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A comparison of the respiratory effects of oxycodone versus morphine: a randomised, double-blind, placebo-controlled investigation.

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Summary

Although oxycodone is widely used as perioperative analgesic, it's respiratory profile (particularly the extent of respiratory depression with respect to morphine) remains to be fully characterised. With ethics approval, ASA I-II adults for elective surgery under general anaesthesia were randomised to receive placebo (n=6), morphine 0.1 $mg.kg^{-1}$, or oxycodone 0.05 $mg.kg^{-1}$, 0.1 $mg.kg^{-1}$, 0.2 $mg.kg^{-1}$ (n=12 in each active group). The study drug was injected intravenously after ten minutes steady state of spontaneous breathing. Monitoring was continued for thirty minutes and data obtained from previously validated wet wedge spirometer breathing system. Any patients meeting the predefined respiratory depression criteria in the first ten minutes of study drug administration received incremental intravenous naloxone. Mean minute volume decreased from baseline in all study groups. All study groups showed significant respiratory depression compared to placebo ($P=0.000018$, $P<0.000001$, $P<0.000001$ and $P=0.000016$ for oxycodone 0.05, 0.1, 0.2 and morphine 0.1 respectively). The mean percentage reduction from baseline was 88.6%, 74.4%,, 53.3%, and 22.6% for oxycodone 0.05, 0.1, 0.2 and morphine 0.1 groups respectively, with significant dose dependent differences between oxycodone groups ($P=0.0007$). The extent and speed of onset of oxycodone induced respiratory depression was dose dependent and greater than an equivalent dose of morphine.

Introduction

Oxycodone is a semi-synthetic thebaine derivative (14-hydroxy-7, 8-dihydrocodine) that has been used in clinical practice since 1917. Clinically it demonstrates analgesia and anti-nociception effect that are predominantly attributed to its μ-opioid receptor agonist actions. Although animal work suggests that there could a possible agonist action at κ opioid receptors especially the κ_2 subunit ligand that may contributing to some of its actions, clinically this is yet to be confirmed and it is unclear whether the κ_2 subunit ligand really exists or rather the changes can be attributed to heterodimerization of the opioid receptors [1-3].

Oxycodone is widely used as an analgesic both in acute and chronic pain practice. Besides an increased oral bioavailability it also confers an added advantage of a more rapid onset of analgesia in comparison to morphine [4-7]. Though often considered equianalgesic to morphine, the equivalence dose for parenteral conversion between the two opioids is quite variable (a range of 0.64 to 1.0 quoted in published literature) [8-9]. Oxycodone is clinically as effective or more so than morphine, with fewer side-effects . It is used orally, having good bioavailability as well as intravenously via a patient controlled analgesia (PCA) regime [6,10,11]. It is thought to be more effective in the treatment of visceral pain, possibly due to activity on the κ receptor, as well as a more favourable profile in the context of any immunosuppressive effects [12-19].

There are further isolated reports suggesting that besides a faster onset of intrinsic antinociceptive effect, oxycodone administration also demonstrates a more rapid onset of its respiratory effects as compared to morphine, however the evidence is lacking in terms of randomised controlled trials [20-23]. The intention of this placebo controlled randomised pilot study, was to demonstrate and characterise the respiratory effects of different doses of intravenous oxycodone and compare them to morphine. This study employs a respiratory model of spontaneously breathing patients under general anaesthesia (previously validated in similar studies characterising effects of opioids on respiratory function), and was conducted in the anaesthetic induction room prior to surgery [20-24]. We performed this study with a primary objective of measuring the

effect and extent of different doses of intravenous oxycodone on minute ventilation and comparing this to morphine and placebo in identical conditions. As a secondary objective this study also performed preliminary observations of the effect of naloxone administration to such changes in the minute ventilation.

Method

Patients

After obtaining local research ethics committee approval, this double blind, randomised, placebo controlled, parallel group pilot study was performed in adults (aged 18-55 years), scheduled for elective surgery of more than 30 minutes duration under general anaesthesia. 54 ASA grade 1-2 patients, weighing 45-100 kg and /or body mass index BMI < 30 gave informed consent and were randomised to one of the five groups in Table 1. Patients with previous history of anaesthetic complications, substance abuse or allergies to morphine, oxycodone or naloxone, long-term opioid use, known conditions predisposing to respiratory depression, gastro-esophageal reflux disease were all excluded.

