced compared to treatment with an equianalgesic dose of fentanyl. Preferably the opioid-
20 related side effects that are reduced compared to an equianalgesic dose of fentanyl are selected from respiratory depression, dizziness, euphoria, nausea, sedation and dysphoria. Of these side effects, as discussed above, respiratory depression is the most dangerous since in extreme cases it can cause patient death. Thus, in particularly preferred methods of the invention, the side effect of respiratory depression
25 is minimised, e.g. reduced.

The level of each of dizziness, euphoria, nausea, sedation and dysphoria associated with an opioid, e.g. (R)-dihydroetorphine, treatment may also be measured and quantified. This can be carried out, for example, by a questionnaire, e.g. as described in the examples herein.

30 In preferred methods of the invention, the side effect of dizziness is minimised. In preferred methods of the invention, the average NAS score for dizziness is 0 to 50, more preferably 0 to 45 and still more preferably 0 to 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

In preferred methods of the invention, the side effect of euphoria is minimised.
35 In preferred methods of the invention, the average NAS score for euphoria is 0 to 60,

more preferably 0 to 50 and still more preferably 0 to 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

In preferred methods of the invention, the side effect of nausea is minimised. In preferred methods of the invention, the average NAS score for nausea is 0 to 40, more preferably 0 to 35 and still more preferably 0 to 30 in the 7.5 hours post administration of (R)-dihydroetorphine.

In preferred methods of the invention, the side effect of sedation is minimised. In preferred methods of the invention, the average NAS score for sedation is 0 to 60, more preferably 0 to 55 and still more preferably 0 to 50 in the 7.5 hours post administration of (R)-dihydroetorphine.

In preferred methods of the invention, the side effect of dysphoria is minimised. In preferred methods of the invention, the average NAS score for dysphoria is 0 to 40, more preferably 0 to 35 and still more preferably 0 to 30 in the 7.5 hours post administration of (R)-dihydroetorphine.

In preferred methods of the invention at least two opioid-related side effects selected from respiratory depression, dizziness, euphoria, nausea, sedation and dysphoria are minimised, e.g. the average NAS scores are less than the values hereinbefore described. In particularly preferred methods at least three, and still more preferably at least four and yet more preferably all of the afore-mentioned opioid-related side effects are minimised, e.g. the average NAS scores are less than the values hereinbefore described.

In still further preferred methods respiratory depression and at least one opioid-related side effect selected from dizziness, euphoria, nausea, sedation and dysphoria are minimised, e.g. the average NAS scores are less than the values hereinbefore described. In particularly preferred methods respiratory depression and at least two, and still more preferably at least three and yet more preferably at least four of the afore-mentioned opioid-related side effects are minimised, e.g. the average NAS scores are less than the values hereinbefore described.

In a particularly preferred method of the invention, during the treating, opioid-related respiratory depression is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine and at least one, preferably at least two, still more preferably at least three, yet more preferably at least four and even more preferably all of the following criteria defining the levels of opioid-related side effects is satisfied in the 7.5 hours post administration of (R)-dihydroetorphine:

average NAS score for dizziness of 0 to 50

average NAS score for euphoria of 0 to 60

average NAS score for nausea of 0 to 40

average NAS score for sedation of 0 to 60

average NAS score for dysphoria of 0 to 40.

5 In further preferred methods of the present invention, opioid-related side effects are reduced compared to the use of another opioid. In further preferred methods, the opioid-related side effects are reduced compared to the use of an equianalgesic dose of fentanyl. A reduction in side-effects compared to fentanyl is highly desirable as fentanyl is currently regarded as the gold standard opioid for treatment of pain and
10 provision of anaesthesia.

When comparing the opioid-related side effects caused by (R)-dihydroetorphine and by another opioid, e.g. fentanyl, the comparison is between doses achieving an equivalent analgesic effect, i.e. an equianalgesic effect. Otherwise the treatments are identical, i.e. the formulation of the opioids is identical or similar, e.g. drug in aqueous
15 solution with tonicity modifier with or without a pH buffering agent, the route of administration is identical and critically the analgesia achieved is identical.

When comparing the opioid-related side effects caused by (R)-dihydroetorphine and by another opioid, e.g. fentanyl, preferably the peak pain threshold values are preferably within $\pm 20\%$, more preferably within $\pm 10\%$ and still more preferably within $\pm$
20 5%. When comparing the opioid-related side effects caused by (R)-dihydroetorphine and by another opioid, e.g. fentanyl, preferably the average pain threshold values are preferably within $\pm 20\%$, more preferably within $\pm 10\%$ and still more preferably within $\pm 5\%$.

25 Examples of some equianalgesic doses of (R)-dihydroetorphine and fentanyl are shown in the table below:

(R)- Dihydroetorphine ($\mu\text{g}/\text{kg}$)	Fentanyl ($\mu\text{g}/\text{kg}$)
0.0125	0.150 to 0.3, preferably 0.185 to 0.3, more preferably 0.225
0.075	0.90 to 1.875, preferably 1.125 to 1.875, more preferably 1.35
0.125	1.500 to 3.125, preferably 1.875 to 3.125, more preferably 2.25
0.15	1.800 to 3.125, preferably 2.25 to 3.75, more preferably 2.7

As discussed above, the level of respiratory depression associated with an opioid, e.g. (R)-dihydroetorphine and fentanyl, treatment may be measured and quantified and therefore compared. In preferred methods of the invention, the respiratory depression is less than with an equianalgesic dose of fentanyl. Particularly preferably the respiratory depression is at least 10% less, more preferably at least 20% less and still more preferably at least 30% less. In some methods of the invention, respiratory depression may be avoided altogether and is 100% less. As above, when comparing the opioid-related side effects caused by (R)-dihydroetorphine and by another opioid, e.g. fentanyl, the comparison is between doses achieving an equivalent analgesic effect.

In further preferred methods of the invention, dizziness is less than with an equianalgesic dose of fentanyl. Particularly preferably dizziness is at least 5% less, more preferably at least 10% less and still more preferably at least 15% less. In some methods of the invention, dizziness may be avoided altogether and is 100% less.

In further preferred methods of the invention, euphoria is less than with an equianalgesic dose of fentanyl. Particularly preferably euphoria is at least 5% less, more preferably at least 10% less and still more preferably at least 15% less. In some methods of the invention, euphoria may be avoided altogether and is 100% less.

In further preferred methods of the invention, nausea is less than with an equianalgesic dose of fentanyl. Particularly preferably nausea is at least 5% less, more preferably at least 10% less and still more preferably at least 15% less. In some methods of the invention, nausea may be avoided altogether and is 100% less.

In further preferred methods of the invention, sedation is less than with an equianalgesic dose of fentanyl. Particularly preferably sedation is at least 5% less, more preferably at least 10% less and still more preferably at least 15% less. In some methods of the invention, sedation may be avoided altogether and is 100% less.

In further preferred methods of the invention, dysphoria is less than with an equianalgesic dose of fentanyl. Particularly preferably dysphoria is at least 5% less, more preferably at least 10% less and still more preferably at least 15% less. In some methods of the invention, dysphoria may be avoided altogether and is 100% less.

In preferred methods of the invention at least two opioid-related side effects selected from respiratory depression, dizziness, euphoria, nausea, sedation and dysphoria are reduced compared to treatment with an equianalgesic dose of fentanyl. In particularly preferred methods at least three, and still more preferably at least four

and yet more preferably all of the afore-mentioned opioid-related side effects are reduced compared to treatment with an equianalgesic dose of fentanyl.

5 In further preferred methods of the present invention respiratory depression and at least one opioid-related side effect selected from dizziness, euphoria, nausea, sedation and dysphoria are reduced compared to treatment with an equianalgesic dose of fentanyl. In particularly preferred methods respiratory depression and at least two, and still more preferably at least three and yet more preferably at least four, e.g. all, of the afore-mentioned opioid-related side effects are reduced compared to treatment with an equianalgesic dose of fentanyl.

10 In the methods of the invention, e.g. for providing pain relief, the (R)-dihydroetorphine may be administered in a variety of ways including for example regionally or systemically. The (R)-dihydroetorphine may also be administered parenterally. Preferably the (R)-dihydroetorphine is administered parenterally and more preferably intravenously.

15 Intravenous delivery of drugs may be carried out by either one or more bolus injections or by a continuous infusion. A bolus injection is defined herein as the injection of (R)-dihydroetorphine, preferably in a relatively high quantity, over a short period of time and is the opposite of gradual administration. Continuous infusion is defined as the administration of (R)-dihydroetorphine over a prolonged period of time.

20 When used for providing anaesthesia, (R)-dihydroetorphine may be administered locally or generally. Local anaesthesia includes regional, epidural and spinal anaesthesia. In the methods of the invention different types of anaesthesia may also be used in combination. For example a regional anaesthesia may be used following a general anaesthesia to relieve post operative pain.

25 The (R)-dihydroetorphine may be formulated in a variety of ways, depending upon the route of administration selected. The quantity of (R)-dihydroetorphine in the formulation also depends upon the route of administration selected. The skilled man will readily be able to determine suitable formulations for use in the present invention.

30 The (R)-dihydroetorphine may be present in the form of a pharmaceutically acceptable salt. Preferred salts are those that retain the biological effectiveness and properties of (R)-dihydroetorphine and are formed from suitable non-toxic organic or inorganic acids. Acid addition salts are preferred. Representative examples of salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those
35 derived from organic acids such as p-toluenesulfonic acid, salicylic acid,

methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid and trifluoro acetic acid. The modification of a compound into a salt is a technique well known to chemists to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. Alternatively, however, (R)-
5 dihydroetorphine is present in the form of free base.

Solutions or suspensions of (R)-dihydroetorphine used for parenteral, e.g. intravenous, administration may include one or more of the following carriers: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as
10 benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in
15 ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Preferred carriers for use in intravenous administration include physiological saline, bacteriostatic water, Cremophor EL.TM. (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). The composition preferably is sterile and should be fluid to the extent that easy syringability exists. The compositions are preferably stable under the
20 conditions of manufacture and storage and preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier may be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating
25 such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as
30 mannitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminium monostearate and gelatin.

Sterile injectable solutions may be prepared by conventional procedures known in the art. In a typical procedure (R)-dihydroetorphine, in a therapeutically effective or
35 beneficial amount, is incorporated into an appropriate solvent with one or a

combination of ingredients mentioned above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating (R)-dihydroetorphine into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those mentioned above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of (R)-dihydroetorphine plus any additional desired ingredient.

(R)-dihydroetorphine may be administered alone, or in combination with one or more other compounds. Combination therapy includes administration of a single pharmaceutical dosage formulation comprising (R)-dihydroetorphine and one or more additional active pharmaceutical ingredients, as well as administration of (R)-dihydroetorphine and each additional pharmaceutical active ingredient, in its own separate pharmaceutical dosage formulation. Where separate dosage formulations are used, (R)-dihydroetorphine and one or more additional pharmaceutical active ingredients may be administered at essentially the same time (e.g., concurrently) or at separately staggered times (e.g., sequentially).

When used in methods for providing anaesthesia, a sedative is preferably administered in addition to (R)-dihydroetorphine. The sedative may be administered simultaneously, separately or sequentially with the (R)-dihydroetorphine, but is preferably administered simultaneously. Preferably the sedative and (R)-dihydroetorphine are in separate dosage forms.

Preferred sedatives include Diprivan® (propofol or 2,6-diisopropylphenol), Lusedra® (fospropofol disodium), Pentothal® (thiopental), Precedex® (dexmedetomidine), Amidate® (etomidate), Ketalar® (ketamine), propanidid (4-[(N,N-diethylcarbamoyl)methoxy]-3-methoxyphenyl]acetic acid propyl ester), Nembutal® (pentobarbital sodium), Brevital® sodium (methohexital sodium) and valium. More preferably the sedative is propofol.

The skilled man in the art is readily able to determine appropriate doses of sedative depending on, inter alia, the weight of the patient and the level of sedation required.

In preferred methods of the invention the pain treated is acute or chronic pain. Examples of pain that may be treated include nociceptive, inflammatory, neuropathic or mixed pain. This includes visceral, somatic, radicular, neuralgic, central pain, pain associated with amputation, complex regional pain syndromes and fibromyalgia. In particularly preferred methods of the invention the pain treated is nociceptive pain.

Such pain is caused by tissue injury detected by nociceptors at the site of injury. After the injury, the site becomes a source of ongoing pain and tenderness. This pain and tenderness are considered "acute" nociceptive pain. In preferred methods of the invention, acute nociceptive pain is treated. Examples of acute nociceptive pain include surgical procedures (post-op pain) and bone fractures.

Even though there may be no permanent nerve damage, "chronic" nociceptive pain results from some conditions when pain extends beyond six months. In other preferred methods of the invention chronic nociceptive pain is treated. Examples of chronic nociceptive pain include osteoarthritis, rheumatoid arthritis, and musculoskeletal conditions (e.g., back pain) and cancer pain.

The present invention will now be described with reference to the following non-limiting example wherein:

Figure 1 illustrates calculation of average respiratory drug effect;

Figure 2a shows the plots of ventilation (L/min) versus time in the pilot study for placebo and eight R-DHE dosages;

Figure 2b shows a plot of ventilation ratio versus R-DHE dose in the pilot study (The data in panel B are mean $\pm$ SD);

Figure 2c shows a plot of % respiratory depression versus R-DHE dose in the pilot study (The data in panel C are mean $\pm$ SD);

Figure 3a shows the plots of ventilation (L/min) versus time in the main phase of the study for placebo and four R-DHE dosages;

Figure 3b shows a plot of ventilation ratio versus R-DHE dose in the main phase of the study (The data in panel B is mean $\pm$ SD);

Figure 3c shows a plot of % respiratory depression versus R-DHE dose in the main phase of the study (The data in panel C is mean $\pm$ SD);

Figure 4a shows the plots of ventilation (L/min) versus time in the main phase of the study for placebo and four fentanyl dosages;

Figure 4b shows a plot of ventilation ratio versus fentanyl dose in the main phase of the study (The data in panel B is mean $\pm$ SD);

Figure 4c shows a plot of % respiratory depression versus fentanyl dose in the main phase of the study;

Figure 5 shows model fits of ventilation ratio versus dose for R-DHE (A) and fentanyl (B);

Figure 6a shows the effect of R-DHE and fentanyl on peak analgesia, defined as the highest value of pain threshold in mA;

Figure 6b shows the effect of R-DHE and fentanyl on average analgesic effect, defined as the area under the pain threshold curve (AUC) from $t = 0$ to $t = 8$ h normalised by the baseline area.

Figure 7a shows the maximum and mean NAS scores for nausea during pain relief treatment with each of a dose of $0.15 \mu\text{g/kg}$ (R)-dihydroetorphine, $3 \mu\text{g/kg}$ fentanyl and placebo;

Figure 7b shows the maximum and mean NAS scores for sedation during pain relief treatment with each of a dose of $0.15 \mu\text{g/kg}$ (R)-dihydroetorphine, $3 \mu\text{g/kg}$ fentanyl and placebo;

Figure 7c shows the maximum and mean NAS scores for dizziness during pain relief treatment with each of a dose of $0.15 \mu\text{g/kg}$ (R)-dihydroetorphine, $3 \mu\text{g/kg}$ fentanyl and placebo;

Figure 7d shows the maximum and mean NAS scores for euphoria during pain relief treatment with each of a dose of $0.15 \mu\text{g/kg}$ (R)-dihydroetorphine, $3 \mu\text{g/kg}$ fentanyl and placebo;

Figure 7e shows the maximum and mean NAS scores for dysphoria during pain relief treatment with each of a dose of $0.15 \mu\text{g/kg}$ (R)-dihydroetorphine, $3 \mu\text{g/kg}$ fentanyl and placebo;

Figure 8 shows the R-DHE dose response in the cold pressor test model for nociceptive pain

EXAMPLES

EXAMPLE 1a

In the examples R-DHE was compared to fentanyl, which is a selective and high affinity MOR agonist that produces dose-dependent respiratory depression and apnoea at high dose ($2\text{--}3 \mu\text{g/kg}$ and greater). Fentanyl is currently the opioid of choice for the treatment of many types of moderate to severe pain.

Methods

The phase 1 study had two parts. Initially a dose-ascending, cohort group, single-blinded pilot study (part 1) was performed for dose-finding. After the pilot study was completed, the R-DHE doses were selected for the main study (part 2), a randomised, double-blind, placebo- and active comparator (fentanyl)-controlled study was performed. Parallel group study was performed.

Subjects

One hundred and two male healthy volunteers (10 in the pilot study and 92 in the main study) participated in the study after approval of the protocol was obtained from the Leiden University Medical Center (LUMC) Human Ethics Committee and the Central Committee on Research Involving Human Subjects (CCMO, The Hague). Written and oral informed consent was obtained prior to enrolment of the volunteers into the study. All volunteers provided a medical history and a physical examination, 12-lead ECG and blood screening was conducted before enrolment. The eligible volunteers were between the ages of 18 and 45 years, weighed between 65 and 100 kg, had a body mass index between 18 and 30 kg/m² and a forced expired lung volume in 1 s of > 85% of predicted. Study subjects were healthy with no history of major medical disease, alcohol abuse, illicit drug use or heavy smoking. Volunteers had not used medication (including vitamins, herbal and/or mineral supplements) in the seven days preceding dosing, or during the course of the study, or opioids or opioid antagonists in the 90 days prior to dosing. Finally, participants had to fast for at least 6 hours prior to the administration of study medication.

Study Design

Pilot study - The respiratory effects of 3 escalating doses of R-DHE and 1 infusion of placebo were tested on 4 separate days with at least 1 week for wash out between test sessions. Three subjects received 0.025, 0.05 and 0.1 µg/kg R-DHE and placebo (cohort 1), three others 0.0125, 0.075 and 0.1 µg/kg R-DHE and placebo (cohort 2) and the last three subjects 0.05, 0.125 and 0.15 µg/kg R-DHE and placebo (cohort 3). From the results of this study the doses of the main study were determined. After infusion of the drug was completed ventilation was continuously measured breath to breath for 1 hour under iso-hypercapnic conditions (see below).

Main study - In this double-blind randomized study 92 volunteers participated. None of them had been part of the pilot study and all were dosed only once. 46 subjects participated in the respiratory part of the study and the 46 other subjects in the analgesia part. In both parts, placebo (n=6), 0.0125 µg/kg R-DHE (n=4), 0.075 µg/kg R-DHE (n=6), 0.125 µg/kg R-DHE (n=6), 0.15 µg/kg R-DHE (n=4), 0.5 µg/kg fentanyl (n=4), 1 µg/kg fentanyl (n=6), 2 µg/kg fentanyl (n=6) and 3 µg/kg fentanyl (n=4) was administered by intravenous infusion over 10 minutes. The randomization list was

prepared by the sponsor of the study and sent to the local pharmacy where blinded syringes were prepared based on the weight of the subject. Each syringe was identical in size, drug volume and color and was unmarked. The randomization list was available to the sponsor, the pharmacy and an independent data safety monitoring committee.

