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A prospective, randomised, double-blind, double-dummy, placebo-controlled investigation of buprenorphine induced respiratory depression and its reversibility with naloxone in anaesthetised patients

S Nikolic, V Mehta, S Ratcliffe,
JP Phillips, P Kyriacou, RM Langford

Background and Aims

Despite its long history and widespread use, some questions remain over buprenorphine's respiratory safety profile.^{1,2} This study investigated respiratory depression and potential reversibility by naloxone at two buprenorphine doses, of which the intramuscularly administered dose was designed to achieve the plasma concentration range seen with transdermal delivery. The buprenorphine doses were compared to morphine administered intravenously.

The IM route was proposed to avoid the characteristic high peak seen after IV bolus injection, to achieve a slow-rising plasma concentration which plateaus at five minutes. The selected intramuscular buprenorphine dose (0.85 mcg/kg) was chosen to achieve a similar plasma concentration at a steady state to that seen with transdermal buprenorphine at 35 mcg/h (the Transtec® 35 mcg/h patch).

Materials and methods

With research ethics committee approval, 84 patients scheduled for elective surgery were randomised to receive: Buprenorphine IM 0.85 mcg/kg (n=24), Buprenorphine IV 3 mcg/kg (n=24), Morphine IV 0.1 mg/kg (n=24) or placebo (saline IV, n=12) during standardised general anaesthesia comprising: propofol, sevoflurane (MAC 1.5) in an oxygen/air mixture. The airway was maintained by a laryngeal mask with no discernible leak. Once breathing spontaneously, the patient was connected to a wet wedge spirometer breathing system³ (Figure 1). A diagrammatic representation of the apparatus is shown in (Figure 2). This is a low resistance, bag in bottle device, which allows the continuous measurement of tidal volume. The output was digitised and stored in a notebook running Labview®.

Using a double dummy and double blind design, after 10 minutes baseline respiratory steady state, study drug was administered both IV and IM. Recording was continued for another 30 minutes. Patients whose respiratory rate decreased by >33% or whose ETCO₂ increased by >1.5 kPa were randomised to receive in a double-blind fashion an intravenous bolus followed by infusion of either naloxone (2mg IV stat plus 1 mg over 20 mins) or normal saline.

Blood samples were taken at 5, 15 and 30 minutes post study drug administration for buprenorphine plasma assay.

At the end of the study, spirometry was discontinued and anaesthesia continued as per routine practice. A safety assessment was made by the blinded investigator prior to discharge from the recovery room.

Statistics

Power calculation:

The sample size of 84 patients:

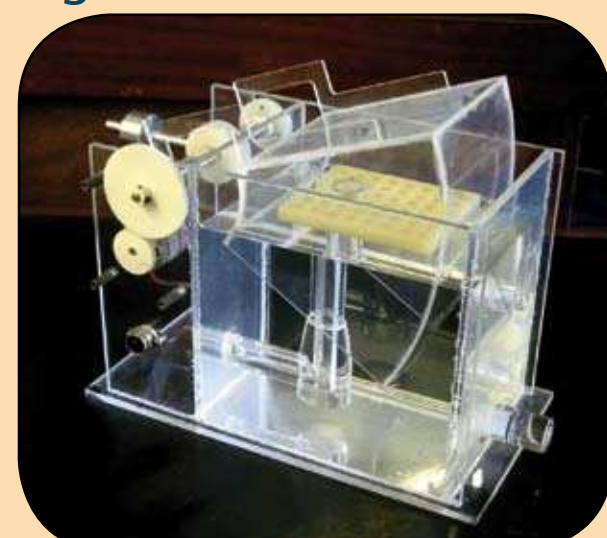
- was to detect differences of >20% in minute volume after study drug administration (alpha = 0.05, beta = 0.2)
- 12 placebo group
- 24 buprenorphine IM group
- 24 buprenorphine IV group
- 24 morphine IV group

Data analysis:

Comparison of minute volume % changes

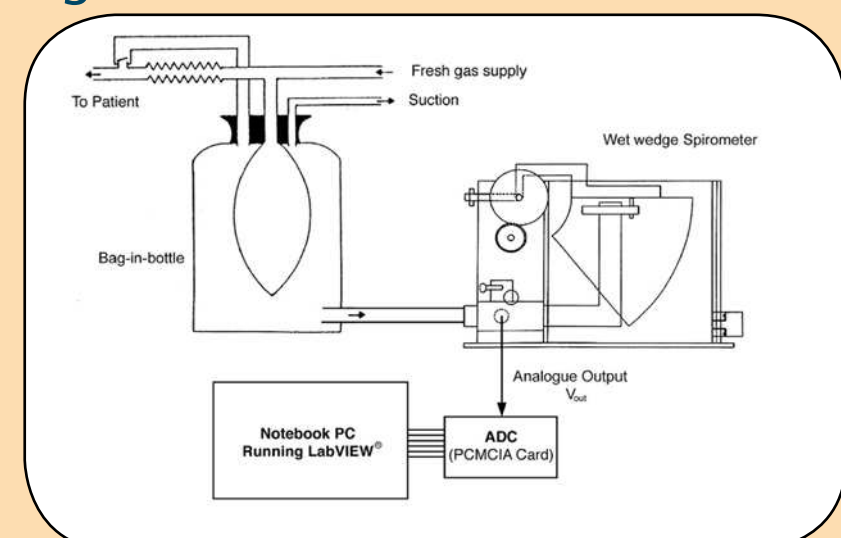
- For change from baseline post study drug (within group comparison)
 - 2-tailed, paired t-test
- For change from baseline post study drug between the groups – 2-tailed, unpaired t-test

Figure 1



Wet wedge spirometer

Figure 2



Diagrammatic representation of the apparatus

Results

In our model, the comparison of buprenorphine at different doses, morphine and placebo has shown that:

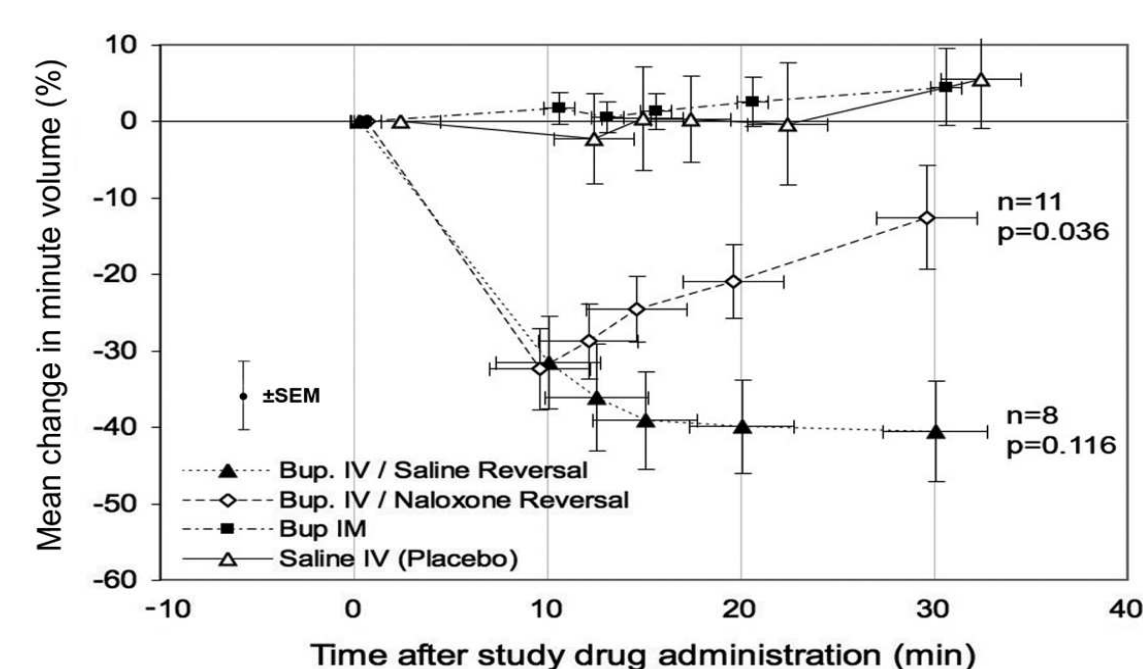
No patients in the buprenorphine IM or placebo groups reached the predefined respiratory depression threshold (Figure 3).