The study medication was prepared by a third party, to maintain the blinding of the investigators. In the anaesthetic room, the clinical investigator sited routine clinical monitoring and intravenous access. Anaesthesia was induced with propofol 3-5 $mg.kg^{-1}$ and maintained with 1 MAC isoflurane, throughout the monitoring period, in a 40% oxygen/air mixture via a laryngeal mask airway ensuring no discernible leak. The sampling line was attached to the end of the laryngeal mask. Once breathing spontaneously, patients were connected to the modified wet wedge spirometer breathing system (Figure 1) based on the principles described by O'Connor et al [24]. The wet-wedge spirometer is a low resistance device that allows continuous volume employing a reservoir bag and relief valve without the need for introduction of any additional valves.

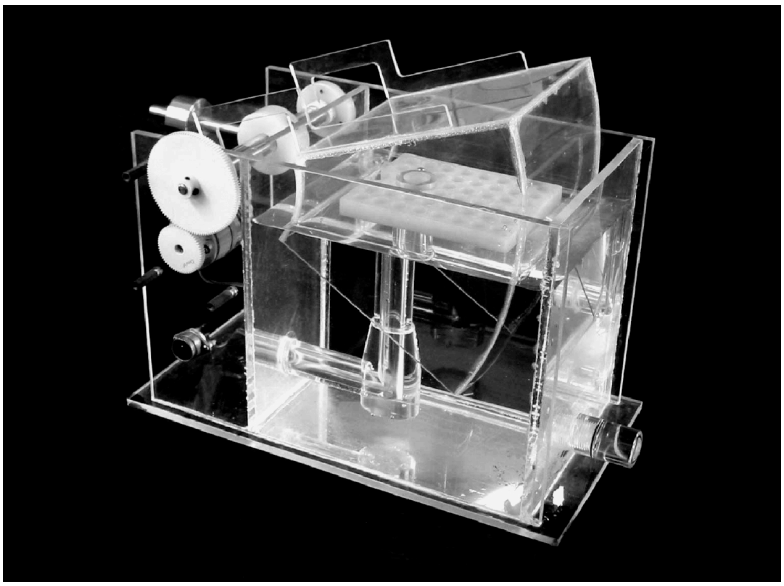

Figure 1. Wet-wedge spirometer.

Using the 'bag-in-bottle' principle, tidal volume is transmitted to the wet wedge spirometer (Figure 2), which is constructed from Perspex, and takes the form of a sector of a hollow cylinder, floating in a tank of water, counterbalanced by a weighted bar. The useable volume of the wedge is approximately 900 ml. Angular displacements of the wedge are transmitted via a gear system to the spindle of a DC/DC angular position transducer (Model No. DS3810, Denny & Giles Potentiometers Ltd., Christchurch, UK). The movement of the spirometer wedge thus causes a resulting change in output voltage which is proportional to changes in the volume. This signal is digitised and stored in a notebook PC running a virtual instrument (VI) program implemented in LabVIEW (National Instruments Corp). The VI displayed a continuous waveform indicating the displacement of the spirometer wedge throughout the study period. Fresh gas flow into the system was exactly balanced by suction, controlled by two needle valves in series, one for coarse adjustment and the other for fine adjustment.

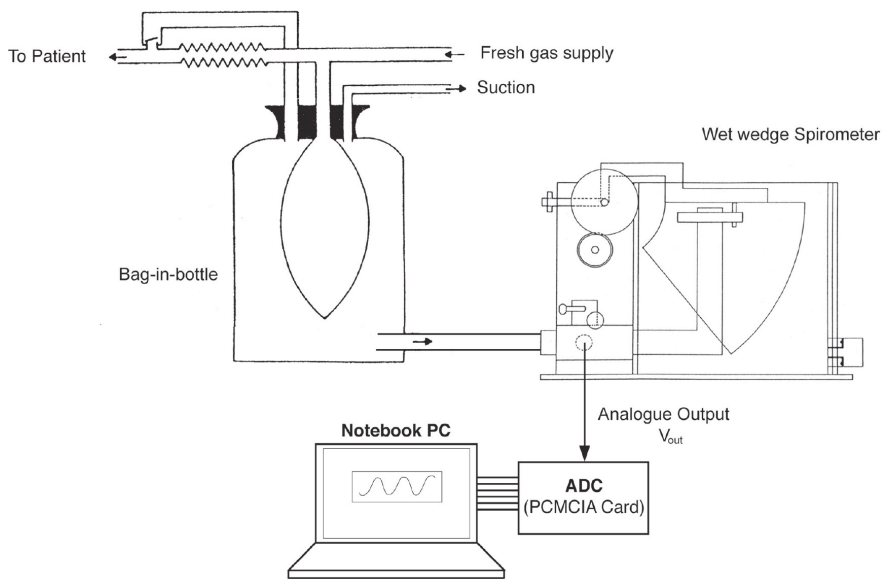

Figure 2. Block diagram of the breathing system.