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Study Medications

Placebo was normal saline (0.9% NaCl).

Fentanyl was obtained from Hameln Pharmaceuticals (Hameln Germany).

10 R-DHE was manufactured by SCM Pharma Limited on behalf of Mundipharma Research Limited (Cambridge, UK).

Solutions of each of R-DHE and fentanyl were prepared by conventional techniques.

All drugs were infused intravenously (through an intravenous line in the arm or hand) using a syringe pump (Beckton Dickinson, St. Etienne, France).

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Respiratory measurements

Following infusion, ventilation was continuously measured on a breath-to-breath basis for 1 hour under iso-hypercapnic conditions. End-tidal gas forcing and data acquisition were performed using the dynamic end-tidal forcing technique. This technique is well established and is described in, *inter alia*, *Journal of Physiology* (1990), 428, 485-499, *PLoS Medicine* (2007), 4, e239, 1195-1203 and *British Journal of Anaesthesia* (2005), 94(6), 825-834, the entire contents of which are hereby incorporated by reference. The advantages of the end-tidal forcing technique are that respiratory response of the test drug is (1) independent of the confounding effects of changes in arterial CO₂ and (2) independent of the speed of administration of the drug. The technique therefore allows reliable comparison of drug effect on the ventilatory control system, i.e. differences induced by R-DHE and fentanyl in dose-response relationships are due to CO₂-independent differences in pharmacokinetics and dynamics.

30 The dynamic end-tidal forcing technique enables the investigator to force end-tidal PCO₂ and end tidal PO₂ to follow a specific pattern over time. In the current study the end-tidal oxygen (O₂) level was clamped to a value of 110 mmHg, while the end-tidal carbon dioxide (CO₂) concentration was slowly increased to a value that caused ventilation levels of 20 ± 2 L/min. This end-tidal CO₂ value was maintained throughout

the study. On average this was achieved by increasing end-tidal PCO_2 to 6.65 kPa (50 mmHg).

The volunteers were comfortably positioned in a hospital bed and breathed through a face mask positioned over their nose and mouth which was connected to a pneumotachograph and differential pressure transducer (#4813, Hans Rudolph, Myandotta, MI). The pneumotachograph received fresh gas from a gas-mixing system consisting of three mass flow controllers (Bronkhorst High Tech, Veenendaal, The Netherlands) for oxygen, carbon dioxide and nitrogen. A personal computer running ACQ software (Erik Kruyt, Leiden University Medical Center, Leiden, The Netherlands) provided control signals to the mass flow controllers, allowing adjustment of the inspired gas concentrations to steer the end-tidal O_2 and CO_2 concentrations according to a pre-set pattern over time. The inspired and expired oxygen and carbon dioxide concentrations and the arterial hemoglobin–oxygen saturation were measured with a Datex Multicap gas monitor (near the mouth) and Datex Satellite Plus pulse oximeter, respectively (Datex-Engstrom, Helsinki, Finland). End-tidal concentrations of oxygen and carbon dioxide, inspired minute ventilation (V_i), and oxygen saturation were collected for further analysis. Ventilation levels and end-tidal concentrations were observed in real time on a breath-to-breath basis on a computer screen.

Respiratory measurements started when the inspired minute ventilation had reached a steady state; 4-5 min later drug infusion was started. Respiratory measurements ended 65 min after the end of drug infusion ($t = 70$ min).

Pain measurements

Pain was induced using a transcutaneous electrical stimulus to the skin over the left tibial bone (10 cm above the ankle). A 20 Hz (pulse duration 0.1 ms) stimulus train was delivered to the subject causing activation of cutaneous nociceptors. The stimulus train started at 0 mA and was increased at a rate of 0.5 mA per 2 s (with a cut-off value of 128 mA). The delivery of the current was controlled by a computer via a current stimulator which was connected to a control box with two buttons. The subject was instructed to press the first button when pain was felt (i.e. pain threshold) and the second button when the subject wanted the stimulus train to stop (i.e. pain tolerance). These respective currents were collected on disc for further analysis. The subject was familiarized with the system prior to the study to obtain reliable baseline values. In this study, the pain threshold values were used in the analysis. Four pain threshold values (i.e. predrug values) were obtained in the 30 minutes prior to drug infusion. These

values were averaged and served as a baseline estimate. Following drug infusion, pain measurements were obtained at the following time points ($t = 0$ is the start of drug infusion): 10 (end of infusion), 15, 30, 45, 65, 75, 90, 105, 120, 150, 180, 210, 240, 300, 365, 420 and 480 min.

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Sample size and statistical analysis

The pilot study was designed to determine which doses of R-DHE to be tested in the main study. Four doses were chosen for the main study, 0.0125 $\mu\text{g/kg}$, 0.125 $\mu\text{g/kg}$, 0.075 $\mu\text{g/kg}$ and 0.15 $\mu\text{g/kg}$.

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For the main study, sample size selection was achieved by performing a power analysis in NONMEM (Beal, B.L., Sheiner, L.B., Boeckman, A.J., Bauer, R.J., User's Guide, Icon Development Solutions, Ellicott City, Maryland, 1989-2011) using estimated data on the effect of opioids on respiratory depression (pilot study and *Clin. Pharmacol. Ther.* 2007, 81: 50-58). An inter-subject variability in effect of 50% ($\omega^2 = 0.25$) and a 10% residual error for effect ($\sigma^2 = 0.01$) and aimed to detect a value of $p < 0.5$ or > 2 (where $C_{50A}(\text{R-DHE})/C_{50R}(\text{R-DHE}) = p \times C_{50A}(\text{FENTANYL})/C_{50R}(\text{FENTANYL})$ and C_{50A} and C_{50R} are the concentrations causing 50% analgesia and respiratory depression for drugs R-DHE (R-DHE) and fentanyl (FENTANYL), respectively) with $\alpha < 0.05$ and $\beta = 0.8$. In the analysis we assumed that $C_{50A}(\text{R-DHE}) = C_{50A}(\text{FENTANYL})$ (i.e. concentrations are equianalgesic). Values of $p < 0.5$ indicated that fentanyl produces respiratory depression at concentrations at least twice as low as R-DHE and vice versa for $p > 2$. It was assumed that the logarithm of the C_{50} ratio has a normal distribution with variance = 1. The sample size selection was then verified by simulations in NONMEM with 1,000 simulated data sets. The analysis resulted in a sample size of 34, which was rounded upwards to 40 (20 subjects per opioid treatment). Six additional subjects were added to receive placebo. The subject number chosen for the analgesia part of the study was identical to that calculated for the respiratory part of the study.

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Average respiratory drug effect

The breath-to-breath data were averaged over 1-min episodes. In order to get an impression of the average drug effect on respiration, we calculated the area below the respiration curve (AUC) from $t = 0$ to $t = 70$. Referring to Figure 1, first the area-under-the curve (AUC) was calculated for the respiration curve (blue line from A to A').

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This AUC (grey field) was subtracted from the area obtained by taking baseline ventilation (A) forward (the arrow from point A to B; the baseline area AUC is the box depicted by the red broken lines ABCD). Next the data were normalized by the baseline area giving an average % of respiratory depression (average drug effect = [baseline area AUC – AUC]/ baseline area AUC). An average drug effect of 40 indicates an average of 40% respiratory depression over the measured time period (0-70 min). The average drug effect and time to peak effect were analyzed using a one-way analysis of variance (factor dose). The R-DHE and fentanyl data were analyzed separately in Sigmaplot v12.3 (Systat Software GmbH, Ekrath, Germany). *P*-values < 0.05 were considered significant. Values given are mean ± SD.

Peak respiratory depression

For each subject peak respiratory depression was calculated as the nadir in ventilation and presented as ratio relative to baseline (e.g. a value of 0.5 indicates a nadir in ventilation in magnitude 50% of baseline ventilation). Using the statistical package R (version 8.2; www.r-project.org), a sigmoid E_{MAX} function was fitted through the R-DHE and fentanyl dose-effect data (effect = peak respiratory depression) using a model of the form:

$$\text{Peak effect(dose)} = 100 + [E_{MIN} - 100] \times [\text{dose}^{\gamma} + ED_{50}^{\gamma}] \quad \text{eqn. (1)}$$

where ED_{50} is the dose causing a 50% effect (ventilation in the middle of baseline ventilation and E_{MIN}), E_{MIN} the asymptotic minimum in ventilation, and γ a shape parameter. *P*-values < 0.01 were considered significant. The data analysis was performed on the complete data set (fentanyl data and R-DHE data from pilot and main studies). The data are presented as mean ± SD.

Analgesic effect

Two measures of analgesic effect were calculated in each experiment: peak analgesia (defined as the highest value of pain threshold in mA) and average analgesic effect (as defined as the area under the pain threshold curve from $t = 0$ to $t = 8$ h normalised by the baseline area, see above). Peak and average analgesic effects were analyzed using a one-way analysis of variance (factor dose). The R-DHE and fentanyl data were analyzed separately using SigmaPlot v 12.3. *P*-values < 0.05 were considered significant. Values given are mean ± SD.

Results

Pilot study - Nine volunteers completed the study without unexpected side effects. One subject developed ECG changes that, although not clinically relevant, precluded proper assessment of the effect of the study medication on the ECG. As a precautionary measure, another subject replaced this subject after having completed a placebo and 0.05 µg/kg R-DHE experiment.

The clamped end-tidal PCO₂ was 6.6 ± 0.5 kPa (49.5 ± 3.8 mmHg) and baseline (pre-drug) ventilation was 21.5 ± 1.7 L/min. The mean respiratory responses to R-DHE are given in Fig. 2A. All dosages of R-DHE displayed a nadir in ventilation, which occurred at $t = 17.1 \pm 3.8$ min following the start of drug infusion. The respiratory responses to R-DHE dosages of 0.075, 0.10, 0.125 and 0.15 µg/kg overlap. The dose-response curves (peak respiratory depression and average drug effect) are given in Fig. 2B and C showing that the dose-response levels off at dosages of 0.075 µg/kg and greater (R-DHE 0.075, 0.125 and 0.15 µg/kg: $P > 0.05$). The peak respiratory depression occurred with doses of 0.075 µg/kg and greater at a ventilation ratio of about 0.4. The average % respiratory depression reached a ceiling of about 40-45 % with doses 0.075 µg/kg and greater. With a 40-45 % average respiratory depression, the average level of respiration achieved in the volunteer who received the drug was 55-60 % relative to baseline.

A small positive trend was observed in the ventilation data as was best observed in the placebo responses. The magnitude of the trend ranged from 30-60 ml.min⁻² (about 1.5-3 % of total ventilation) and corresponds with the presence of a slow component (time constant about 1 hr) in the ventilatory response to CO₂.

Main study: Respiration. All 46 subjects completed the study without unexpected side effects. In the R-DHE experiments, the end-tidal PCO₂ was clamped at 6.8 ± 0.2 kPa (51.0 ± 1.5 mmHg) and baseline (pre-drug) ventilation was 19.3 ± 1.4 L/min. The mean respiratory responses to R-DHE are given in Fig. 3A. No nadir in ventilation was observed in the placebo data and the lowest R-DHE dose tested. The time to peak effect was dose-independent and occurred at 17.3 ± 5.5 min. The dose-response curves (for peak respiratory depression and average drug effect) are given in Figs. 3B and C respectively showing that the dose-response levels off at a ventilation level of approximately 40% of baseline. Specifically the peak respiratory depression occurred with doses of 0.075 µg/kg and greater and at a ventilation ratio of about 0.5. The average % respiratory depression reached a ceiling of about 30-40 % with doses 0.075 µg/kg and greater. With a 30-40 % average respiratory depression, the level of

respiration achieved in the volunteer who received the drug was 60-70 % relative to baseline. None of the subjects that received R-DHE developed irregular breathing or apnoea.

5 In the fentanyl experiments, the end-tidal PCO₂ was clamped at 6.6 ± 0.1 kPa (49.5 ± 0.8 mmHg) and baseline (pre-drug) ventilation was 20.2 ± 0.9 L/min. A nadir in respiratory response was observed for all doses tested (Fig. 4A). The time to peak effect was dose-independent and occurred on average at 12.8 ± 2.1 min. The dose-response curves (for peak respiratory depression and average drug effect) are given in Figs. 4B and C respectively. Dose-dependent respiratory depression was apparent in peak ventilation (P<0.001) and average drug effect (P<0.001). The maximum
10 observed respiratory depression was observed at the highest fentanyl dose tested (3 µg/kg; peak effect = 19% of baseline). Two subjects developed irregular breathing after the highest dose of fentanyl, one of which developed apnoea (defined by the absence of breathing activity > 20 s), just after ending the 10-min fentanyl infusion.

15 The parameter estimates of the model analysis of peak respiratory depression are given in Table 1 below.

Table 1 - Parameter estimates of the model analysis of peak respiratory depression

Parameter	Mean	SD	2.5% percentile	97.5% percentile
ED ₅₀ R-DHE (µg/kg)	0.04	0.009	0.026	0.06
ED ₅₀ Fentanyl (µg/kg)	1.27	0.116	1.04	1.50
Y	1.80	0.32	1.23	2.51
E _{MIN} R-DHE (% of baseline)	32.8	0.06	16.7	42.6
E _{MIN} Fentanyl	0	-	-	-
σ ²	0.014	0.002	0.010	0.019

20 ED₅₀ is the dose causing a 50% reduction in ventilation, E_{MIN} the asymptotic minimum in ventilation, γ a shape parameter and σ² is the variance of the residual error.

25 The model fits are given in Figs. 5A (R-DHE) and B (fentanyl). On the y-axis, ventilation is relative to pre-drug baseline ventilation. The continuous thick lines are the model fits and the thin lines are the 2.5% and 97.5% percentiles. The curves are extrapolated to 0.3 µg/kg (R-DHE) and 6 µg/kg (fentanyl). In panel A, the closed circles are data from the main study, the open circles are data from the pilot study. In panels A and B, the respective ED₅₀ and E_{MIN} values are depicted by the symbol × and broken

grey lines. For both drugs the ED_{50} is the dose half-way between baseline ventilation and E_{MIN} ; for fentanyl this is at 50% respiratory depression, for R-DHE at 33.6%

Two parameters were significantly different between treatments ($P < 0.01$): ED_{50} and E_{MIN} . An apparent 30-fold difference in potency was observed with ED_{50} values of 0.04 $\mu\text{g/kg}$ for R-DHE and 1.27 $\mu\text{g/kg}$ for fentanyl. For fentanyl the value of E_{MIN} or the asymptotic minimum ventilation was not different from zero, but greater than zero for R-DHE: 32.8% of baseline ventilation or 6.6 L/min ($P < 0.01$). The shape parameter γ and residual error variance (σ^2) did not differ between treatments.

Main study: Analgesia – All 46 subjects completed the study without unexpected side effects. Baseline pain thresholds were 11.8 ± 0.9 mA (R-DHE), 12.7 ± 0.4 mA (fentanyl) and 11.0 ± 0.6 mA (placebo). The effect of placebo was limited with an effect no greater than 10% of baseline. Both R-DHE and fentanyl produced dose-dependent effects in terms of peak analgesic effect and average drug effect (Figs. 6A and B; drug-effect: $P < 0.01$) with no indication of reaching a ceiling.

In our study we observed that over the dose range tested, both fentanyl and R-DHE displayed a dose-dependent increase in peak pain response and average analgesic effect (Figs. 6A and B). These data provide proof that for R-DHE, in contrast to respiration, pain relief does not display ceiling over the dose range tested. At the highest dose tested both drugs produced an increase in pain threshold of about 100% (R-DHE 0.15 $\mu\text{g/kg}$ response = $1.95 \times$ pre-drug response; Fentanyl 3.0 $\mu\text{g/kg}$ response = $2.1 \times$ pre-drug response). This indicates a R-DHE-fentanyl difference in potency of 18.5. This difference is smaller than the apparent potency difference observed for respiratory depression (factor = 30). However, since the ED_{50} is an estimation of ventilation in the middle of baseline ventilation and E_{MIN} , a better comparison than ED_{50} would be the dose causing 50% depression of ventilation (in absolute values). For fentanyl this is identical to ED_{50} (1.27 $\mu\text{g/kg}$), and for R-DHE this is 0.075 $\mu\text{g/kg}$. This then suggests a potency difference of 17 very similar to the value observed for antinociception.

The mechanism responsible for achieving ceiling effect is not clear. One possibility is that concurrent activation of ORL1-receptors compromises the MOR-mediated antinociceptive effect. However although R-DHE has affinity for the ORL1 receptor, its K_i is several orders of magnitude higher than for the MOR. Whether such low affinity for the ORL1 receptor is sufficient to cause the profound ceiling observed is

questionable. Another possible mechanism may be related to R-DHE's high affinity for the KOR, which is approximately 1 order of magnitude lower than for the MOR. It may be, for example, that at high doses the R-DHE-induced and MOR-mediated respiratory depression is antagonised by the effect of R-DHE at the KOR.

5 A final proposed mechanism involves the intra neuronal regulatory protein β -arrestin. Opioid receptors belong to the 7-transmembrane G-protein-coupled receptors that, upon activation, bind to intracellular G-proteins and β -arrestin 1 and/or β -arrestin 2 proteins. It has been shown that absence of β -arrestin 2 protein causes the attenuation of morphine-induced respiratory depression with maintained antinociception. It was
10 hypothesized that (G-protein independent) activation of β -arrestin 2 is involved in MOR signal transduction of respiratory neurons but not in neurons involved in modulation of pain pathways. It may well be that extent of G protein and of β -arrestin 2 activation is ligand specific. The findings in this study may be explained by a lesser ability of R-DHE to activate β -arrestin 2.

15 The mechanism of the differential R-DHE effect on respiration and analgesia is also not clear. It may be due to a difference in receptor density at brain sites involved in analgesia versus brain sites involved in respiratory depression. Another mechanism involved may be the lesser ability of R-DHE to engage the transduction protein β -arrestin 2, as discussed above. This latter mechanism explains both the observed
20 ceiling effect in R-DHE-mediated respiratory depression and the selectivity of the ceiling effect.

Other Opioid-related side effects

25 Other opioid-related side effects associated with treatment of each of 0.15 μ g/kg (R)-dihydroetorphine and 3 μ g/kg fentanyl were assessed at intervals for 7.5 hours, starting 1 hour after administration of drug was ceased, by asking the patients to complete the questionnaire shown below wherein the scale 0-100 for each side effect is a NAS score.