19 patients in the buprenorphine IV group exhibited the predefined thresholds and were randomised to receive naloxone (n=11), or saline (n=8). Naloxone showed statistically significant improvement in minute ventilation, unlike the group that received placebo for naloxone (Figure 3).

All patients in the morphine IV group exhibited the predefined respiratory depression thresholds. The respiratory depression was readily and fully reversed with naloxone.

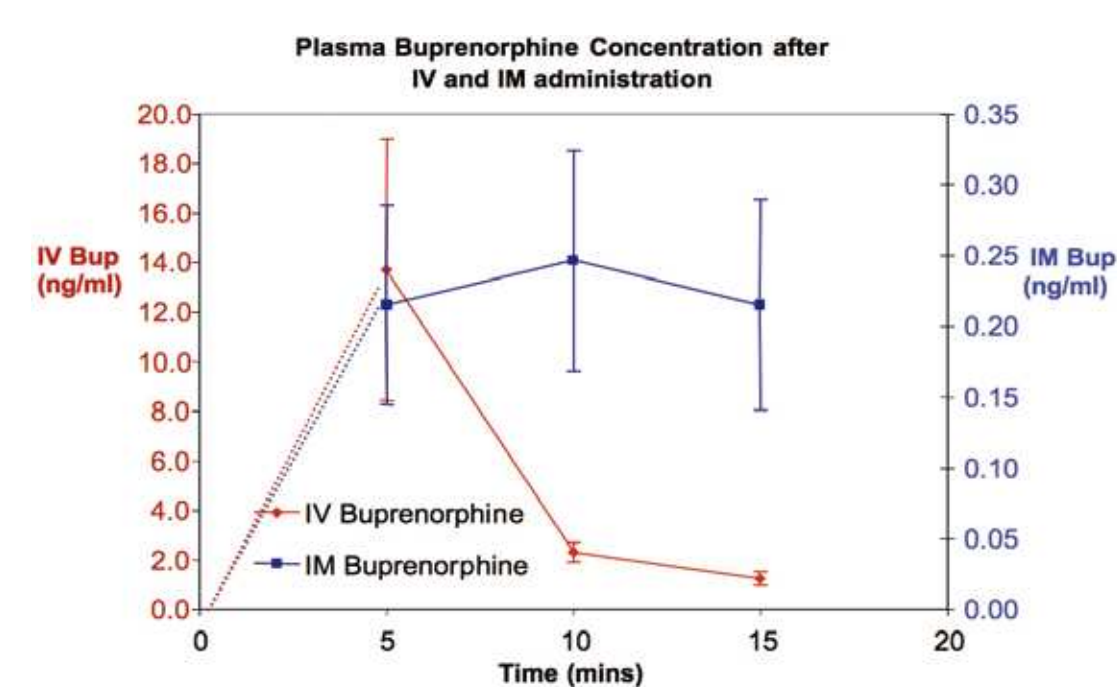
The average plasma concentration following IM buprenorphine was found to be in the 0.2-0.3 ng/ml range (Figure 4).

Figure 3



% change in minute ventilation for four groups: placebo, buprenorphine IM and buprenorphine IV patients who received naloxone, or placebo for naloxone.

Figure 4



Plasma buprenorphine concentrations (ng/ml)

Conclusion

In this sensitive model to detect respiratory depression, intramuscular dosing designed to achieve plasma buprenorphine levels in the range seen with the 35 mcg/h patch did not cause significant change from baseline, in contrast to the IV higher bolus dose, which in the majority of patients reached the predefined respiratory depression threshold. In the latter patients, naloxone achieved significant increase in minute ventilation, which represented clinically relevant reversal of respiratory depression.

Acknowledgement

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