The spirometer was calibrated before each patient study, with air using a 250 ml syringe connected to the input port of the spirometer. The suction was adjusted until the spirometer wedge remained stationary when there was no tidal flow in or out of the breathing system. The patient was then connected to the spirometry breathing system once satisfactory spontaneous breathing was established.

Recordings of respiratory rate, end-expiratory carbon dioxide, oxygen saturation and minute volume were recorded. After a 10 minute period of baseline respiratory steady state, the study was given intravenously by the blinded investigator. If at any point during the first 10 minutes after the study medication was administered, the respiratory rate had fallen by $\geq$33% and/or the end-expiratory CO_2 had risen by $\geq$1.5 kPa, then naloxone 400mcg was administered intravenously. If at any stage, the following were to occur: apnoea $\geq$ 1 minute, end-expiratory CO_2 $\geq$10 kPa or SpO_2 < 90%; the patient's lungs were then manually ventilated for one minute, aiming for SpO2 $\geq$ 96% and end-expiratory CO2 < 8, followed by a trial of spontaneous respiration, with the same criteria as above for restarting manual ventilation. Spirometry readings were continued for a period of 30 minutes after the study drug was given. At the end of the 30 minute period, spirometry was discontinued and a standard breathing system re-attached to the patient. The patient was then transferred to the operating theatre and anaesthesia was then continued as per

routine practice for the surgery. The clinical anaesthetist was informed of the identity of the study drug by the third party who had prepared the drug initially, so as to ensure that the patient received the appropriate analgesic management intra- and post-operatively. Re-emergence and recovery was conducted as normal, with all patients discharged safely to the ward when standard recovery criteria had been met.

Study Drug	Dose	Number
Oxycodone ($mg.kg^{-1}$)	0.05	12
Oxycodone ($mg.kg^{-1}$)	0.1	12
Oxycodone ($mg.kg^{-1}$)	0.2	12
Morphine ($mg.kg^{-1}$)	0.1	12
Placebo (ml)	5	6

Table 1. Study drug groups

Statistical analysis

The sample size of 54 patients (12 per active drug, 6 in the placebo group) was chosen to detect differences of ≥20% in minute volume after opioid administration (alpha = 0.05, beta = 0.2). Mean (±SD) minute volume percentage change in each group from the baseline was calculated. Minute volume percentage changes for each active group were compared from baseline to post administration of opioid and pre-naloxone administration time point to the end of study using 2-tailed, paired *t*-test. Comparison to placebo was done using 2-tailed, unpaired *t*-test. A value of $P < 0.05$ was considered significant. To calculate the difference in extent and rate of onset of respiratory depression between all the groups, an ANOVA test was used. Probability values of $P<0.05$ were considered significant.

Results

Out of 54 patients recruited the data of two patients could not be extracted due to technical failure and was excluded from final analysis. Both of these patients were in the oxycodone 0.2 $mg.kg^{-1}$ group. Patient characteristics are shown in Table 2.

Drug	Placebo	Morphine	Oxycodone ($0.05 mg.kg^{-1}$)	Oxycodone ($0.1 mg.kg^{-1}$)	Oxycodone ($0.2 mg.kg^{-1}$)
No. of Patients	6	12	12	12	10
Age (Years)	37.3(26-54)	36.8(18-51)	37.2 (20-51)	32.33 (23-49)	33.2 (20-46)
Weight (Kg)	74.8 (54-92)	68.8 (56-80)	70.4 (56-104)	74.6 (53-95)	72.5 (57-95)
M:F	4:2	7:5	7:5	7:5	3:7

Table 2. Patient characteristics. Data are mean (range) or absolute numbers

	Placebo n=6	Oxycodone 0.05 $mg.kg^{-1}$	Oxycodone 0.1 $mg.kg^{-1}$	Oxycodone 0.2 $mg.kg^{-1}$	Morphine 0.1 $mg.kg^{-1}$
n	6	12	12	10	12
zero doses of naloxone	6	3	0	0	9
one dose of naloxone	0	9	8	4	3
More than one dose of naloxone	0	0	4	6	0
Mean time to first dose (s)	N/A	100	92	67	275
P values					

Table 3. Table showing the number of patients in each group who received naloxone.