Questionnaire

1 h After Infusion Stopped

Circle ONE number only to indicate how you feel your dizziness, euphoria, nausea, sedation and your dysphoria is at the moment.

Actual Time

The average NAS score for each side effect was calculated.

EXAMPLE 1b

5 In a follow up study the effect of higher doses of R-DHE were investigated. The study was conducted on 19 healthy volunteers.

The selection of subjects, formulation of R-DHE, administration (10 min i.v.), respiratory measurements (using the dynamic end-tidal forcing technique) and statistical analysis was identical to the main study described above, except that the doses of R-DHE tested were 0.2 µg/kg (6 subjects), 0.25 µg/kg (6 subjects), 0.3 µg/kg (6 subjects) and 0.4 µg/kg (6 subjects).

The ventilation ratio determined for each drug dose is shown in the table below.

Dose of R-DHE ($\mu\text{g/kg}$)	Ventilation Ratio
0.2	0.4
0.25	0.25
0.3	0.25
0.4	0.2

These results show that the ceiling effect in respiratory depression extends to higher doses of R-DHE than are required to achieve clinically useful analgesic levels.

5 At a dose of 0.2 $\mu\text{g/kg}$ of R-DHE the level of respiration in the volunteers was still about 40%. At higher doses (0.3 $\mu\text{g/kg}$ and 0.4 $\mu\text{g/kg}$) an increase in peak mean respiratory depression was observed but this was stable at about 20 to 25 %. Such levels are acceptable in controlled environments.

10 EXAMPLE 2: Cold Pressor Test to determine analgesic effect

The cold pressor test is an established model for nociceptive pain assessment in healthy volunteers. The test was carried out according to conventional procedures.

15 The R-DHE doses tested in the cold pressor model were 0.05 $\mu\text{g/kg}$ (8 subjects), 0.1 $\mu\text{g/kg}$ (8 subjects), 0.2 $\mu\text{g/kg}$ (8 subjects) or 0.3 $\mu\text{g/kg}$ (8 subjects) or placebo, all given as a 10 minute i.v. infusion.

20 In the study, the healthy volunteers immersed their non-dominant hand in a stirred, thermostatically-controlled cold water bath having a temperature of 3 °C for 2 minutes. During the immersion the volunteer rated the pain he or she experienced continuously with 0 representing no pain and 100 representing the worst pain imaginable. The volunteer also rated the pain experienced at time points (pre-dose, 10 minutes, 30 min, 1, 2, 4, 8, 12 and 24 hours post-infusion. The cumulative area under the curve of the visual analogue scale-time profile from 0 to 120 seconds for each cold pain test was calculated. A graph of the AUC versus baseline was plotted for each time point.

25 The % change from baseline was calculated as follows: $100 \times (\text{AUC at } t \text{ (time)} - \text{baseline}) / \text{AUC at } t \text{ baseline}$ and the results are shown in Figure 8. Thus, for example, if the AUC for baseline was 100 and the AUC at time 10 minutes for R-DHE was 20, then the % change from baseline is $100 \times ((20 - 100) / 100)$, i.e. -80 %. This is plotted on Figure 8 as 20%. Similarly if the AUC for
30 baseline was 100 and the AUC at time 10 minutes for R-DHE was 80, then the %

change from baseline is $100 \times ((80-100)/100)$, i.e. -20 % and this is plotted on Figure 8 as 80%. Thus in Figure 8, 100% shows that no pain relief versus baseline is achieved and 0 % shows that complete pain relief is achieved.

5 Figure 8 shows that for a dose of R-DHE of 0.05 µg/kg, 0.1 µg/kg, 0.2 µg/kg or 0.3 µg/kg significant levels of analgesia are achieved. Significantly Figure 8 shows that the level of analgesia achieved is dose dependent. In other words, Figure 8 shows that, unlike for respiratory depression, no ceiling effect in analgesia is observed.

10 The results for placebo shown in Figure 8 are a change from the baseline of approximately 18 %, which is in line with the expected value of about 20%. Notably the results for R-DHE are significantly greater than a 20% change from baseline and for the higher doses of R-DHE (0.2 µg/kg or 0.3 µg/kg) are greater than 50% of baseline, even 1 hour after administration. Even at 4 hours after administration, the higher doses of R-DHE (0.2 µg/kg or 0.3 µg/kg) show a change from baseline that is significantly greater than the placebo.

CLAIMS:

1. A method of providing pain relief in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose of at least 0.01 $\mu\text{g/kg}$, preferably at least 0.05 $\mu\text{g/kg}$, and the level of respiratory depression in said subject is 65 or less % relative to the baseline level pre-administration of (R)-dihydroetorphine.
2. A method as claimed in claim 1, wherein the level of respiration in said subject is 35 to 100% relative to the baseline level pre-administration of (R)-dihydroetorphine.
3. A method as claimed in claim 1 or 2, wherein said (R)-dihydroetorphine is administered in a dose of 0.075 to 0.15 $\mu\text{g/kg}$.
4. A method as claimed in any one of claims 1 to 3, wherein the level of respiratory depression in said subject is between 40 and 65 % relative to the baseline level pre-administration of (R)-dihydroetorphine.
5. A method as claimed in any one of claims 1 to 4, wherein said (R)-dihydroetorphine is administered in a dose of 0.075 to 0.15 $\mu\text{g/kg}$ and the level of respiratory depression in said subject is between 50 and 65 % relative to the baseline level pre-administration of (R)-dihydroetorphine.
6. A method as claimed in any one of claims 1 to 5, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour following administration of said (R)-dihydroetorphine intravenously over 10 minutes.
7. A method as claimed in any one of claims 1 to 6, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of $20 \pm 2\text{L/min}$.
8. A method as claimed in claim 7, wherein said end tidal carbon dioxide level is clamped at 50 mmHg.

9. A method as claimed in any one of claims 1 to 8, wherein said method provides a level of analgesia which, as measured by the cold pressor test, is at least a -20 % change, preferably at least a -40 % change, compared to baseline level.

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10. A method as claimed in any one of claims 1 to 9, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.2 times, preferably at least 1.5 times.

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11. A method as claimed in any one of claims 1 to 10, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by 1.2 to 3.0 times.

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12. A method as claimed in claim 10 or 11, wherein said pain threshold levels are measured by applying pain using a transcutaneous electrical stimulus to the skin over the tibial bone and increasing the electrical stimulus at a rate of 0.5 mA per 2s.

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13. A method as claimed in any one of claims 1 to 12, wherein during said method one or more opioid-related effects selected from dizziness, euphoria, nausea, sedation and dysphoria are minimised.

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14. A method as claimed in any one of claims 1 to 12, wherein said opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

15. A method as claimed in claim 13 or 14, wherein the average NAS score for dizziness is less than 50 in the 7.5 hours post administration of (R)-dihydroetorphine.

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16. A method as claimed in any one of claims 13 to 15, wherein the average NAS score for euphoria is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

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17. A method as claimed in any one of claims 13 to 16, wherein the average NAS score for nausea is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

18. A method as claimed in any one of claim 13 to 17, wherein the average NAS score for sedation is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

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19. A method as claimed in any one of claims 13 to 18, wherein the average NAS score for dysphoria is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

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20. A method of providing pain relief in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose of at least 0.01 $\mu\text{g/kg}$, preferably at least 0.05 $\mu\text{g/kg}$, and the peak respiratory depression in said subject is 20 to 80 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

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21. A method as claimed in claim 20, wherein the nadir in the level of respiration in said subject is 20 to 80% relative to the baseline level pre-administration of (R)-dihydroetorphine.

20

22. A method as claimed in claim 20 or 21, wherein said (R)-dihydroetorphine is administered in a dose of 0.075 to 0.15 $\mu\text{g/kg}$.

23. A method as claimed in any one of claims 20 to 22, wherein the peak respiratory depression in said subject is 25 to 45 % relative to the baseline level prior to administration of (R)-dihydroetorphine.

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24. A method as claimed in any one of claims 20 to 23, wherein the peak respiratory depression in said subject is 30 to 40 % relative to the baseline level prior to administration of (R)-dihydroetorphine.

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25. A method as claimed in any one of claims 20 to 24, wherein said (R)-dihydroetorphine is administered in a dose of 0.075 to 0.15 $\mu\text{g/kg}$ and the peak respiratory depression in said subject is between 25 to 45 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

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26. A method as claimed in any one of claims 20 to 25, wherein said peak respiratory depression is measured under iso-hypercapnic conditions for 1 hour following administration of said (R)-dihydroetorphine intravenously over 10 minutes.
- 5 27. A method as claimed in any one of claims 20 to 26, wherein said peak respiratory depression is measured under iso-hypercapnic conditions for 1 hour with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of 20 ± 2 L/min.
- 10 28. A method as claimed in claim 27, wherein said end tidal carbon dioxide level is clamped at 50 mmHg.
- 15 29. A method as claimed in any one of claims 20 to 28, wherein said method provides a level of analgesia which, as measured by the cold pressor test, is at least a -20 % change, preferably at least a -40 % change, compared to baseline level.
- 20 30. A method as claimed in any one of claims 20 to 29, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.2 times, preferably at least 1.5 times.
- 25 31. A method as claimed in any one of claims 20 to 30, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by 1.2 to 3.0 times.
- 30 32. A method as claimed in claim 30 or 31, wherein said pain threshold levels are measured by applying pain using a transcutaneous electrical stimulus to the skin over the tibial bone and increasing the electrical stimulus at a rate of 0.5 mA per 2s.
- 35 33. A method as claimed in any one of claims 20 to 32, wherein during said method one or more opioid-related effects selected from dizziness, euphoria, nausea, sedation and dysphoria are minimised.
34. A method as claimed in any one of claims 29 to 33, wherein said opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

35. A method as claimed in claim 33 or 34, wherein the average NAS score for dizziness is less than 50 in the 7.5 hours post administration of (R)-dihydroetorphine.

5 36. A method as claimed in any one of claims 33 to 35, wherein the average NAS score for euphoria is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

10 37. A method as claimed in any one of claims 33 to 36, wherein the average NAS score for nausea is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

15 38. A method as claimed in any one of claim 33 to 37, wherein the average NAS score for sedation is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

20 39. A method as claimed in any one of claims 33 to 38, wherein the average NAS score for dysphoria is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

40. A method of providing analgesia in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose of at least 0.01 $\mu\text{g/kg}$, preferably at least 0.05 $\mu\text{g/kg}$, and the resulting ventilation ratio in said subject is at least 0.3.

25 41. A method as claimed in claim 40, wherein said (R)-dihydroetorphine is administered in a dose of 0.05 to 0.175 $\mu\text{g/kg}$.

30 42. A method as claimed in claim 40 or 41, wherein said (R)-dihydroetorphine is administered in a dose of 0.075 to 0.15 $\mu\text{g/kg}$.

43. A method as claimed in any one of claims 40 to 442, wherein the resulting ventilation ratio in said subject is between 0.3 and 0.6.

44. A method as claimed in any one of claims 40 to 43, wherein said (R)-dihydroetorphine is administered in a dose of 0.075 to 0.15 $\mu\text{g/kg}$ and the resulting ventilation ratio in said subject is 0.3 to 0.5.

5 45. A method as claimed in any one of claims 40 to 44, wherein the ventilation ratio is determined by measuring respiration pre-administration of (R)-dihydroetorphine and post-administration administration of (R)-dihydroetorphine intravenously over 10 minutes for 1 hour under iso-hypercapnic conditions .

10 46. A method as claimed in any one of claims 40 to 45, wherein the ventilation ratio is determined by measuring respiration pre-administration of (R)-dihydroetorphine and post-administration administration of (R)-dihydroetorphine intravenously over 10 minutes for 1 hour under iso-hypercapnic with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of 20
15 $\pm 2\text{L/min}$.

47. A method as claimed in claim 46, wherein said end tidal carbon dioxide level is clamped at 50 mmHg.

20 48. A method as claimed in any one of claims 40 to 47, wherein said method provides a level of analgesia which, as measured by the cold pressor test, is at least a -20 % change, preferably at least a -40 % change, compared to baseline level.

25 49. A method as claimed in any one of claims 40 to 48, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by at least at least 1.2 times, preferably at least 1.5 times.

30 50. A method as claimed in any one of claims 40 to 49, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by 1.2 to 3.0 times.

35 51. A method as claimed in claim 49 or 50, wherein said pain threshold levels are measured by applying pain using a transcutaneous electrical stimulus to the skin over the tibial bone and increasing the electrical stimulus at a rate of 0.5 mA per 2s.

52. A method as claimed in any one of claims 40 to 51, wherein during said method one or more opioid-related effects selected from dizziness, euphoria, nausea, sedation and dysphoria are minimised.

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53. A method as claimed in any one of claims 40 to 52, wherein said opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

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54. A method as claimed in claim 52 or 53, wherein the average NAS score for dizziness is less than 50 in the 7.5 hours post administration of (R)-dihydroetorphine.

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55. A method as claimed in any one of claims 52 to 54, wherein the average NAS score for euphoria is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

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56. A method as claimed in any one of claims 52 to 55, wherein the average NAS score for nausea is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

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57. A method as claimed in any one of claims 52 to 56, wherein the average NAS score for sedation is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

58. A method as claimed in any one of claims 52 to 57, wherein the average NAS score for dysphoria is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

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59. A method of providing pain relief in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose greater than the ED₇₅ dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

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60. A method as claimed in claim 59, wherein (R)-dihydroetorphine is administered in a dose greater than the ED₈₅ dose.

61. A method as claimed in claim 59 or 60, wherein (R)-dihydroetorphine is administered in a dose greater than the ED₉₀ dose.

5 62. A method as claimed in any one of claims 59 to 61, wherein (R)-dihydroetorphine is administered in a dose between the ED₇₅ dose and the ED₉₅ dose.

63. A method as claimed in any one of claims 59 to 62, wherein the level of respiratory depression in said subject is between 40 and 65 % relative to the baseline
10 level pre-administration of (R)-dihydroetorphine.

64. A method of providing pain relief in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose greater than the ED₅₀ dose and less than the ED₇₅ dose and
15 the level of respiratory depression in said subject is 50 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

65. A method of providing pain relief in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine
20 is administered in a dose greater than the ED₇₅ dose and less than the ED₉₅ dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

66. A method as claimed in any one of claims 59 to 65, wherein said respiratory
25 depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour following administration of said (R)-dihydroetorphine intravenously over 10 minutes.

67. A method as claimed in any one of claims 59 to 66, wherein said respiratory
30 depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of 20 ± 2 L/min.

68. A method as claimed in claim 67, wherein said end tidal carbon dioxide level is
35 clamped at 50 mmHg.

69. A method as claimed in any one of claims 59 to 68, wherein said method provides a level of analgesia which, as measured by the cold pressor test, is at least a -20 % change, preferably at least a -40 % change, compared to baseline level.

5

70. A method as claimed in any one of claims 59 to 69, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.2 times, preferably at least 1.5 times.

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71. A method as claimed in any one of claims 59 to 60, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by 1.2 to 3.0 times.

15

72. A method as claimed in claim 70 or 71, wherein said pain threshold levels are measured by applying pain using a transcutaneous electrical stimulus to the skin over the tibial bone and increasing the electrical stimulus at a rate of 0.5 mA per 2s.

20

73. A method as claimed in any one of claims 59 to 72, wherein during said method one or more opioid-related effects selected from dizziness, euphoria, nausea, sedation and dysphoria are minimised.

25

74. A method as claimed in any one of claims 59 to 73, wherein said opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

75. A method as claimed in claim 73 or 74, wherein the average NAS score for dizziness is less than 50 in the 7.5 hours post administration of (R)-dihydroetorphine.

30

76. A method as claimed in any one of claims 73 to 75, wherein the average NAS score for euphoria is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

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77. A method as claimed in any one of claims 73 to 76, wherein the average NAS score for nausea is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

78. A method as claimed in any one of claims 73 to 77, wherein the average NAS score for sedation is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

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79. A method as claimed in any one of claims 73 to 78, wherein the average NAS score for dysphoria is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

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80. A method of providing pain relief to a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose that increases the pain threshold value relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.2 times and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

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81. A method as claimed in claim 80, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.5 times.

20

82. A method as claimed in claim 80 or 81, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by 1.2 to 3.0 times.

25

83. A method as claimed in any one of claims 80 to 82, wherein said pain threshold levels are measured by applying pain using a transcutaneous electrical stimulus to the skin over the tibial bone and increasing the electrical stimulus at a rate of 0.5 mA per 2s.

30

84. A method as claimed in any one of claims 80 to 83, wherein the level of respiratory depression in said subject is between 40 and 65 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

35

85. A method as claimed in any one of claims 80 to 84, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic

conditions for 1 hour following administration of said (R)-dihydroetorphine intravenously over 10 minutes.

5 86. A method as claimed in any one of claims 80 to 85, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of 20 ± 2 L/min.

10 87. A method as claimed in claim 86, wherein said end tidal carbon dioxide level is clamped at 50 mmHg.

15 88. A method as claimed in any one of claims 80 to 87, wherein during said method one or more opioid-related effects selected from dizziness, euphoria, nausea, sedation and dysphoria are minimised.

89. A method as claimed in any one of claims 80 to 88, wherein said opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

20 90. A method as claimed in any one of claims 80 to 89, wherein the average NAS score for dizziness is less than 50 in the 7.5 hours post administration of (R)-dihydroetorphine.

25 91. A method as claimed in any one of claims 80 to 90, wherein the average NAS score for euphoria is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

30 92. A method as claimed in any one of claims 80 to 91, wherein the average NAS score for nausea is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

93. A method as claimed in any one of claims 80 to 92, wherein the average NAS score for sedation is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

94. A method as claimed in any one of claims 80 to 93, wherein the average NAS score for dysphoria is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

5 95. A method of providing pain relief in a human subject in need thereof whilst minimising risk of apnoea comprising administering a dose of (R)-dihydroetorphine that provides dose dependent pain relief and dose-independent respiratory depression.

10 96. A method as claimed in claim 95, wherein said (R)-dihydroetorphine is administered in a dose of 0.05 to 0.175 $\mu\text{g/kg}$.

97. A method as claimed in claim 95 or 96, wherein said (R)-dihydroetorphine is administered in a dose of 0.075 to 0.15 $\mu\text{g/kg}$.

15 98. A method as claimed in any one of claims 95 to 97, wherein the level of respiratory depression in said subject is between 40 and 65 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

20 99. A method as claimed in any one of claims 95 to 98, wherein the level of respiratory depression is at a E_{MIN} of 30 to 35 % $\pm$ 10%.

25 100. A method as claimed in any one of claims 95 to 99, wherein said (R)-dihydroetorphine is administered in a dose of 0.075 to 0.175 $\mu\text{g/kg}$ and the level of respiratory depression in said subject is between 30 and 50 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

30 101. A method as claimed in any one of claims 95 to 100, wherein the peak respiratory depression in said subject is 20 to 80 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

102. A method as claimed in any one of claims 95 to 101, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour following administration of said (R)-dihydroetorphine intravenously over 10 minutes.

103. A method as claimed in any one of claims 95 to 102, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of 20 ± 2 L/min.

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104. A method as claimed in claim 103, wherein said end tidal carbon dioxide level is clamped at 50 mmHg.

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105. A method as claimed in any one of claims 95 to 104, wherein said method provides a level of analgesia which, as measured by the cold pressor test, is at least a -20 % change, preferably at least a -40 % change, compared to baseline level.

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106. A method as claimed in any one of claims 95 to 105, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.2 times, preferably at least 1.5 times.

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107. A method as claimed in any one of claims 95 to 106, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by 1.2 to 3.0 times.

25

108. A method as claimed in claim 106 or 107, wherein said pain threshold levels are measured by applying pain using a transcutaneous electrical stimulus to the skin over the tibial bone and increasing the electrical stimulus at a rate of 0.5 mA per 2s.

30

109. A method as claimed in any one of claims 95 to 108, wherein during said method one or more opioid-related effects selected from dizziness, euphoria, nausea, sedation and dysphoria are minimised.

110. A method as claimed in any one of claims 95 to 109, wherein said opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

35

111. A method as claimed in claim 109 to 110, wherein the average NAS score for dizziness is less than 50 in the 7.5 hours post administration of (R)-dihydroetorphine.

112. A method as claimed in any one of claims 109 to 111, wherein the average NAS score for euphoria is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

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113. A method as claimed in any one of claims 109 to 112, wherein the average NAS score for nausea is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

10

114. A method as claimed in any one of claims 109 to 113, wherein the average NAS score for sedation is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

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115. A method as claimed in any one of claims 109 to 114, wherein the average NAS score for dysphoria is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

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116. A method of providing maximum pain relief in a human subject in need thereof whilst minimising risk of apnoea comprising administering a dose of (R)-dihydroetorphine which causes a E_{MIN} in ventilation of 30-50 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

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117. A method as claimed in claim 116, wherein said (R)-dihydroetorphine is administered in a dose of 0.05 to 0.175 $\mu\text{g/kg}$.

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118. A method as claimed in claim 116 or 117, wherein said (R)-dihydroetorphine is administered in a dose of 0.075 to 0.15 $\mu\text{g/kg}$.

119. A method as claimed in any one of claims 116 to 118, wherein the level of ventilation in said subject is between 30 and 40 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

120. A method as claimed in any one of claims 116 to 119, wherein said (R)-dihydroetorphine is administered in a dose of 0.075 to 0.175 $\mu\text{g/kg}$ and the level of

ventilation in said subject is between 30 and 50 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

5 121. A method as claimed in any one of claims 116 to 120, wherein said ventilation is the average measured under iso-hypercapnic conditions for 1 hour following administration of said (R)-dihydroetorphine intravenously over 10 minutes.

10 122. A method as claimed in any one of claims 116 to 121, wherein said ventilation is the average measured under iso-hypercapnic conditions for 1 hour with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of 20 ± 2 L/min.

15 123. A method as claimed in claim 122, wherein said end tidal carbon dioxide level is clamped at 50 mmHg.

124. A method as claimed in any one of claims 116 to 123, wherein said method provides a level of analgesia which, as measured by the cold pressor test, is at least a -20 % change, preferably at least a -40 % change, compared to baseline level.

20 125. A method as claimed in any one of claims 116 to 124, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.2 times, preferably at least 1.5 times.

25 126. A method as claimed in any one of claims 116 to 125, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by 1.2 to 3.0 times.

30 127. A method as claimed in claim 125 or 126, wherein said pain threshold levels are measured by applying pain using a transcutaneous electrical stimulus to the skin over the tibial bone and increasing the electrical stimulus at a rate of 0.5 mA per 2s.

35 128. A method as claimed in any one of claims 116 to 127, wherein during said method one or more opioid-related effects selected from dizziness, euphoria, nausea, sedation and dysphoria are minimised.

129. A method as claimed in any one of claims 116 to 128, wherein said opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

5

130. A method as claimed in claim 128 or 129, wherein the average NAS score for dizziness is less than 50 in the 7.5 hours post administration of (R)-dihydroetorphine.

10

131. A method as claimed in any one of claims 128 to 130, wherein the average NAS score for euphoria is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

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132. A method as claimed in any one of claims 128 to 131, wherein the average NAS score for nausea is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

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133. A method as claimed in any one of claims 128 to 132, wherein the average NAS score for sedation is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

134. A method as claimed in any one of claims 128 to 133, wherein the average NAS score for dysphoria is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

25

135. A method of treating pain in a human subject comprising administering to said subject an effective dose of (R)-dihydroetorphine, wherein during said treating at least one opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

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136. A method as claimed in claim 135, wherein said (R)-dihydroetorphine is administered in a dose of 0.05 to 0.175 $\mu\text{g/kg}$.

137. A method as claimed in claim 135 or 136, wherein said (R)-dihydroetorphine is administered in a dose of 0.075 to 0.15 $\mu\text{g/kg}$.

35

138. A method as claimed in any one of claims 135 to 137, wherein said opioid-related side effect is selected from respiratory depression, dizziness, euphoria, nausea, sedation and dysphoria.

5 139. A method as claimed in any one of claims 135 to 138, wherein said opioid-related side effect is respiratory depression.

140. A method as claimed in claim 139, wherein said respiratory depression is 0 to 65 %.

10

141. A method as claimed in any one of claims 135 to 140, wherein the peak respiratory depression in said subject is 20 to 80 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

15

142. A method as claimed in any one of claims 138 to 140, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour following administration of said (R)-dihydroetorphine intravenously over 10 minutes.

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143. A method as claimed in any one of claims 138 to 142, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of 20 ± 2 L/min.

25

144. A method as claimed in claim 143, wherein said end tidal carbon dioxide level is clamped at 50 mmHg.

145. A method as claimed in any one of claims 135 to 144, wherein said opioid-related side effect is dizziness.

30

146. A method as claimed in any one of claims 135 to 145, wherein said opioid-related side effect is euphoria.

35

147. A method as claimed in any one of claims 135 to 146, wherein said opioid-related side effect is nausea.

148. A method as claimed in any one of claims 135 to 147, wherein said opioid-related side effect is sedation.

5 149. A method as claimed in any one of claims 135 to 148, wherein said opioid-related side effect is dysphoria.

150. A method as claimed in any one of claims 135 to 149, wherein said method provides a level of analgesia which, as measured by the cold pressor test, is at least a
10 -20 % change, preferably at least a -40 % change, compared to baseline level.

151. A method as claimed in any one of claims 135 to 150, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.2 times, preferably at least 1.5
15 times.

152. A method as claimed in any one of claims 135 to 151, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by 1.2 to 3.0 times.
20

153. A method as claimed in claim 151 or 152, wherein said pain threshold levels are measured by applying pain using a transcutaneous electrical stimulus to the skin over the tibial bone and increasing the electrical stimulus at a rate of 0.5 mA per 2s.

25 154. A method of treating pain in a human subject comprising administering to said subject an effective dose of (R)-dihydroetorphine, wherein during said treating opioid-related respiratory depression is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine and at least one of the following criteria defining the levels of opioid-related side effects is satisfied in the 7.5 hours post administration
30 of (R)-dihydroetorphine:

average NAS score for dizziness of 0 to 50

average NAS score for euphoria of 0 to 60

average NAS score for nausea of 0 to 40

average NAS score for sedation of 0 to 60

35 average NAS score for dysphoria of 0 to 40.

155. A method as claimed in claim 154, wherein said (R)-dihydroetorphine is administered in a dose of 0.05 to 0.175 $\mu\text{g/kg}$.

5 156. A method as claimed in claim 154 or 155, wherein said (R)-dihydroetorphine is administered in a dose of 0.075 to 0.15 $\mu\text{g/kg}$.

157. A method as claimed in any one of claims 154 to 156, wherein the level of respiratory depression in said subject is between 40 and 65 % relative to the baseline level pre-administration of (R)-dihydroetorphine.
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158. A method as claimed in any one of claims 154 to 157, wherein said (R)-dihydroetorphine is administered in a dose of 0.075 to 0.15 $\mu\text{g/kg}$ and the level of respiratory depression in said subject is between 50 and 65 % relative to the baseline level pre-administration of (R)-dihydroetorphine.
15

159. A method as claimed in any one of claims 154 to 158, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour following administration of said (R)-dihydroetorphine intravenously over 10 minutes.
20

160. A method as claimed in any one of claims 154 to 159, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of $20 \pm 2\text{L/min}$.
25

161. A method as claimed in claim 160, wherein said end tidal carbon dioxide level is clamped at 50 mmHg.

30 162. A method as claimed in any one of claims 154 to 161, wherein the average NAS score for dizziness is less than 50 in the 7.5 hours post administration of (R)-dihydroetorphine.

163. A method as claimed in any one of claims 154 to 162, wherein the average NAS score for euphoria is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

5 164. A method as claimed in any one of claims 154 to 163, wherein the average NAS score for nausea is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

10 165. A method as claimed in any one of claims 154 to 164, wherein the average NAS score for sedation is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

15 166. A method as claimed in any one of claims 154 to 165, wherein the average NAS score for dysphoria is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

20 167. A method as claimed in any one of claims 154 to 166, wherein said method provides a level of analgesia which, as measured by the cold pressor test, is at least a -20 % change, preferably at least a -40 % change, compared to baseline level.

25 168. A method as claimed in any one of claims 154 to 167, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.2 times, preferably at least 1.5 times.

169. A method as claimed in any one of claims 154 to 168, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by 1.2 to 3.0 times.

30 170. A method as claimed in claim 168 or 169, wherein said pain threshold levels are measured by applying pain using a transcutaneous electrical stimulus to the skin over the tibial bone and increasing the electrical stimulus at a rate of 0.5 mA per 2s.

35 171. A method as claimed in any preceding claim, wherein the dose of (R)-dihydroetorphine is administered intravenously.

172. A method as claimed in any preceding claim, wherein the pain treated is nociceptive pain.

5 173. A method of providing anaesthesia in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose of at least 0.15 $\mu\text{g/kg}$ and the level of respiratory depression in said subject is 65 or less % relative to the baseline level pre-administration of (R)-dihydroetorphine.

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174. A methods as claimed in claim 173, wherein the level of respiration in said subject is 35 to 100% relative to the baseline level pre-administration of (R)-dihydroetorphine.

15

175. A method as claimed in claim 173 or 174, wherein said (R)-dihydroetorphine is administered in a dose of 0.15 to 0.4 $\mu\text{g/kg}$.

176. A method as claimed in claim 173 or 174, wherein said (R)-dihydroetorphine is administered in a dose of 0.2 to 0.3 $\mu\text{g/kg}$.

20

177. A method as claimed in any one of claims 173 to 176, further comprising administering a sedative to said subject.

25

178. A method as claimed in any one of claims 173 to 177, wherein the level of respiratory depression in said subject is between 40 and 65 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

30

179. A method as claimed in any one of claims 173 to 178, wherein said (R)-dihydroetorphine is administered in a dose of 0.15 to 0.4 $\mu\text{g/kg}$ and the level of respiratory depression in said subject is between 50 and 65 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

180. A method as claimed in any one of claims 173 to 179, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic

conditions for 1 hour following administration of said (R)-dihydroetorphine intravenously over 10 minutes.

5 181. A method as claimed in any one of claims 173 to 180, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of 20 ± 2 L/min.

10 182. A method as claimed in claim 181, wherein said end tidal carbon dioxide level is clamped at 50 mmHg.

15 183. A method as claimed in any one of claims 173 to 182, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.5 times.

184. A method as claimed in any one of claims 173 to 183, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by 1.5 to 3.0 times.

20 185. A method as claimed in claim 183 or 184, wherein said pain threshold levels are measured by applying pain using a transcutaneous electrical stimulus to the skin over the tibial bone and increasing the electrical stimulus at a rate of 0.5 mA per 2s.

25 186. A method as claimed in any one of claims 173 to 185, wherein during said method one or more opioid-related effects selected from dizziness, euphoria, nausea, sedation and dysphoria are minimised.

30 187. A method as claimed in any one of claims 173 to 186, wherein said opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

188. A method as claimed in claim 186 or 187, wherein the average NAS score for dizziness is less than 50 in the 7.5 hours post administration of (R)-dihydroetorphine.

189. A method as claimed in any one of claims 186 to 188, wherein the average NAS score for euphoria is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

5 190. A method as claimed in any one of claims 186 to 189, wherein the average NAS score for nausea is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

10 191. A method as claimed in any one of claim 186 to 190, wherein the average NAS score for sedation is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

15 192. A method as claimed in any one of claims 186 to 191, wherein the average NAS score for dysphoria is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

20 193. A method of providing anaesthesia in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose of at least 0.15 µg/kg and the peak respiratory depression in said subject is 20 to 80 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

25 194. A method as claimed in claim 193, wherein said (R)-dihydroetorphine is administered in a dose of 0.15 to 0.4 µg/kg.

195. A method as claimed in claim 193 or 194, wherein said (R)-dihydroetorphine is administered in a dose of 0.2 to 0.3 µg/kg.

30 196. A method as claimed in any one of claims 193 to 195, further comprising administering a sedative to said subject.

35 197. A method as claimed in any one of claims 193 to 196, wherein the peak respiratory depression in said subject is 25 to 45 % relative to the baseline level prior to administration of (R)-dihydroetorphine.

198. A method as claimed in any one of claims 193 to 197, wherein the peak respiratory depression in said subject is 30 to 40 % relative to the baseline level prior to administration of (R)-dihydroetorphine.

5 199. A method as claimed in any one of claims 194 to 198, wherein said (R)-dihydroetorphine is administered in a dose of 0.15 to 0.4 $\mu\text{g/kg}$ and the peak respiratory depression in said subject is between 25 to 45 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

10 200. A method as claimed in any one of claims 193 to 199, wherein said peak respiratory depression is measured under iso-hypercapnic conditions for 1 hour following administration of said (R)-dihydroetorphine intravenously over 10 minutes.

15 201. A method as claimed in any one of claims 193 to 200, wherein said peak respiratory depression is measured under iso-hypercapnic conditions for 1 hour with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of $20 \pm 2\text{L/min}$.

20 202. A method as claimed in claim 201, wherein said end tidal carbon dioxide level is clamped at 50 mmHg.

25 203. A method as claimed in any one of claims 193 to 202, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.5 times.

204. A method as claimed in any one of claims 193 to 203, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by 1.5 to 3.0 times.

30 205. A method as claimed in claim 203 or 204, wherein said pain threshold levels are measured by applying pain using a transcutaneous electrical stimulus to the skin over the tibial bone and increasing the electrical stimulus at a rate of 0.5 mA per 2s.

206. A method as claimed in any one of claims 203 to 205, wherein during said

method one or more opioid-related effects selected from dizziness, euphoria, nausea, sedation and dysphoria are minimised.

5 207. A method as claimed in claim 206, wherein said opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

208. A method as claimed in claim 206 or 207, wherein the average NAS score for dizziness is less than 50 in the 7.5 hours post administration of (R)-dihydroetorphine.

10 209. A method as claimed in any one of claims 206 to 208, wherein the average NAS score for euphoria is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

15 210. A method as claimed in any one of claims 206 to 209, wherein the average NAS score for nausea is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

20 211. A method as claimed in any one of claim 206 to 210, wherein the average NAS score for sedation is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

25 212. A method as claimed in any one of claims 206 to 211, wherein the average NAS score for dysphoria is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

30 213. A method of providing anaesthesia in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose of at least 0.15 µg/kg and the resulting ventilation ratio in said subject is at least 0.3.

214. A method as claimed in claim 213, wherein said (R)-dihydroetorphine is administered in a dose of 0.15 to 0.4 µg/kg.

35 215. A method as claimed in claim 213 or 214, wherein said (R)-dihydroetorphine is administered in a dose of 0.2 to 0.3 µg/kg.

216. A method as claimed in any one of claims 213 to 215, further comprising administering a sedative to said subject.

5 217. A method as claimed in any one of claims 213 to 216, wherein the resulting ventilation ratio in said subject is between 0.3 and 0.6.

218. A method as claimed in any one of claims 213 to 217, wherein said (R)-dihydroetorphine is administered in a dose of 0.15 to 0.4 $\mu\text{g/kg}$ and the resulting
10 ventilation ratio in said subject is 0.3 to 0.5.

219. A method as claimed in any one of claims 213 to 218, wherein the ventilation ratio is determined by measuring respiration pre-administration of (R)-dihydroetorphine and post-administration administration of (R)-dihydroetorphine intravenously over 10
15 minutes for 1 hour under iso-hypercapnic conditions .

220. A method as claimed in any one of claims 213 to 219, wherein the ventilation ratio is determined by measuring respiration pre-administration of (R)-dihydroetorphine and post-administration administration of (R)-dihydroetorphine intravenously over 10
20 minutes for 1 hour under iso-hypercapnic with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of $20 \pm 2\text{L/min}$.

221. A method as claimed in claim 220, wherein said end tidal carbon dioxide level is
25 clamped at 50 mmHg.

222. A method as claimed in any one of claims 213 to 221, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.5 times.

30 223. A method as claimed in any one of claims 213 to 222, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by 1.5 to 3.0 times.

35 224. A method as claimed in claim 222 or 223, wherein said pain threshold levels are

measured by applying pain using a transcutaneous electrical stimulus to the skin over the tibial bone and increasing the electrical stimulus at a rate of 0.5 mA per 2s.

5 225. A method as claimed in any one of claims 213 to 224, wherein during said method one or more opioid-related effects selected from dizziness, euphoria, nausea, sedation and dysphoria are minimised.

10 226. A method as claimed in any one of claims 213 to 225, wherein said opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

227. A method as claimed in claim 225 or 226, wherein the average NAS score for dizziness is less than 50 in the 7.5 hours post administration of (R)-dihydroetorphine.

15 228. A method as claimed in any one of claims 222 to 227, wherein the average NAS score for euphoria is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

20 229. A method as claimed in any one of claims 222 to 228, wherein the average NAS score for nausea is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

25 230. A method as claimed in any one of claims 222 to 229, wherein the average NAS score for sedation is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

30 231. A method as claimed in any one of claims 222 to 230, wherein the average NAS score for dysphoria is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

35 232. A method of providing anaesthesia in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose greater than the ED₇₅ dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

233. A method as claimed in claim 232, wherein (R)-dihydroetorphine is administered in a dose greater than the ED₈₅ dose.