In the placebo group, there was no significant change in minute volume (P=0.714) from baseline and hence no naloxone was given to the patients in that group. An average time at which naloxone was administered within each of the active groups was calculated as an indicator of the onset of respiratory depression, as set out in the study criteria, and calculated the mean minute volume in each of the groups at that time point. There was a significant reduction in minute volume from baseline (SD) in the morphine group 22.6 (10.4) (P=0.000003). In the three oxycodone groups, mean minute volume decreased

significantly from baseline (*P*=0.000067, P<0.000001, P<0.000001) for oxycodone 0.05, 0.1, 0.2 respectively) and there was a significant difference in the fall in minute volume between the three oxycodone groups (ANOVA *P*=0.0007). For all patients, the % decrease from baseline (SD) was 53.3 (27.2), 74.4 (12.9) and 88.6 (13.5) for the oxycodone 0.05, 0.1 and 0.2 $mg.kg^{-1}$ respectively. All study groups showed significant respiratory depression compared to placebo (P=0.000018, P<0.000001, P<0.000001 and P=0.000016 for oxycodone 0.05, 0.1, 0.2 and morphine 0.1 respectively). Table 3 shows the number of patients in each group who received naloxone, the number of doses given, and the mean time of the first naloxone administration. Figure 3 shows the mean percent changes in volume for patients who recieved naloxone. It can be seen that following naloxone administration, all naloxone groups showed a significant improvement in minute volume from the pre-naloxone values (P= 0.000011, P<0.000001, P<0.000001 for oxycodone 0.05, 0.1, 0.2 respectively).

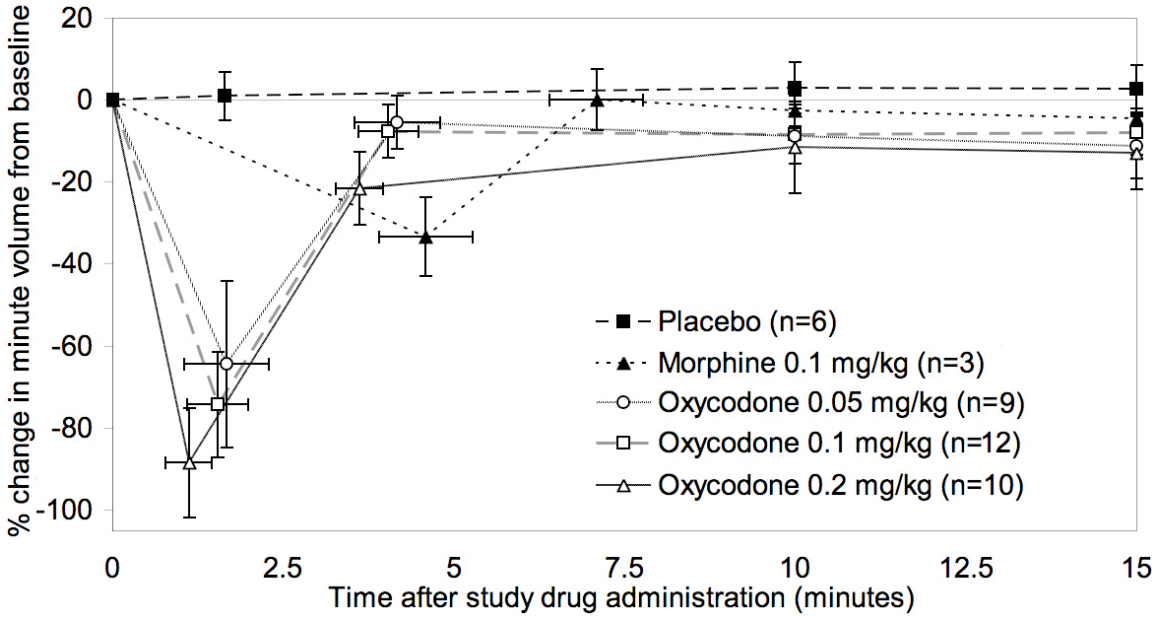

Figure 3. Graph showing mean (SD) percent change in minute volume at various times for all patients who received naloxone. The maximal reduction in minute volume following administration of the study drug ('Depressed') is shown, followed by the change in minute volume *three* minutes after administration of naloxone ('Recovered'). The minute volume changes 10 and 15 minutes after administration of the study drug ('SD+10' and 'SD+15') are also shown