5 234. A method as claimed in claim 232 or 233, wherein (R)-dihydroetorphine is administered in a dose greater than the ED₉₀ dose.

235. A method as claimed in any one of claims 232 to 234, wherein (R)-dihydroetorphine is administered in a dose between the ED₇₅ dose and the ED₉₅ dose.

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236. A method as claimed in any one of claims 232 to 235, further comprising administering a sedative to said subject.

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237. A method as claimed in any one of claims 232 to 236, wherein the level of respiratory depression in said subject is between 40 and 65 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

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238. A method of providing anaesthesia in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose greater than the ED₅₀ dose and less than the ED₇₅ dose and the level of respiratory depression in said subject is 50 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

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239. A method of providing anaesthesia in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose greater than the ED₇₅ dose and less than the ED₉₅ dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

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240. A method as claimed in claim 238 or 239, further comprising administering a sedative to said subject.

241. A method as claimed in any one of claims 232 to 240, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic

conditions for 1 hour following administration of said (R)-dihydroetorphine intravenously over 10 minutes.

5 242. A method as claimed in any one of claims 232 to 241, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of 20 ± 2 L/min.

10 243. A method as claimed in claim 242, wherein said end tidal carbon dioxide level is clamped at 50 mmHg.

15 244. A method as claimed in any one of claims 232 to 243, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.5 times.

245. A method as claimed in any one of claims 232 to 244, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by 1.5 to 3.0 times.

20 246. A method as claimed in claim 244 or 245, wherein said pain threshold levels are measured by applying pain using a transcutaneous electrical stimulus to the skin over the tibial bone and increasing the electrical stimulus at a rate of 0.5 mA per 2s.

25 247. A method as claimed in any one of claims 232 to 246, wherein during said method one or more opioid-related effects selected from dizziness, euphoria, nausea, sedation and dysphoria are minimised.

30 248. A method as claimed in any one of claims 232 to 247, wherein said opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

249. A method as claimed in claim 247 or 248, wherein the average NAS score for dizziness is less than 50 in the 7.5 hours post administration of (R)-dihydroetorphine.

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250. A method as claimed in any one of claims 247 to 249, wherein the average NAS score for euphoria is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

5 251. A method as claimed in any one of claims 247 to 250, wherein the average NAS score for nausea is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

10 252. A method as claimed in any one of claims 247 to 251, wherein the average NAS score for sedation is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

15 253. A method as claimed in any one of claims 247 to 252, wherein the average NAS score for dysphoria is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

20 254. A method of providing anaesthesia to a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose that increases the pain threshold value relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.5 times and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

25 255. A method as claimed in claim 254, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by 1.5 to 3.0 times.

30 256. A method as claimed in claim 254 or 255, further comprising administering a sedative to said subject.

257. A method as claimed in any one of claims 254 to 256, wherein said pain threshold levels are measured by applying pain using a transcutaneous electrical stimulus to the skin over the tibial bone and increasing the electrical stimulus at a rate of 0.5 mA per 2s.

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258. A method as claimed in any one of claims 254 to 257, wherein the level of respiratory depression in said subject is between 40 and 65 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

5 259. A method as claimed in any one of claims 254 to 258, wherein the peak respiratory depression in said subject is 20 to 80 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

10 260. A method as claimed in any one of claims 254 to 259, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour following administration of said (R)-dihydroetorphine intravenously over 10 minutes.

15 261. A method as claimed in any one of claims 254 to 260, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of 20 ± 2 L/min.

20 262. A method as claimed in claim 261, wherein said end tidal carbon dioxide level is clamped at 50 mmHg.

25 263. A method as claimed in any one of claims 254 to 262, wherein during said method one or more opioid-related effects selected from dizziness, euphoria, nausea, sedation and dysphoria are minimised.

264. A method as claimed in any one of claims 254 to 263, wherein said opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

30 265. A method as claimed in claim 263 or 264, wherein the average NAS score for dizziness is less than 50 in the 7.5 hours post administration of (R)-dihydroetorphine.

35 266. A method as claimed in any one of claims 263 to 265, wherein the average NAS score for euphoria is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

267. A method as claimed in any one of claims 263 to 266, wherein the average NAS score for nausea is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

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268. A method as claimed in any one of claims 263 to 267, wherein the average NAS score for sedation is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

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269. A method as claimed in any one of claims 263 to 268, wherein the average NAS score for dysphoria is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

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270. A method of providing anaesthesia in a human subject in need thereof whilst minimising risk of apnoea comprising administering a dose of (R)-dihydroetorphine that provides dose dependent pain relief and dose-independent respiratory depression.

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271. A method as claimed in claim 270, wherein said (R)-dihydroetorphine is administered in a dose of 0.15 to 0.4 $\mu\text{g/kg}$.

272. A method as claimed in claim 270 or 271, wherein said (R)-dihydroetorphine is administered in a dose of 0.2 to 0.3 $\mu\text{g/kg}$.

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273. A method as claimed in any one of claims 270 to 272, further comprising administering a sedative to said subject.

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274. A method as claimed in any one of claims 270 to 273, wherein the level of respiratory depression in said subject is between 40 and 65 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

275. A method as claimed in any one of claims 270 to 274, wherein the level of respiratory depression is at a E_{MIN} of 30 to 35 % $\pm$ 10%.

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276. A method as claimed in any one of claims 270 to 275, wherein said (R)-dihydroetorphine is administered in a dose of 0.15 to 0.4 $\mu\text{g/kg}$ and the level of

respiratory depression in said subject is between 30 and 50 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

5 277. A method as claimed in any one of claims 270 to 276, wherein the peak respiratory depression in said subject is 20 to 80 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

10 278. A method as claimed in any one of claims 270 to 277, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour following administration of said (R)-dihydroetorphine intravenously over 10 minutes.

15 279. A method as claimed in any one of claims 270 to 278, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of 20 ± 2 L/min.

20 280. A method as claimed in claim 279, wherein said end tidal carbon dioxide level is clamped at 50 mmHg.

281. A method as claimed in any one of claims 270 to 280, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.5 times.

25 282. A method as claimed in any one of claims 270 to 280, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by 1.5 to 3.0 times.

30 283. A method as claimed in claim 281 or 282, wherein said pain threshold levels are measured by applying pain using a transcutaneous electrical stimulus to the skin over the tibial bone and increasing the electrical stimulus at a rate of 0.5 mA per 2s.

35 284. A method as claimed in any one of claims 270 to 283, wherein during said method one or more opioid-related effects selected from dizziness, euphoria, nausea, sedation and dysphoria are minimised.

285. A method as claimed in any one of claims 270 to 284, wherein said opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

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286. A method as claimed in claim 284 or 285, wherein the average NAS score for dizziness is less than 50 in the 7.5 hours post administration of (R)-dihydroetorphine.

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287. A method as claimed in any one of claims 284 to 286, wherein the average NAS score for euphoria is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

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288. A method as claimed in any one of claims 284 to 287, wherein the average NAS score for nausea is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

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289. A method as claimed in any one of claims 284 to 288, wherein the average NAS score for sedation is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

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290. A method as claimed in any one of claims 284 to 289, wherein the average NAS score for dysphoria is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

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291. A method of providing maximum anaesthesia in a human subject in need thereof whilst minimising risk of apnoea comprising administering a dose of (R)-dihydroetorphine which causes a E_{MIN} in ventilation of 30-50 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

292. A method as claimed in claim 291, wherein said (R)-dihydroetorphine is administered in a dose of 0.15 to 0.4 $\mu\text{g/kg}$.

293. A method as claimed in claim 292 or 293, wherein said (R)-dihydroetorphine is administered in a dose of 0.2 to 0.3 $\mu\text{g/kg}$.

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294. A method as claimed in any one of claims 291 to 293, further comprising administering a sedative to said subject.

5 295. A method as claimed in any one of claims 291 to 294, wherein the level of ventilation in said subject is between 30 and 40 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

10 296. A method as claimed in any one of claims 291 to 295, wherein said (R)-dihydroetorphine is administered in a dose of 0.15 to 0.4 $\mu\text{g/kg}$ and the level of ventilation in said subject is between 30 and 50 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

15 297. A method as claimed in any one of claims 291 to 295, wherein said ventilation is the average measured under iso-hypercapnic conditions for 1 hour following administration of said (R)-dihydroetorphine intravenously over 10 minutes.

20 298. A method as claimed in any one of claims 291 to 297, wherein said ventilation is the average measured under iso-hypercapnic conditions for 1 hour with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of $20 \pm 2\text{L/min}$.

299. A method as claimed in claim 298, wherein said end tidal carbon dioxide level is clamped at 50 mmHg.

25 300. A method as claimed in any one of claims 291 to 299, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.5 times.

30 301. A method as claimed in any one of claims 291 to 300, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by 1.5 to 3.0 times.

35 302. A method as claimed in claim 300 or 301, wherein said pain threshold levels are measured by applying pain using a transcutaneous electrical stimulus to the skin over the tibial bone and increasing the electrical stimulus at a rate of 0.5 mA per 2s.

303. A method as claimed in any one of claims 291 to 302, wherein during said method one or more opioid-related effects selected from dizziness, euphoria, nausea, sedation and dysphoria are minimised.

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304. A method as claimed in any one of claims 291 to 303, wherein said opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

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305. A method as claimed in claim 303 or 304, wherein the average NAS score for dizziness is less than 50 in the 7.5 hours post administration of (R)-dihydroetorphine.

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306. A method as claimed in any one of claims 303 to 305, wherein the average NAS score for euphoria is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

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307. A method as claimed in any one of claims 303 to 306, wherein the average NAS score for nausea is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

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308. A method as claimed in any one of claims 303 to 307, wherein the average NAS score for sedation is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

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309. A method as claimed in any one of claims 303 to 308, wherein the average NAS score for dysphoria is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

310. A method of providing anaesthesia in a human subject comprising administering to said subject an effective dose of (R)-dihydroetorphine, wherein during said treating at least one opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

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311. A method as claimed in claim 310, wherein said (R)-dihydroetorphine is administered in a dose of 0.15 to 0.4 $\mu\text{g/kg}$.

312. A method as claimed in claim 310 or 311, wherein said (R)-dihydroetorphine is administered in a dose of 0.2 to 0.3 $\mu\text{g/kg}$.

5 313. A method as claimed in any one of claims 310 to 312, further comprising administering a sedative to said subject.

10 314. A method as claimed in any one of claims 310 to 313, wherein said opioid-related side effect is selected from respiratory depression, dizziness, euphoria, nausea, sedation and dysphoria.

315. A method as claimed in any one of claims 310 to 314, wherein said opioid-related side effect is respiratory depression.

15 316. A method as claimed in claim 315, wherein said respiratory depression is 0 to 65 %.

20 317. A method as claimed in any one of claims 310 to 316, wherein the peak respiratory depression in said subject is 20 to 80 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

25 318. A method as claimed in any one of claims 310 to 317, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour following administration of said (R)-dihydroetorphine intravenously over 10 minutes.

30 319. A method as claimed in any one of claims 310 to 318, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of $20 \pm 2\text{L/min}$.

320. A method as claimed in claim 319, wherein said end tidal carbon dioxide level is clamped at 50 mmHg.

321. A method as claimed in any one of claims 310 to 320, wherein said opioid-related side effect is dizziness.

5 322. A method as claimed in any one of claims 310 to 321, wherein said opioid-related side effect is euphoria.

323. A method as claimed in any one of claims 310 to 322, wherein said opioid-related side effect is nausea.

10 324. A method as claimed in any one of claims 310 to 323, wherein said opioid-related side effect is sedation.

325. A method as claimed in any one of claims 310 to 324, wherein said opioid-related side effect is dysphoria.

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326. A method as claimed in any one of claims 310 to 325, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.5 times.

20 327. A method as claimed in any one of claims 310 to 326, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by 1.5 to 3.0 times.

25 328. A method as claimed in claim 326 or 327, wherein said pain threshold levels are measured by applying pain using a transcutaneous electrical stimulus to the skin over the tibial bone and increasing the electrical stimulus at a rate of 0.5 mA per 2s.

329. A method of providing anaesthesia in a human subject comprising administering to said subject an effective dose of (R)-dihydroetorphine, wherein during said treating opioid-related respiratory depression is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine and at least one of the following criteria defining the levels of opioid-related side effects is satisfied in the 7.5 hours post administration of (R)-dihydroetorphine:

30 average NAS score for dizziness of 0 to 50

35 average NAS score for euphoria of 0 to 60

average NAS score for nausea of 0 to 40

average NAS score for sedation of 0 to 60

average NAS score for dysphoria of 0 to 40.

5 330. A method as claimed in claim 329, wherein said (R)-dihydroetorphine is administered in a dose of 0.15 to 0.4 µg/kg.

331. A method as claimed in claim 329 or 330, wherein said (R)-dihydroetorphine is administered in a dose of 0.2 to 0.3 µg/kg.

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332. A method as claimed in any one of claims 329 to 331, further comprising administering a sedative to said subject.

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333. A method as claimed in any one of claims 329 to 332, wherein the level of respiratory depression in said subject is between 40 and 65 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

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334. A method as claimed in any one of claims 329 to 333, wherein said (R)-dihydroetorphine is administered in a dose of 0.075 to 0.15 µg/kg and the level of respiratory depression in said subject is between 50 and 65 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

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335. A method as claimed in any one of claims 329 to 334, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour following administration of said (R)-dihydroetorphine intravenously over 10 minutes.

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336. A method as claimed in any one of claims 329 to 335, wherein said respiratory depression is the average respiratory depression measured under iso-hypercapnic conditions for 1 hour with end tidal oxygen level clamped at 110 mmHg and end tidal carbon dioxide clamped at a level causing ventilation levels of 20 ± 2 L/min.

337. A method as claimed in claim 336, wherein said end tidal carbon dioxide level is clamped at 50 mmHg.

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338. A method as claimed in any one of claims 329 to 337, wherein the average NAS score for dizziness is less than 50 in the 7.5 hours post administration of (R)-dihydroetorphine.

5 339. A method as claimed in any one of claims 329 to 338, wherein the average NAS score for euphoria is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

10 340. A method as claimed in any one of claims 329 to 339, wherein the average NAS score for nausea is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

15 341. A method as claimed in any one of claims 329 to 340, wherein the average NAS score for sedation is less than 60 in the 7.5 hours post administration of (R)-dihydroetorphine.

20 342. A method as claimed in any one of claims 329 to 341, wherein the average NAS score for dysphoria is less than 40 in the 7.5 hours post administration of (R)-dihydroetorphine.

343. A method as claimed in any one of claims 329 to 342, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.5 times.

25 344. A method as claimed in any one of claims 329 to 343, wherein said method increases the pain threshold level in said subject relative to the baseline level pre-administration of (R)-dihydroetorphine by 1.5 to 3.0 times.

30 345. A method as claimed in claim 343 or 344, wherein said pain threshold levels are measured by applying pain using a transcutaneous electrical stimulus to the skin over the tibial bone and increasing the electrical stimulus at a rate of 0.5 mA per 2s.

346. A method as claimed in any preceding claim, wherein the dose of (R)-dihydroetorphine is administered intravenously.

347. A method as claimed in any preceding claim, wherein the pain treated is nociceptive pain.

5 348. (R)-dihydroetorphine for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of at least 0.01 $\mu\text{g/kg}$, preferably at least 0.05 $\mu\text{g/kg}$, and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

10 349. (R)-dihydroetorphine for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of at least 0.01 $\mu\text{g/kg}$, preferably at least 0.05 $\mu\text{g/kg}$, and the peak respiratory depression in said subject is 20 to 80 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

15 350. (R)-dihydroetorphine for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of at least 0.01 $\mu\text{g/kg}$, preferably at least 0.05 $\mu\text{g/kg}$, and the ventilation ratio in said subject is at least 0.3.

20 351. (R)-dihydroetorphine for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{75} dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

25 352. (R)-dihydroetorphine for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{50} dose and less than the ED_{75} dose and the level of respiratory depression in said subject is 50 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

30 353. (R)-dihydroetorphine for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{75} dose and less than the ED_{95} dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

35 354. (R)-dihydroetorphine for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose that increases the pain threshold value relative to the baseline level pre-administration of (R)-dihydroetorphine by at

least 1.2 times and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

5 355. (R)-dihydroetorphine for the treatment of pain whilst minimising risk of apnoea, wherein during said treatment a dose of (R)-dihydroetorphine that provides dose dependent pain relief and dose-independent respiratory depression is administered.

10 356. (R)-dihydroetorphine for the treatment of pain whilst minimising risk of apnoea wherein during said treatment a dose of (R)-dihydroetorphine which causes a E_{MIN} in ventilation of 30-50 % relative to the baseline level pre-administration of (R)-dihydroetorphine is administered.

15 357. (R)-dihydroetorphine for the treatment of pain, wherein during said treatment at least one opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

20 358. (R)-dihydroetorphine for the treatment of pain, wherein during said treatment opioid-related respiratory depression is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine and at least one of the following criteria is satisfied in the 7.5 hours post administration of (R)-dihydroetorphine:
average NAS score for dizziness of 0 to 50
average NAS score for euphoria of 0 to 60
average NAS score for nausea of 0 to 40
average NAS score for sedation of 0 to 60
25 average NAS score for dysphoria of 0 to 40.

30 359. Use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of at least 0.01 $\mu\text{g/kg}$, preferably at least 0.05 $\mu\text{g/kg}$, and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

35 360. Use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during treatment said (R)-dihydroetorphine is administered in a dose of at least 0.01 $\mu\text{g/kg}$, preferably at least 0.05 $\mu\text{g/kg}$, and the peak respiratory

depression in said subject is 20 to 80 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

5 361. Use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of at least 0.01 $\mu\text{g/kg}$, preferably at least 0.05 $\mu\text{g/kg}$, and the ventilation ratio in said subject is at least 0.3.

10 362. Use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{75} dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

15 363. Use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{50} dose and less than the ED_{75} dose and the level of respiratory depression in said subject is 50 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

20 364. Use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{75} dose and less than the ED_{95} dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

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30 365. Use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during said treatment said (R)-dihydroetorphine is administered in a dose that increases the pain threshold value relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.2 times and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

35 366. Use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during said treatment a dose of (R)-dihydroetorphine that

provides dose dependent pain relief and dose-independent respiratory depression is administered.

5 367. Use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during said treatment a dose of (R)-dihydroetorphine which causes a E_{MIN} in ventilation of 30-50 % relative to the baseline level pre-administration of (R)-dihydroetorphine is administered.

10 368. Use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during said treatment at least one opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

15 369. Use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain, wherein during said treatment opioid-related respiratory depression is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine and at least one of the following criteria is satisfied in the 7.5 hours post administration of (R)-dihydroetorphine:

average NAS score for dizziness of 0 to 50

average NAS score for euphoria of 0 to 60

20 average NAS score for nausea of 0 to 40

average NAS score for sedation of 0 to 60

average NAS score for dysphoria of 0 to 40.

25 370. (R)-dihydroetorphine for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of at least 0.15 $\mu\text{g/kg}$ and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

30 371. (R)-dihydroetorphine for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of at least 0.15 $\mu\text{g/kg}$ and the peak respiratory depression in said subject is 20 to 80 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

372. (R)-dihydroetorphine for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of at least 0.15 $\mu\text{g/kg}$ and the ventilation ratio in said subject is at least 0.3.

5 373. (R)-dihydroetorphine for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{75} dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

10 374. (R)-dihydroetorphine for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{50} dose and less than the ED_{75} dose and the level of respiratory depression in said subject is 50 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

15 375. (R)-dihydroetorphine for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{75} dose and less than the ED_{95} dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

20 376. (R)-dihydroetorphine for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose that increases the pain threshold value relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.5 times and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

25

377. (R)-dihydroetorphine for providing anaesthesia whilst minimising risk of apnoea, wherein during said treatment a dose of (R)-dihydroetorphine that provides dose dependent pain relief and dose-independent respiratory depression is administered.

30 378. (R)-dihydroetorphine for providing anaesthesia whilst minimising risk of apnoea, wherein during said treatment a dose of (R)-dihydroetorphine which causes a E_{MIN} in ventilation of 30-50 % relative to the baseline level pre-administration of (R)-dihydroetorphine is administered.

379. (R)-dihydroetorphine for providing anaesthesia, wherein during said treatment at least one opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

5 380. (R)-dihydroetorphine for providing anaesthesia, wherein during said treatment opioid-related respiratory depression is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine and at least one of the following criteria is satisfied in the 7.5 hours post administration of (R)-dihydroetorphine:

average NAS score for dizziness of 0 to 50

10 average NAS score for euphoria of 0 to 60

average NAS score for nausea of 0 to 40

average NAS score for sedation of 0 to 60

average NAS score for dysphoria of 0 to 40.

15 381. Use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of at least 0.15 $\mu\text{g/kg}$ and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

20 382. Use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during treatment said (R)-dihydroetorphine is administered in a dose of at least 0.15 $\mu\text{g/kg}$ and the peak respiratory depression in said subject is 20 to 80 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

25 383. Use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of at least 0.15 $\mu\text{g/kg}$ and the ventilation ratio in said subject is at least 0.3.

30 384. Use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{75} dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

385. Use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{50} dose and less than the ED_{75} dose and the level of respiratory depression in said subject is 50 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

386. Use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose greater than the ED_{75} dose and less than the ED_{95} dose and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

387. Use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia n, wherein during said treatment said (R)-dihydroetorphine is administered in a dose that increases the pain threshold value relative to the baseline level pre-administration of (R)-dihydroetorphine by at least 1.5 times and the level of respiratory depression in said subject is 65 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

388. Use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during said treatment a dose of (R)-dihydroetorphine that provides dose dependent pain relief and dose-independent respiratory depression is administered.

389. Use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during said treatment a dose of (R)-dihydroetorphine which causes a E_{MIN} in ventilation of 30-50 % relative to the baseline level pre-administration of (R)-dihydroetorphine is administered.

390. Use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during said treatment at least one opioid-related side effect is reduced compared to treatment with an equianalgesic dose of fentanyl.

391. Use of (R)-dihydroetorphine in the manufacture of a medicament for providing anaesthesia, wherein during said treatment opioid-related respiratory depression is 65

% or less relative to the baseline level pre-administration of (R)-dihydroetorphine and at least one of the following criteria is satisfied in the 7.5 hours post administration of (R)-dihydroetorphine:

average NAS score for dizziness of 0 to 50

5 average NAS score for euphoria of 0 to 60

average NAS score for nausea of 0 to 40

average NAS score for sedation of 0 to 60

average NAS score for dysphoria of 0 to 40.

10 392. A method of providing pain relief or anaesthesia in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose of 0.20 to 0.5 $\mu\text{g/kg}$ and the level of respiratory depression in said subject is 85 or less % relative to the baseline level pre-administration of (R)-dihydroetorphine.

15

393. A method of providing pain relief or anaesthesia in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose of 0.20 to 0.5 $\mu\text{g/kg}$ and the peak respiratory depression in said subject is 15 to 80 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

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394. A method of providing pain relief or anaesthesia in a human subject in need thereof comprising administering (R)-dihydroetorphine to said subject, wherein said (R)-dihydroetorphine is administered in a dose of 0.20 to 0.5 $\mu\text{g/kg}$ and the resulting ventilation ratio in said subject is at least 0.15.

25

395. (R)-dihydroetorphine for providing pain relief or anaesthesia, wherein said (R)-dihydroetorphine is administered in a dose of 0.20 to 0.5 $\mu\text{g/kg}$ and the level of respiratory depression in the subject is 85 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

30

396. (R)-dihydroetorphine for providing pain relief or anaesthesia, wherein said (R)-dihydroetorphine is administered in a dose of 0.20 to 0.5 $\mu\text{g/kg}$ and the peak respiratory depression in the subject is 15 to 80 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

35

397. (R)-dihydroetorphine for providing pain relief or anaesthesia, wherein said (R)-dihydroetorphine is administered in a dose of 0.20 to 0.5 $\mu\text{g/kg}$ and the ventilation ratio in the subject is at least 0.15.

5

398. Use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain or anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of 0.20 to 0.5 $\mu\text{g/kg}$ and the level of respiratory depression in said subject is 85 % or less relative to the baseline level pre-administration of (R)-dihydroetorphine.

10

399. Use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain or anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of 0.20 to 0.5 $\mu\text{g/kg}$ and the peak respiratory depression in said subject is 15 to 80 % relative to the baseline level pre-administration of (R)-dihydroetorphine.

15

400. Use of (R)-dihydroetorphine in the manufacture of a medicament for the treatment of pain or anaesthesia, wherein during said treatment said (R)-dihydroetorphine is administered in a dose of 0.20 to 0.5 $\mu\text{g/kg}$ and the ventilation ratio in said subject is at least 0.3.