Discussion

Oxycodone a synthetic opioid has action on both μ and κ opioid receptors [8,12,16]. It has a high oral bioavailability (60-90%) and an analgesic potency 30-50 % greater than morphine [9]. The increased potency may contribute to a stronger anti-nociceptive effect at equivalent dose of morphine hence the ongoing debate about the actual equivalence rate after parenteral administration. Oxycodone may produce a dose dependent decrease in respiration although the exact nature and comparison to morphine remains to be substantiated using randomised controlled trials [8,9,16,25]. The primary objective of this pilot study was to characterise the respiratory profile of oxycodone in a spontaneously breathing anaesthetised patient and compare it with morphine when administered intravenously. The additive effect of opioids and volatile maintained general anaesthesia on spontaneous ventilation facilitates a sensitive model that has been used in previous studies evaluating the respiratory effects of opioids [24, 26].

Using this model of patients under general anaesthesia on spontaneous ventilation, the wet-wedge spirometer in our pilot study characterised the respiratory depression produced by various doses of oxycodone. The mechanical signal from the spirometer was digitised and stored in a notebook PC running a virtual instrument (VI) program implemented in LabVIEW (National Instruments Corp).

The equivalent dose when converting between parenteral morphine and oxycodone is variable with a suggested ratio of 0.65 to 1.0 when converting between the two. Interestingly some reports have quoted an even higher conversion ratio of 1.5 when converting the two drugs. Three doses of oxycodone were chosen (0.05, 0.1 and 0.2 $mg.kg^{-1}$) in our study reflecting doses that are a 0.5, 1.0 and 1.5 conversion ratio respectively. The different doses of oxycodone were chosen on the assumption that the middle dose maybe equi-analgesic to morphine, and the other two were half and double respectively.

All three doses of oxycodone used in the study provided a dose dependent statistically significant respiratory depression. The rate of onset of this respiratory depression was significantly quicker as well compared to morphine. The mean minute volume decreased significantly from baseline and there was a significant difference in the fall in minute

volume between the three oxycodone groups. This would correlate well with the dose dependent direct effect on the respiration.

In the morphine group, three out of the twelve patients needed a single dose of naloxone each. This was in contrast to the patients in the low dose oxycodone (0.05 $mg.kg^{-1}$) group, in which nine out of 12 patients received a single dose of naloxone. In the oxycodone 0.1 $mg.kg^{-1}$group, all 12 patients received at least one dose with four patients receiving a second dose and in the 0.2 $mg.kg^{-1}$ group, all ten patients received naloxone with three of the ten receiving a second dose, two receiving a third dose, and a further one patient receiving four doses in total. The increased naloxone requirement in the oxycodone groups suggest that the extent of respiratory depression characterised by decrease in the minute volume was greater even in the oxycodone 0.05 $mg.kg^{-1}$ group as compared to patients receiving morphine.

There was a significant difference in the onset of respiratory depression (measured by the time needed to receive first naloxone dose) between the four groups. In patients who reached the respiratory threshold values, the mean time to first naloxone dose was 275 seconds in the morphine group, and 100, 92, and 67 seconds in the oxycodone 0.05, 0.1, 0.2 $mg.kg^{-1}$ groups respectively.

Oxycodone has similar lipid solubility to morphine and similar protein binding with clear agonist properties at the μ opioid receptor. It is thought, however, that its active metabolite- oxymorphone- has a great μ receptor binding ability compared to morphine, and could be the reason for the faster onset, respiratory depression and potency of the drug [10, 27-30].

Absence of placebo control for naloxone precludes any definite statement about the reversal following naloxone administration, though it might be conjectured that naloxone administration did stop the ongoing negative trend in change of minute volume. In our model, this comparison of oxycodone and morphine has shown that the extent and speed of onset of oxycodone induced respiratory depression was significantly greater than that seen in the morphine group. It was seen that naloxone increased minute volume in all four opioid groups with some higher dose oxycodone patients requiring multiple doses to maintain respiratory depression criteria above threshold values.

These preliminary results suggest that respiratory depression may be greater with oxycodone than an equivalent analgesic dose of morphine and a further larger study is needed.

Competing Interests

This own-account research study was performed independently without any industry involvement or financial support. VM has been a speaker, and RML a speaker and consultant for NAPP Pharmaceuticals Limited. The department has received research funding for another study from Mundipharma Europe.

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