20

25

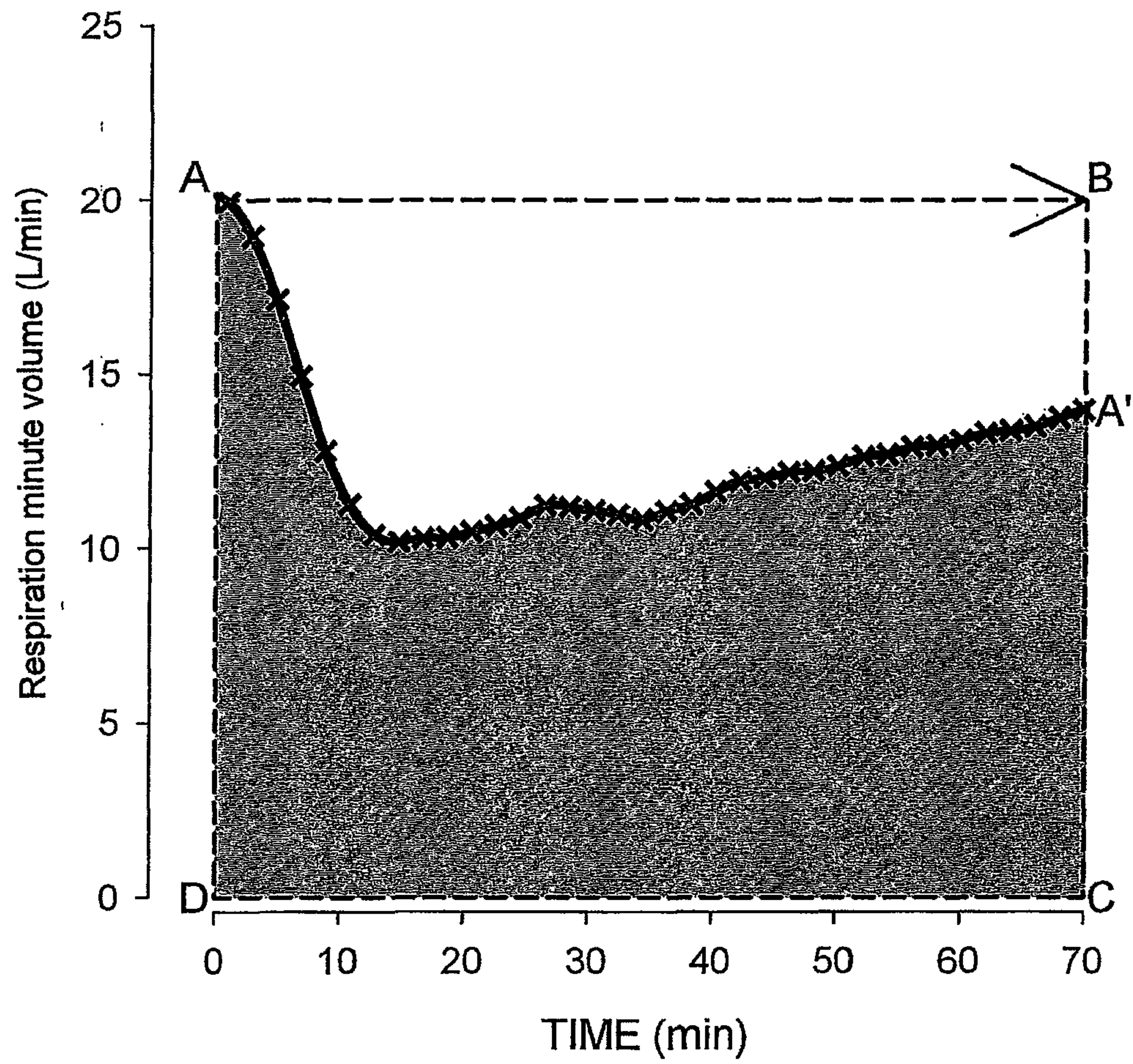


Figure 1

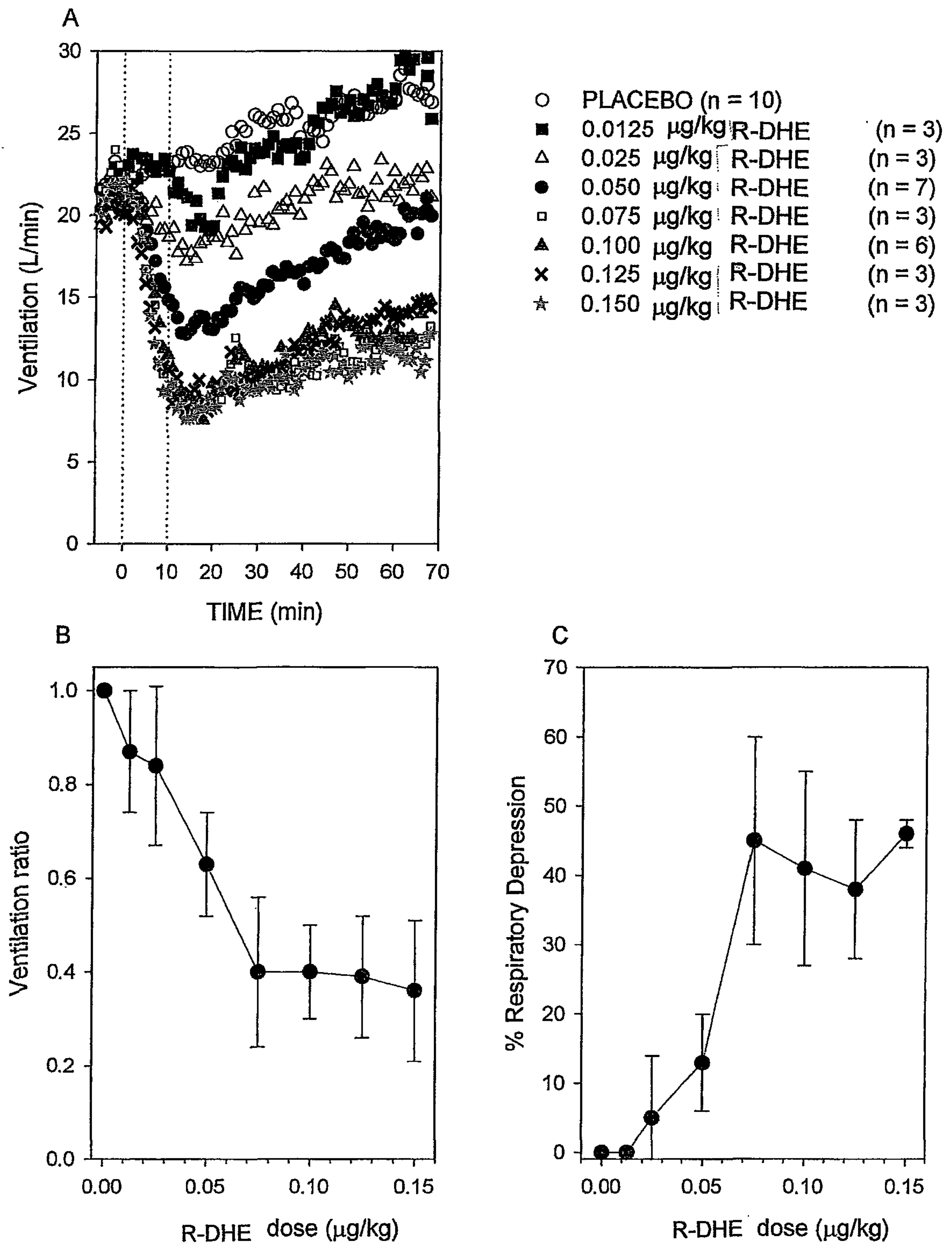


Figure 2

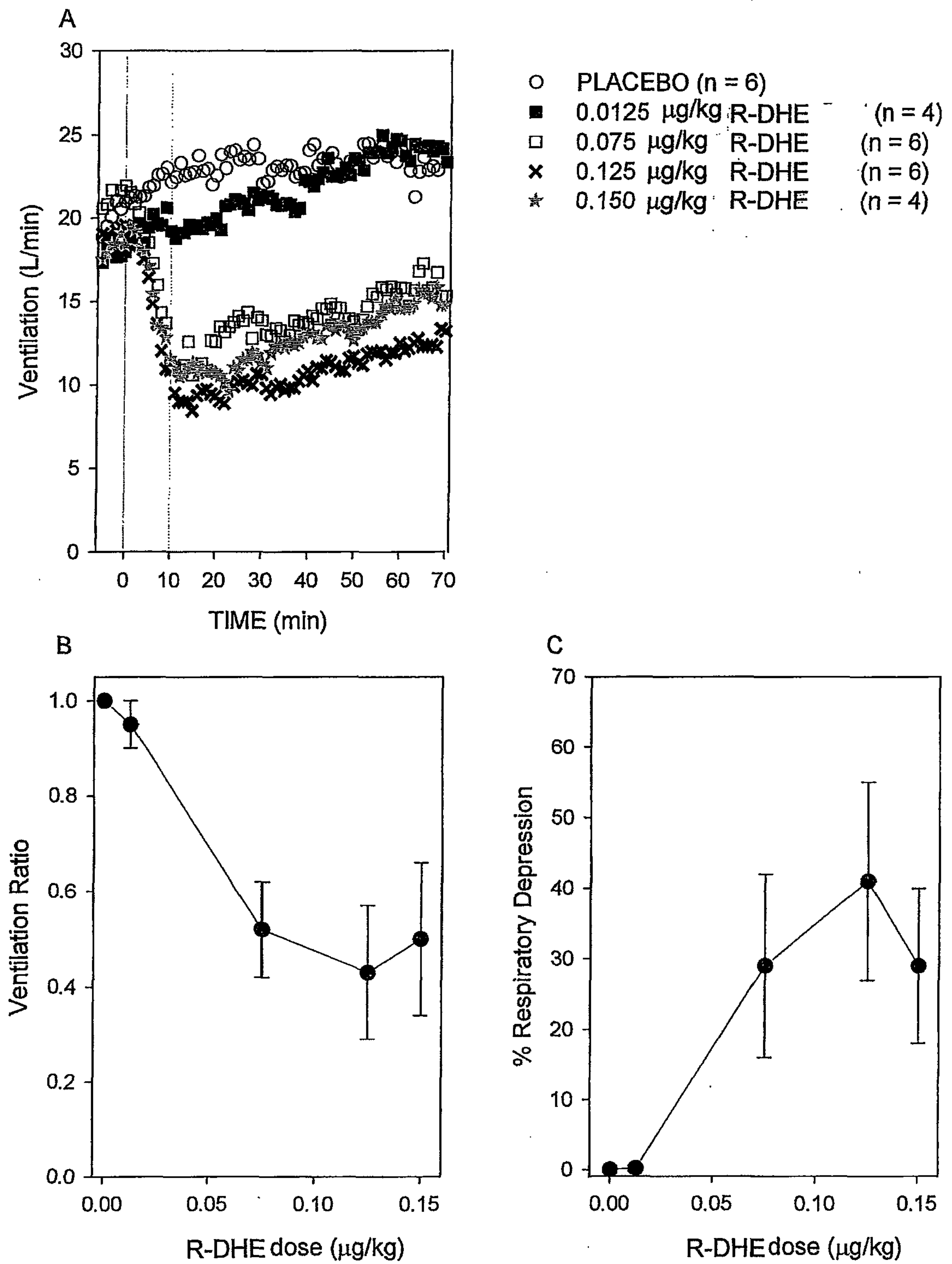


Figure 3

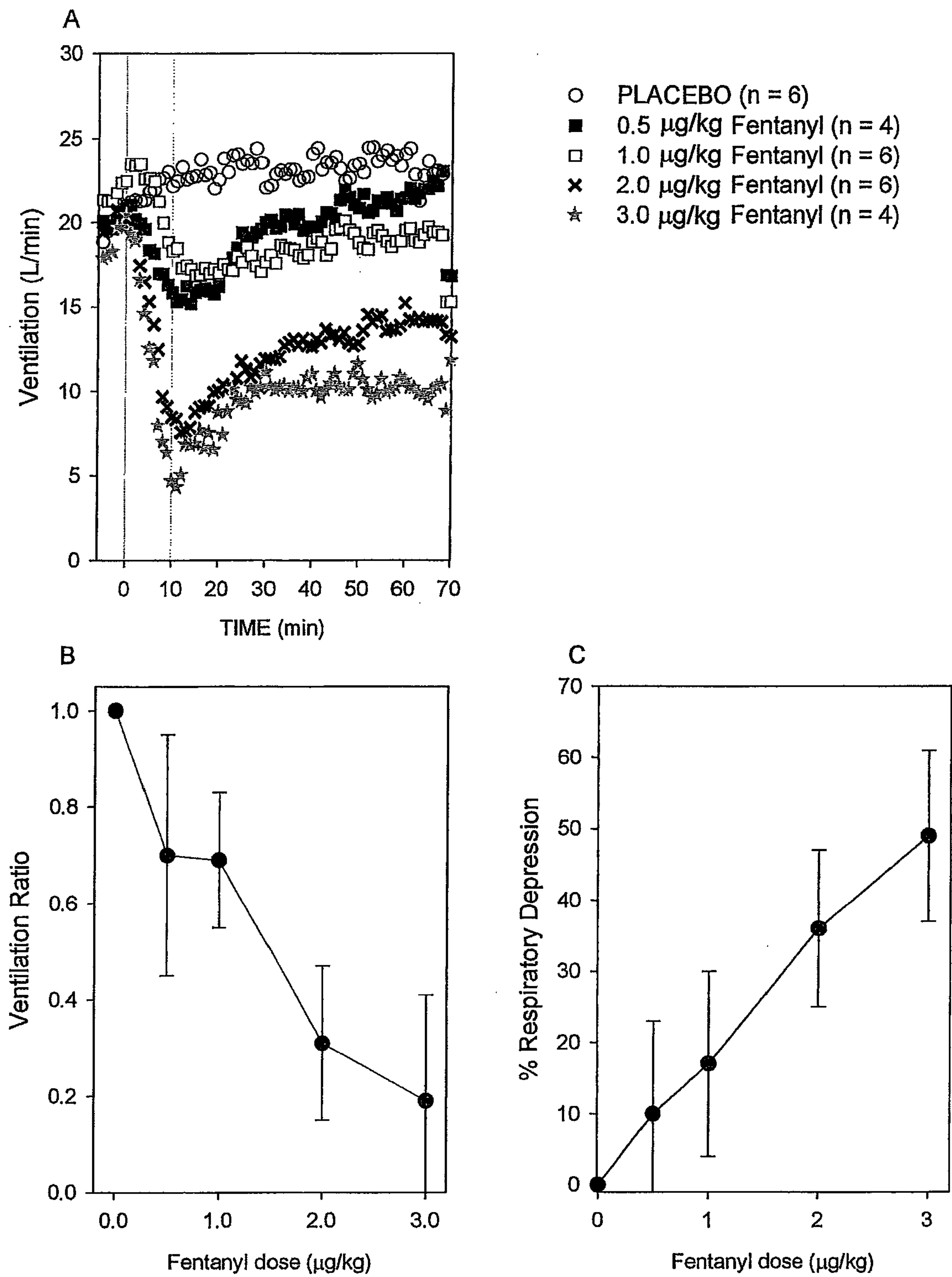


Figure 4

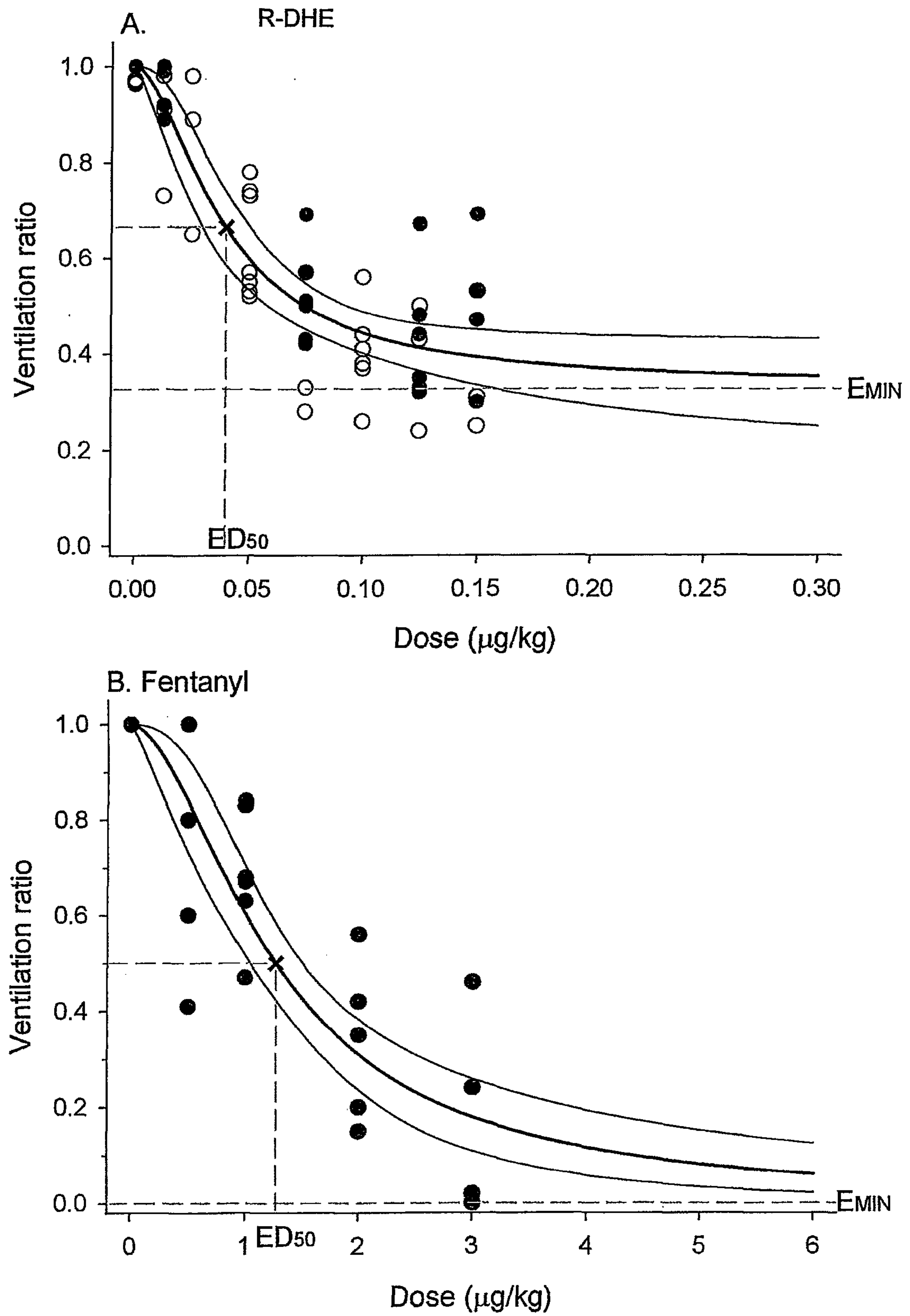


Figure 5

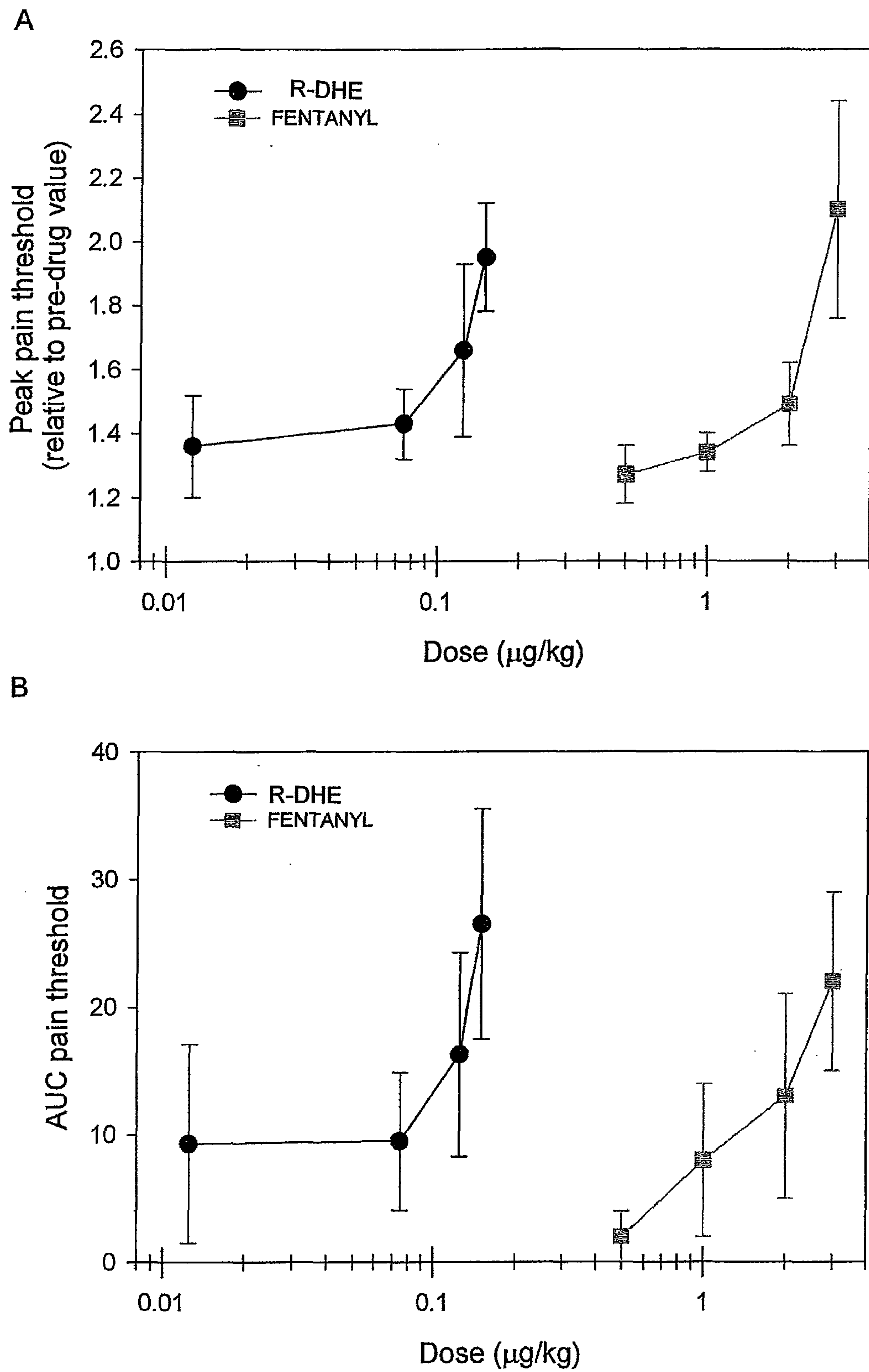


Figure 6

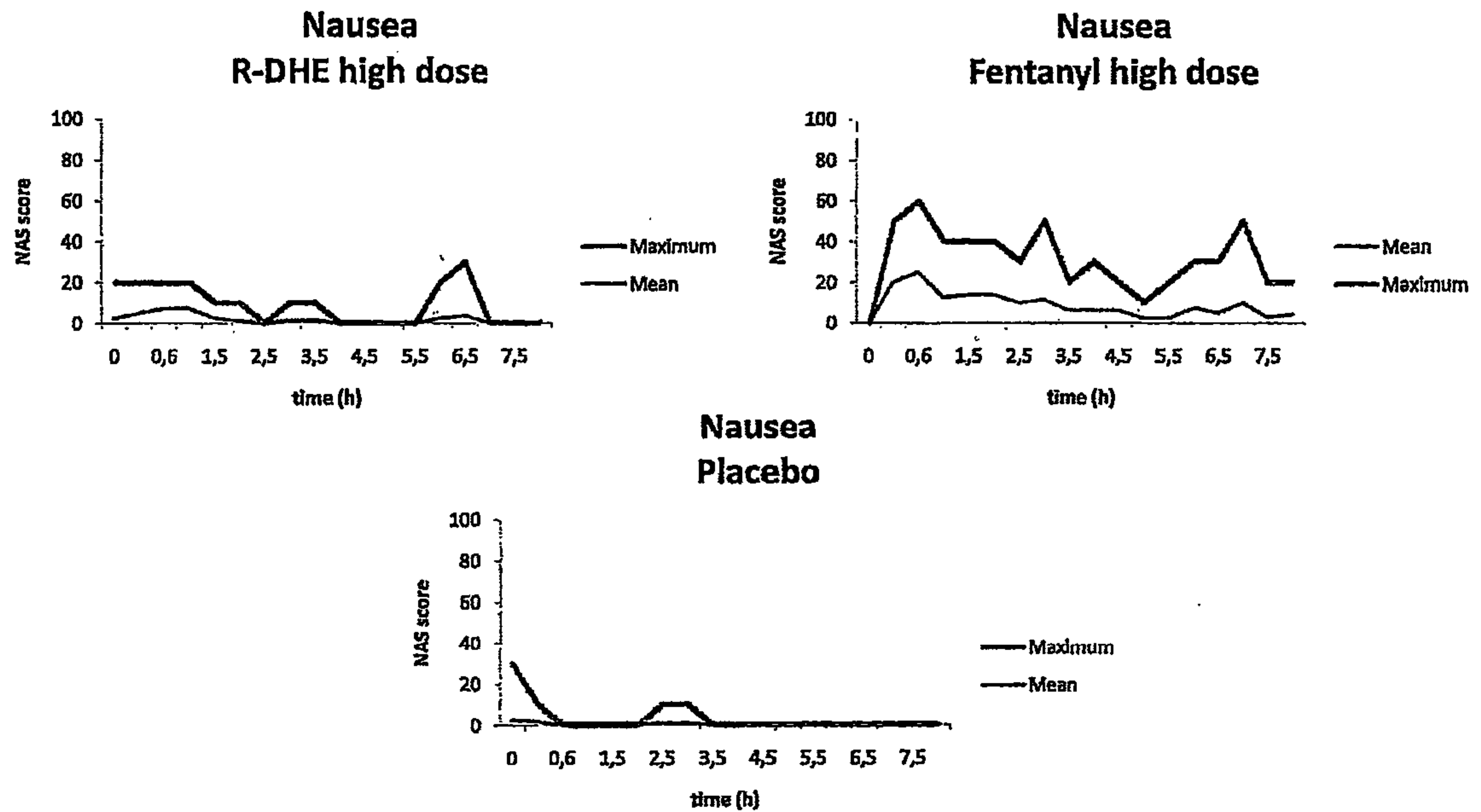


Figure 7a

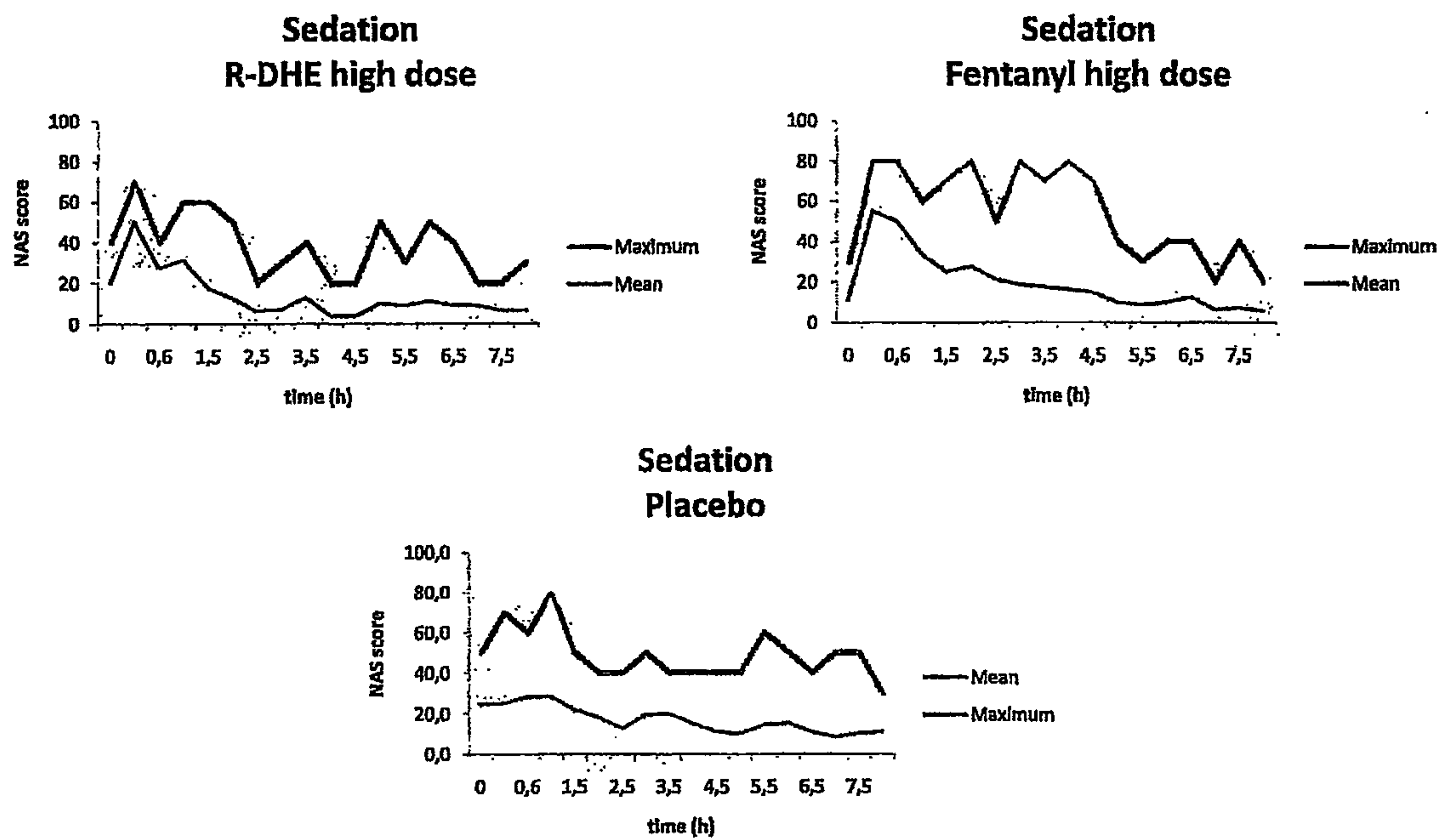


Figure 7b

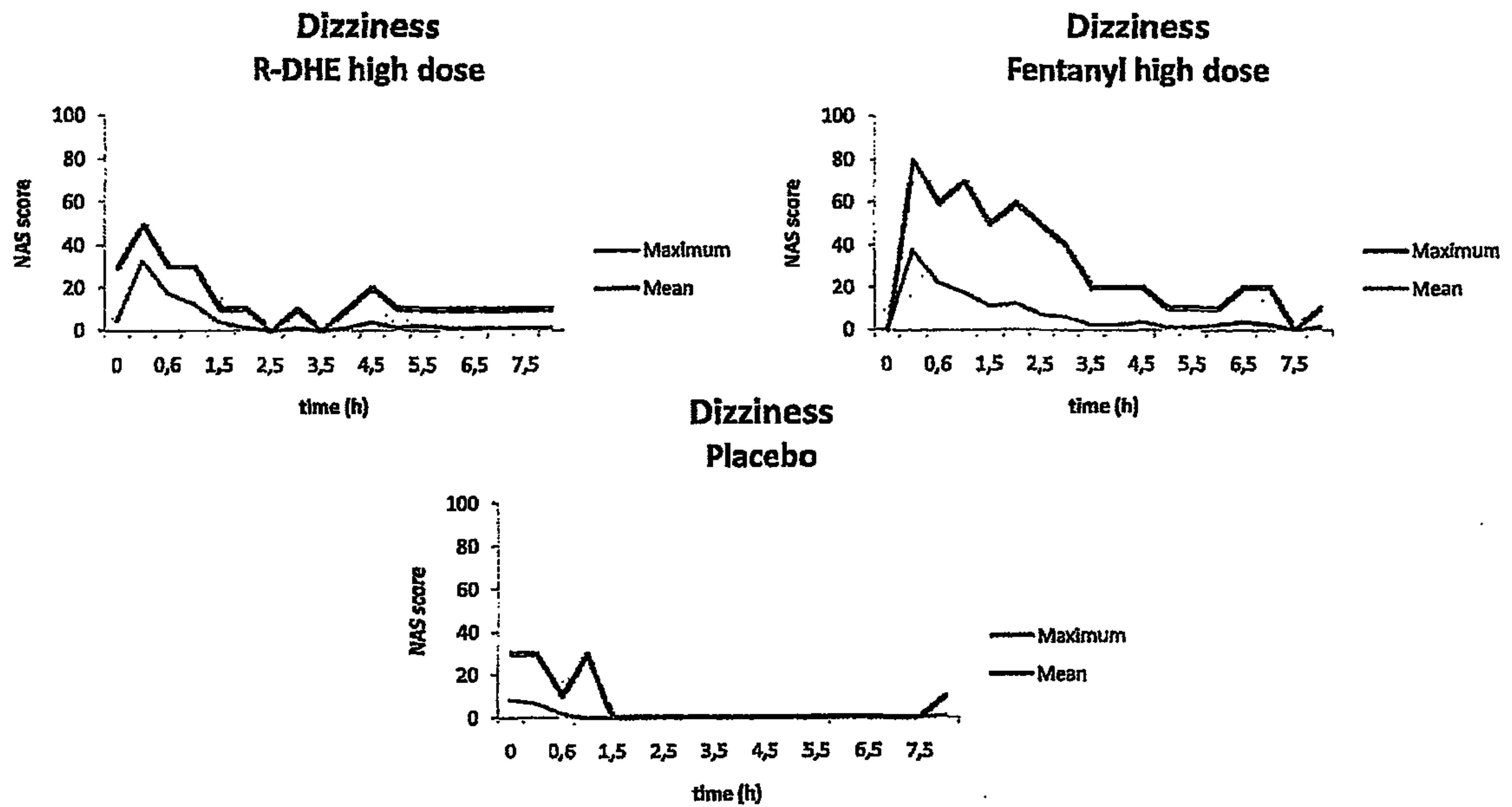


Figure 7c

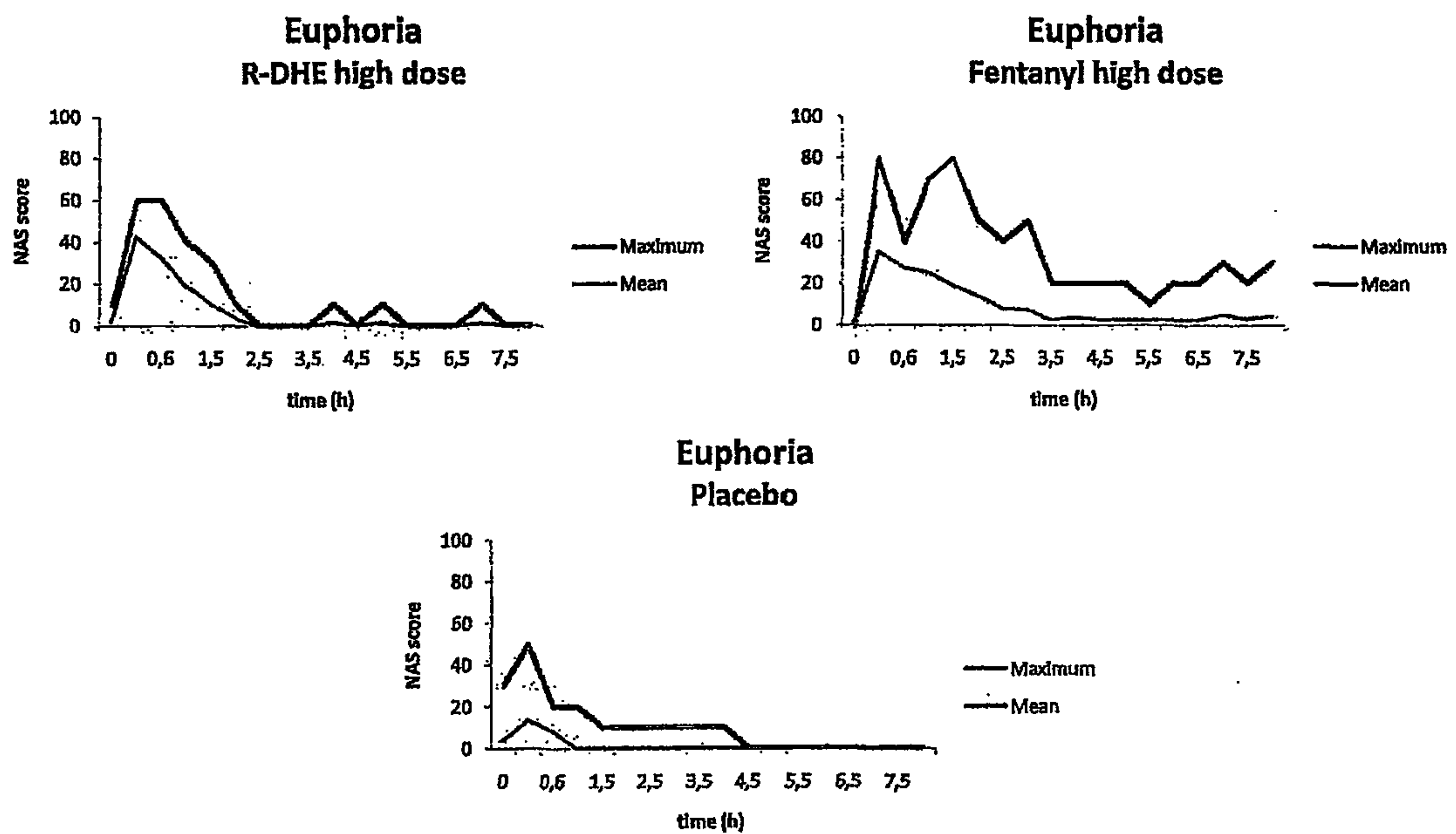


Figure 7d

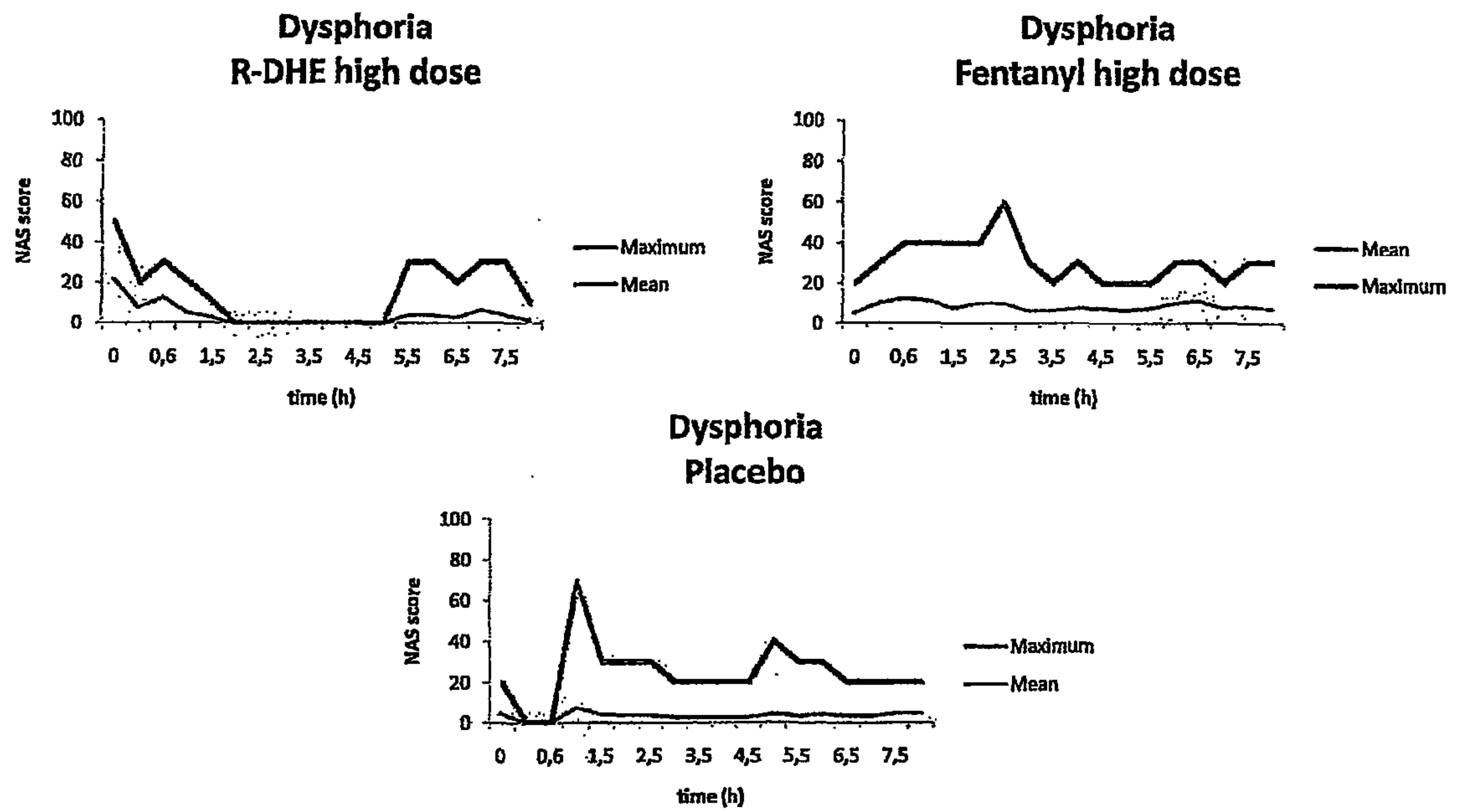


Figure 7e

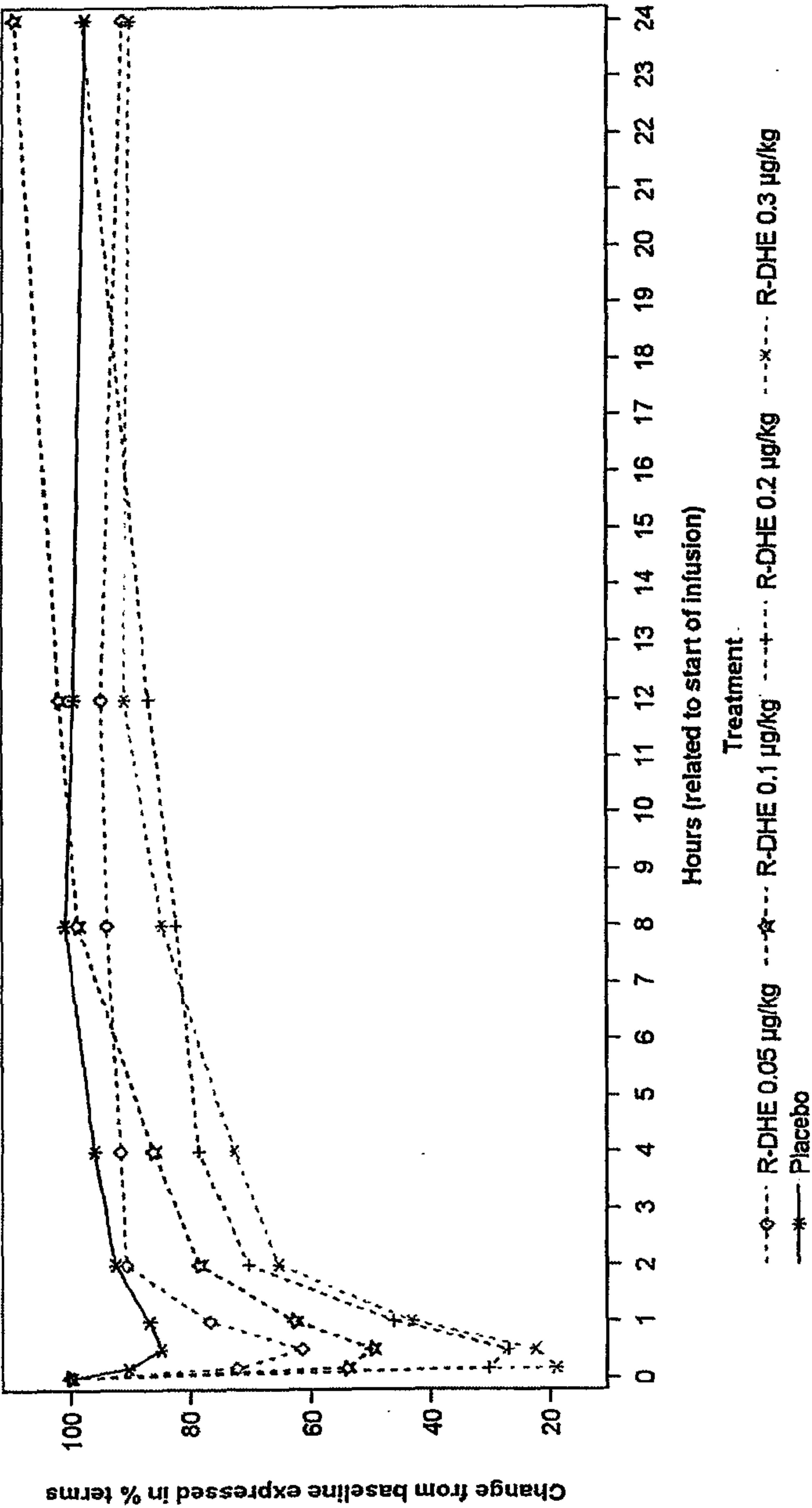


Figure 8

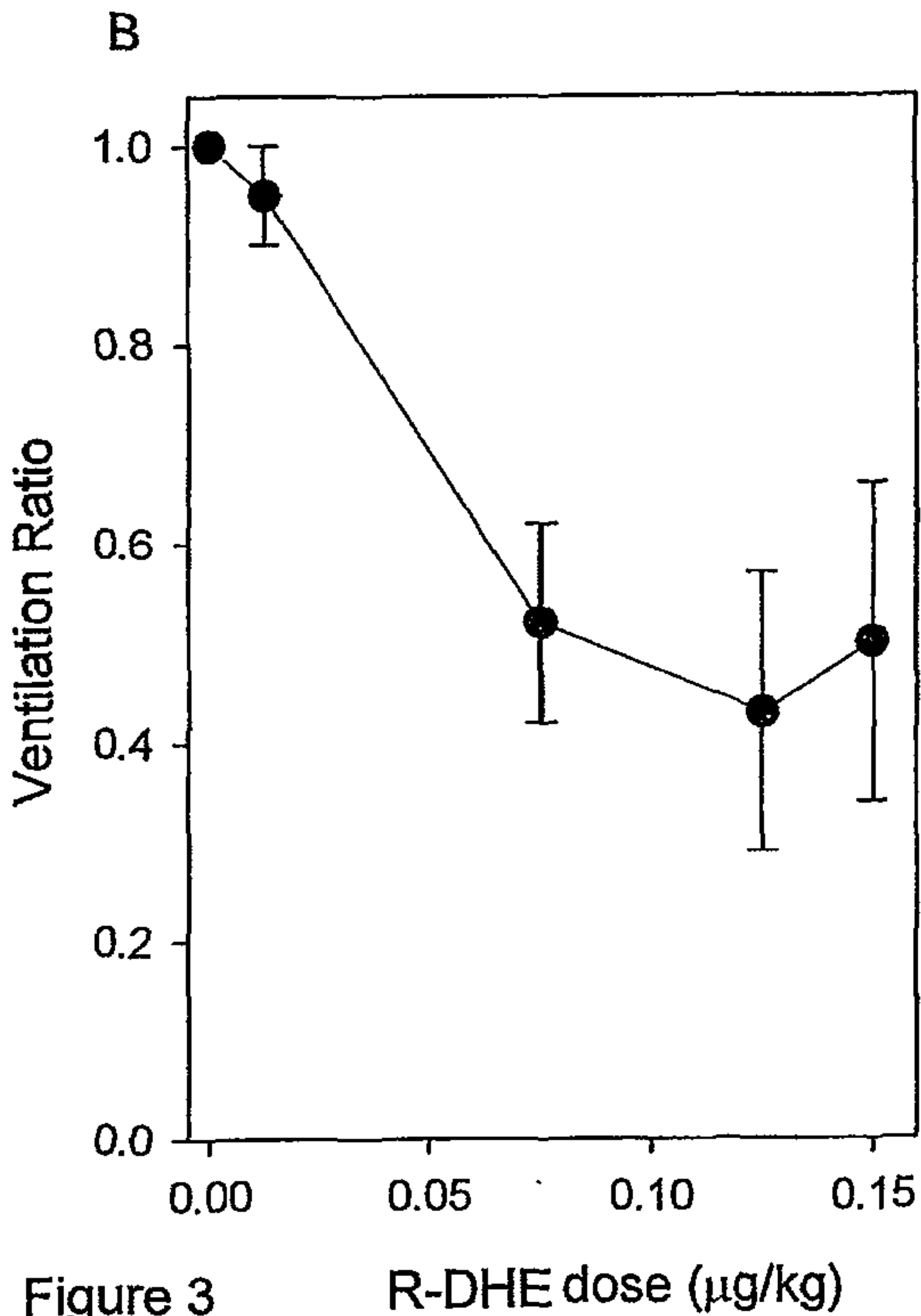


Figure 3